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Efficacy of One-Stage Microdiscectomy and Radiofrequency Denervation of Intervertebral Joints Compared to Microdiscectomy in Patients with Spinal Disc Herniation

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The article analyzes the early and long-term outcomes in 113 patients who underwent surgical treatment for lumbosacral disc herniations. The first group of patients (n=32) underwent microdiscectomy in a combination with radiofrequency destruction (RFD) of the facet nerves. The control group patients (n=81) underwent microdiscectomy only. This study demonstrates the advantage of combining RFD with open surgery. In this case, regression of both nerve root and back pain is achieved, which greatly accelerates rehabilitation of patients, restoration of their work ability, and therefore their return to normal life.

Keywords: spondylarthrosis, disc herniation, radiofrequency destruction, microdiscectomy.

Degenerative diseases of the spine, which are commonly accompanied by pain syndromes, hold one of the first places in the prevalence pattern of CNS diseases. The frequency of this pathology in the general population ranges from 12 to 45% [2]. Herniations of the intervertebral discs of the lumbosacral spine occupy the first place in the pattern of degenerative diseases requiring surgical treatment [1]. About 300,000 such operations are annually carried out in the USA. Discectomy and microdiscectomy are the main variants of surgical treatment. The frequency of excellent and good outcomes of surgical treatment of herniated discs is 90—95% [5]. However, the most often reason to visit a doctor is not isolated radicular pain but vertebrogenic pain caused by lesion of the intervertebral discs and the intervertebral joints, with the number of nociceptors being much more in the latter case [2]. Many patients continue to experience lumbosacral pain after microdiscectomy. Potential generators of this pain include the intervertebral disc, ligaments of the spinal motion segment, sacroiliac joints as well as facet (intervertebral) joints [4]. During microdiscectomy, the surgeon performs nerve root decompression, eliminating disco-radicular conflict. However, the problem associated with the pain syndrome caused by spondylarthrosis can persist. According to the literature, spondylarthrosis is the cause of pain syndrome in the lumbosacral region in 80—90% of cases. Therefore, in some cases, the patient is not fully satisfied with the quality of treatment, because the pain syndrome in the lumbosacral spine prevents the return to normal everyday and professional life.

The most effective and safe method to treat spondylarthrosis (facet syndrome) is radiofrequency destruction (RFD) of the facet nerves. Investigation of the advisability of one-stage microdiscectomy and RFD is important.

The aim of the study was to evaluate the efficacy of one-stage microdiscectomy and RFD of the lumbar segments in patients with herniation of the intervertebral disc of the lumbosacral spine in comparison with simple microdiscectomy in elimination of vertebrogenic lumbar pain.

Material and Methods

The study included 113 patients who underwent surgical treatment for herniations of the intervertebral discs of the lumbosacral spine between 2010 and 2012. All patients were divided into two groups.

The 1st group consisted of 32 patients (18 females and 14 males) aged 32 to 58 years (mean age of 45.7 years) who underwent microdiscectomy in a combination with RFD; the 2nd group (control) consisted of 81 patients (46 females and 35 males) aged 33 to 59 years (mean age of 44.3 years) who underwent microdiscectomy only.

Prior to surgery, all patients underwent an examination, including a neurological examination, an examination of biomechanics, roentgenography, and MRI and CT of the lumbosacral spine. Subchondral sclerosis of the terminal (end) plates of the vertebral bodies, reduced height of the intervertebral space, herniation of the intervertebral disc as well as sclerosis and deformation of the articular surfaces and disturbance of their congruency were observed during interpretation of the neuroimaging data, which indicated the development of spondylarthrosis of corresponding spinal segments [3].

Before surgery, all patients underwent, under the guidance of an electron-optical image intensifier (EOII), para-articular blocks with 2% lidocaine at the lesion level with diagnostic and therapeutic purposes (with obligatory introduction of steroids — 1.0 mL of diprospan). A temporary reduction in the intensity or complete regression of pain syndrome in the lumbar spine indicated that a compromised intervertebral joint was the pain generator.

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Fig. 1. Examination of lumbar spine biomechanics using a three-dimensional motion analyzer Zebris.

Evaluation the treatment efficacy was carried out using a special scale developed at the Burdenko Neurosurgical Institute. This scale consists of 5 blocks. This scale is used to evaluate social adaptation of the patient to the disease at the study time, quantitative and qualitative characteristics of pain syndrome, the orthopedic and neurological status, spine biomechanics, and neuroimaging data (roentgenography, CT, and MRI).

An examination of biomechanics of the lumbar spine was performed using a Zebris 3-D Motion Analyzer (Zebris medizintechnik, Germany). A disturbance of biomechanics of the lumbar spine was found in all patients. It was manifested as the limitation of extension and the amplitude asymmetry of tilting and rotational motions (Fig. 1).

Based on clinical and roentgenologic examinations of patients in both groups, degenerative changes in the intervertebral (facet) joints were found to be the cause of the pain syndrome. The L3—L4, L4—L5, and L5—S1 segments were involved most frequently (97%). In the 1st group, disc herniation was detected at the L3—L4 level in 6 (18.7%) patients, at the L4—L5 level in 14 (43.8%), and at the L5—S1 level in 12 (37.5%). In the 2nd group, disc herniation was detected at the L3—L4 level in 16 (19.8%) patients, at the L4—L5 level in 35 (43.2%), and at the L5—S1 level in 30 (37.0%). Therefore, the diagnosis was formulated as osteochondrosis, spondylarthrosis of the lumbosacral spine, protrusion/extrusion of the intervertebral disc, musculo-tonic and root (radicular) syndrome with indication of a specific nerve root.

Given the fact that not all clinicians make account of the intervertebral joints as one of the main generators of back pain, it is necessary to elaborate on some anatomical aspects of the innervation of the intervertebral (facet, zygapophyseal) joint as well as the clinical presentation of the facet syndrome. The intervertebral, facet or zygapophyseal (art. zygapophysiales) joint is by formed the superior and inferior articular processes and is surrounded by the joint capsule that is attached to the edge of the articular cartilage. The joint is innervated by the medial rami of the posterior (dorsal) branch of the spinal nerve. Each medial ramus goes around the base of the superior articular process and passes through the fossa formed by lig. mammillolaccessory. At this point, small nerve rami branch to the joint capsule. A medial descending ramus goes caudally and, dividing into several parts, innervates muscles, ligaments, and, partially, the subjacent intervertebral joint. Therefore, the innervation of each joint is provided from, at least, two levels (according to some data, from three levels). The pain onset is often associated with extension and rotation of the spine. Movements in the lumbar spine, mainly extension, are usually limited. The appearance of short-term morning stiffness and an increase in pain by the end of the day are typical signs. Unloading of the spine reduces the pain syndrome intensity. Flattening of the lumbar lordosis, rotation or curvature...
in the lumbosacral spine, and tension in the paravertebral muscles on the affected side can be detected by a physical examination. The typical sign is local tenderness during palpation of the projection of the intervertebral joints. The isolated facet syndrome is usually not accompanied by sensory, motor and reflex disorders. All this makes it possible to consider the intervertebral (facet) joint as a potential source of back pain.

Preoperative preparation of all patients was carried out according to a standard procedure. Patients of the 1st group underwent RFD in the operating room, immediately before microdiscectomy. A para-articular region puncture was carried out in the area of the nerves going to the joint capsule, with the patient being in the prone position, under local anesthesia with a 0.5% novocaine solution (10.0 mL), and under the guidance of an electron-optical image intensifier. The puncture was performed at the herniated disc level, on both sides. The needle position was controlled in two projections (Fig. 2).

Next, facet nerve electrostimulation with a frequency of 50 Hz was conducted using a Stryker Interventional Spine MultiGen RF Console radio-frequency generator to identify the correct needle position. The patient was to feel a tingling sensation in the area of the corresponding facet joint, in the range of 0.4 to 0.6 V. Further, the frequency was lowered to 2 Hz, and the state of the extremity muscles was assessed. The lack of muscle contractions in the extremities indicated the correct position of the electrode. A 0.5% novocaine solution (not more than 2.0 mL) was injected into the intended destruction area with the purpose of anesthesia, followed by RFD. No complication was detected. Next, the patient received anesthesia care, and microdiscectomy was performed according to a standard procedure.

Patients of the 2nd group underwent microdiscectomy only.

Postoperative management of patients in both groups was identical. Activation of patients was carried out using a semi-rigid lumbar corset on the 1st day, with support on both lower extremities. All patients were transferred to the rehabilitation department on the 7—10th day, where they received rehabilitation treatment (therapeutic exercises, physiotherapy) and anti-inflammatory therapy for 2 weeks. Wearing a corset for 2 months was recommended, sitting without limitations was permitted 1 month after surgery. Patients were discharged to work through 1—1.5 months after discharge from the hospital.

**Results and Discussion**

Relief of nerve root (radicular) pain was detected in patients of both groups in the early postoperative period. The results of treatment of the lumbar pain syndrome were evaluated before discharge of the patient to work and 1 year after surgery.

According to the treatment efficacy scale, pain syndrome and social adaptation appeared to be most dynamic in both groups of patients. In the 1st group of patients, a high intensity of the preoperative pain syndrome was observed that amounted to 66±5 points (32 points due to lumbar pain and 34 points due to lower extremity pain). The pain syndrome regressed to 17±4 points by the time of discharge (14 points due to lumbar pain and 3 points due to lower extremity pain). Pains in the spine and lower extremities were completely relieved 12 months after surgery. According to the scale, this indicator did not exceed 5±1 points (4 points due to lumbar pain and 1 point due to lower extremity pain). A high score for the block of social adaptation before surgery (8±2) became 1 point after 12 months, which indicates almost complete return of patients in this group to the previous life quality.

In turn, the pain syndrome intensity in the control group was assessed as 68±4 points (33 points due to lumbar pain and 35 points due to lower extremity pain) before surgical treatment, 25±3 points (21 points due to lumbar pain and 4 points due to lower extremity pain) by the time of discharge, and 11±2 points (10 points due to lumbar pain and 1 point due to lower extremity pain) after 1 year (Fig. 3). Postoperatively, patients reported regression of extremity pain but persistence of lumbar pain. The mean score for the block of social adaptation was 7±2 points before surgery and 3±1 points after 12 months.

An examination of biomechanics of the lumbar spine before and 1 year after surgery revealed a moderate increase in the amplitude and speed of movements in the spinal segments in the group of patients who underwent microdiscectomy in a combination with RFD compared to patients who underwent microdiscectomy only.

In the 1st group, the maximal range of flexion in the lumbar spine was increased by 33’ (from 25±3.4 to 58±5.1°);
The prevalence of degenerative diseases of the spine is truly impressive. Apart from the fact that diseases of the lumbar spine hold the leading position in the pattern of most common diseases (pain in the neck is at the fourth place), the duration of total disability due to spinal diseases is 5,000,000 years throughout a country (such as the USA) or 6 days per year for each resident.

The problem solved by the authors of this article is very important and aimed at increasing the efficacy of surgical treatment of discogenic radicular syndromes using microdiscectomy in the lumbar spine.

The problem of a modern unified approach to treatment of discogenic compression of the spine originates from rigidity in interpretation of existing clinical syndrome and MRI data. The algorithm that has already been mastered by most neurosurgeons includes radicular pain syndrome + no effect of conservative treatment for at least 4 weeks and the presence of discogenic compression of the corresponding nerve root identified by MRI. It serves as the almost unambiguous clinical indication for microdiscectomy or endoscopic discectomy. The spine pain syndrome is sometimes underestimated or serves the cause to stabilize the operated segment, being considered as instability.

In this case, the rate of developing spondylarthrosis, which accompanies a degenerative process in the spine, amounts up to 90% and is significantly higher than the rate of developing discogenic nerve root compression (30—40). The manifestations of spondylarthrosis, like those of any joint disease, include the development of back pain aggravated by movement. There is a simple but not too effective (70%) way to treat this disease using radiofrequency destruction of the medial branches in the facet joint area.

The authors compared groups where patients with a combination of radicular pains and lumbo-dynias underwent RFD before microdiscectomy. The group that received this combined treatment, of course, had significantly greater regression...
of back pains compared to the group where only discectomy was performed.

The problem of an adequate approach to the clinical symptoms of the patient, especially in the case of combined syndromes, always faces administrative limitations when only one nosology (in the given case, disc herniation is combined with spondylarthrosis) can be cured in a single operation. The use of a simple puncture RFD combined with microdiscectomy baffles health care administrators and specialists in medical and economic standards. It must be admitted that practicing neurosurgeons have to diverge from the standards of care to perform procedures and operations to the full extent. The practice described by the authors is an example of this non-standard approach and can be used as a practical guide to choosing the optimal treatment tactics.

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A Comparative Analysis of the Effectiveness and Potential of Endoscopic and Microsurgical Resection of Disc Herniations in the Lumbosacral Spine

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The issue regarding the advantages of endoscopic treatment of spinal disc herniations is debatable. Throughout their development, endoscopic technologies have been compared to microsurgical methods. The two-year experience of applying endoscopic methods was analyzed. The study included 183 patients. The effectiveness of the performed treatment was evaluated according to the MacNab scale of surgical treatment outcomes. Good and excellent outcomes were achieved in 170 (92.9%) cases. This cure rate was compared to that for good and excellent outcomes of microsurgical treatment method according to the literature data. The article by American authors who conducted a multicenter study (Lumbar microdiscectomy: a historical perspective and current technical considerations. Koebbe C.J., Maroon J.C., Abla A., El-Kadi H., Bost J. Neurosurg Focus 2002 Aug 15; 13(2): E3) was used. Our findings demonstrated that endoscopic discectomy was more effective than the microsurgical technique. The technical capabilities of the endoscopic method for removing spinal disc herniations in comparison to those of minimally invasive microsurgical techniques were meticulously analyzed. No significant instrumental limitations were found for using endoscopic techniques, while angled optics and excellent color rendition enable better visualization of the surgical wound structures and more efficient use of the approach space. Given that the technical characteristics and capabilities of this method are not inferior to those of the microsurgical technique, the former technology can be used instead of the standard technique for removing intervertebral disc herniations. Furthermore, the technical capabilities of the method allow performing wide decompression of the neural structures during surgery, which can be used to treat spinal stenoses.

Keywords: portal endoscopic discectomy, lumbosacral disc herniation, endoscopic spinal surgery.

According to the WHO, 80—83% of the adult population of the world is currently suffering from disc herniations in the lumbosacral spine. The prevalence of people at the height of their productive age among the affected makes the importance of developing the most effective treatment for disc herniations in the lumbosacral spine indisputable.

However, no consensus exists today on the preferable treatment method. Different countries develop treatment algorithms for disc herniations, which take into account the full range of capabilities of conservative treatment, and it is already evident that not every disc herniation requires surgical intervention. If there are indications for surgical treatment, the most adequate approach needs to be selected in each case.

The advances in all types of surgery aim to minimize surgical trauma. The North American Association of Spine Surgery (NASS) defines a minimally invasive procedure as the one that is performed through a small incision. However, a smaller incision size is not always associated with reduction of surgical trauma, and it is definitely not a marker of a minimally invasive procedure in most cases, since an injury to substructures is also important. This leads to an issue regarding the rational use of the approach space. Historically, it has been felt that microsurgical resection is the only correct and sufficiently effective method of surgical treatment of disc herniation (the so-called “gold standard”). On the one hand, this approach provides excellent visualization and convenience for a surgeon, thereby allowing the removal of any disc herniation through a sufficiently standard and minimalistic approach. However, on the other hand, this approach has certain disadvantages as well, including the width of the approach and frequent destruction of important anatomical structures that define spine mobility, such as intervertebral joints and ligaments surrounding intervertebral joints. Due to the aggressive nature of microsurgical techniques, numerous attempts have been made to minimize the approach and randomized trials have been conducted [1]; however, no statistically significant difference between minimally invasive microsurgical techniques and “open” methods has been discovered. Minimally invasive techniques are associated with a significant increase in the incidence of undesired damage to the dura mater [1]. Despite its unquestionable positive properties, theminimally invasive approach limits the field of view, which may affect the quality of a surgical intervention. Therefore, “open” method for removing disc herniation has been chosen to be used as the comparison group as it is the most effective and reliable way to achieve surgical goals.

The selected endoscopic method for resecting disc herniations is a video-assisted technique using tubular distractor. The method was first proposed by Medtronik company (as a MetrX system) in 2003, but it only achieved its technical perfection in 2007 through the work of M. Oertel [2]. This method is not a purely endoscopic one. Hardly any distinction of surgical techniques based on technical specifications...
exists in the literature. The American Medical Association has divided all existing types of approaches into four fundamentally different techniques:

1) percutaneous ones: the surgery is performed using tools directly passing through the skin under radiography control or any other type of indirect navigation;

2) endoscopic ones: the surgery is performed through a working channel of an endoscope;

3) minimally invasive ones: a surgeon controls the operation visually; any type of distractors (tubular or any other) can be used for the approach to reduce the exposure of surrounding tissues to surgical injury. The approach is performed through muscle separation without skeletonization. Visualization can be supplemented by a microscope or an endoscope;

4) open ones: a surgeon controls the operation visually; the surgery is performed through an open incision within direct vision, using muscle skeletonization. The approach involves the removal of bone and ligament apparatus from the surgical site.

According to this classification, this method is the video-assisted minimally invasive.

Compared to using an operating microscope, lack of three-dimensional visualization of the structures in the approach space is the main technical disadvantage. In 2008, we carried meticulously compared the endoscopic resection of disc herniation to the standard microsurgical approach [3]; no differences in clinical outcomes of a surgery have been revealed. However, the faster patients’ recovery and better quality of their lives were observed for endoscopic discectomy. Over the next 10 years, the advances in the technology led to the emergence of more sophisticated methods for disc herniation resection; however, no comprehensive comparison of the effectiveness of standard methods has been reported in the literature.

**Material and Methods**

The study included 183 patients (97 men, 86 women, mean age of 38 years), who have been operated on over 2 years (from January 2012 to January 2014) at the neurosurgical department of the State Center of Neurology, Russian Academy of Medical Sciences. As at that point the authors have almost completely stopped using microsurgical techniques; the group of patients described in the literature was used as a comparison group. The following article has been used: C. Koebbe et al. [4], published in Neurosurgical Focus 2002 Aug 15; 13(2): E3. This paper was chosen because it describes the largest number of patients included in the study: 3000 patients with disc herniations in the lumbosacral spine. The comparison was performed based on clinical outcomes of the surgery as measured using the MacNab criteria (see Table). Table provides correlation of symptoms to the MacNab scale score. A method is considered to be effective if it achieves good or excellent outcomes according to the MacNab criteria. The ‘effectiveness’ concept refers to the sum of incidence rates of good and excellent outcomes according to the MacNab criteria expressed as a percentage.

The study included patients aged 20 to 69 years with radicular pain syndrome persisting for more than 4 weeks for whom conservative treatment proved to be ineffective. The diagnosis of disc herniation was confirmed by MRI. We excluded patients with recurrent spinal surgery in the area of surgical interest, as well as those with confirmed instability or hypermobility of the spinal motion segment, with non-discogenic spinal canal stenosis or spondylolisthesis. All patients underwent complete neurological examination before and after surgery as well as 6 months after surgery to determine the effectiveness of the surgical intervention based on the MacNab scale (see Table).

**Table**

<table>
<thead>
<tr>
<th>The outcome according to the scale</th>
<th>Corresponding symptoms</th>
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<tr>
<td>Excellent</td>
<td>Complete elimination of the symptoms</td>
</tr>
<tr>
<td>Good</td>
<td>Moderate pain that has completely regressed at discharge</td>
</tr>
<tr>
<td>Fair</td>
<td>Mild dull pain that disappeared within a week after discharge</td>
</tr>
<tr>
<td>Poor</td>
<td>Recurrence of intervertebral disk herniation requiring reoperation</td>
</tr>
</tbody>
</table>

**Surgical Technique Used in the Study**

A video-assisted method featuring a tubular dilator has been used in our hospital since 2007. This method has recently become a routine for all possible variants of disc herniation in the lumbosacral spine.

All surgeries were performed under general anesthesia. The knee-chest position was used to minimize intraoperative bleeding from epidural veins [5], as well as to minimize required resection of bone structures during the approach due to a positional increase in the intralaminar space.

The first stage of the surgery consists of fluoroscopic control of the level of the surgery using an electron-optical image converter (EOIC). A sterile needle for intramuscular injection is used for control (Fig. 1).

It is very important to position the needle exactly perpendicular to patient’s skin, as it allows establishing a clear vector in relation to which the skin incision is planned. The needle is positioned in the direction of the target intervertebral disc using the EOIC. After determining the surgery level based on a radiography image, the location of the intervertebral disc is marked in relation to the planned approach trajectory. If a vertebral arch appears in the approach trajectory, a small caudal shift of the incision is recommended for better visualization of the ligamentum flavum and convenience of operating in the intralaminar space. We also believe that at this stage one needs to estimate the position of the disc herniation with respect to...
the bone structures that will appear in the approach space (such as intervertebral joints, pedicle arch of vertebra, and margins of an underlying vertebral body). The next step consists in incision of skin and subcutaneous tissue, 0.5 cm lateral to the midline. After opening the erector spinae aponeurosis by a linear cut, the dilators are installed to form approach trajectory through muscles for a working port. The latter is docked to the operating table via a holder (Fig. 2).

From that moment on, all manipulations are performed under endoscopic control. The intralaminar space is freed from fiber and soft tissues, and the ligamentum flavum is opened. We recommend using blunt incision to open the ligamentum flavum due to the lack of three-dimensional endoscopic picture and the high risk of damaging the dura mater if the incision of the ligamentum flavum is performed with a sharp instrument. After partial resection of the ligamentum flavum, we strongly recommend visualizing the spinal nerve origin. Rotation of the endoscope in respect to the portal helps visualize the area behind the intervertebral joints and prevent its excessive resection (Fig. 3).

After the nerve was displaced medially, the disc herniation is extracted. At this stage of the surgery particular attention should be given to hemostasis, since aggressive removal of disc herniation is usually accompanied by damage to ventrally located veins, making further manipulations in a narrow space of endoscopic approach very difficult. Opening and removal of disc herniation is not the final stage of the surgery. It is also necessary to open the posterior longitudinal ligament, inspect the ventral surface of the dural sac using endoscope rotation and changing the angle of the portal. The next step is removing free fragments of the intervertebral disc and creating excessive hydraulic pressure in the disk cavity to check the completeness of hernia excision and to prevent an acute relapse. We always perform a minimalistic foraminotomy as the last stage to increase the reserve space for the spinal nerve.

The endpoint of the surgical intervention is eliminating compression of the neural structures in the approach space. Taking this into account, we did not remove the central osteophyte in most cases, since it does not compress the neural structures. We did not perform curettage of intervertebral disc in any of the cases because of the high risk of development of spondylodiscitis according to the literature data.

Results

A total of 183 patients have been operated on for herniated intervertebral discs in the lumbosacral spine between January 2012 and January 2014. The neurological status of the patients prior to the surgery varied in terms of the intensity of radicular pain and disease duration. Complete regression of radicular pain was observed for most patients immediately after the surgery. The same activity limitations were prescribed to all patients: limiting the axial load and the mandatory use of orthopedic lumbar corset for 1 month after the surgery.

Among 183 patients in the endoscopic group, two (1.1%) had a relapse that required reoperation. Four (2.2%) patients experienced pain lasting 1 month after the discharge, which corresponded to poor outcome according to the MacNab criteria. Seven (3.8%) patients reported brief dull pain lasting no more than 1 week after surgery. Eleven (6%) patients reported short-lived sensations, which they described as dull pain in the same dermatomal distribution as prior to the surgery, but the sensations regressed within 1—2 days after the surgery. The remaining 159 (86.9%) patients reported complete disappearance of all symptoms and returned to normal life soon after discharge. Thus, the effectiveness of the endoscopic method is 92.9%.

According to C. Koebbe et al. [4], excellent and good outcomes were observed in 90% of cases in the comparison group. The incidence rate of complications (dural tears, discitis or root injury) was 2%; the reoperation rate for recurrent disc herniation was 5%.

The technical characteristics and applicability of the endoscopic discectomy method was analyzed in this study and compared to those of the microsurgical technique. It was
Fig. 3. Changing the field of view by rotating the endoscope.

noted that the endoscopic technique allows using standard microsurgical instruments; the technical possibility of rotating the endoscope around the portal permits more efficient use of the approach space during endoscopic interventions.

Discussion

An analysis of the outcomes of disc herniation resection using the portal endoscopic approach was accessed 6 months after the surgery and demonstrated that the portal endoscopic techniques are highly effective and minimally traumatic. According to our data, the effectiveness of portal endoscopic microdiscectomy in disc herniation resection is 92.9%, while this parameter for microsurgical discectomy is 90%.

Recurrence of disc herniations is the most significant complication for both types of surgery. Group 1 patients had a relapse in 1.1% of cases, while group 2 patients, in 5%. These results may be associated with greater aggressiveness of surgical intervention, segment destabilization in the postoperative period and the subsequent development of disc herniation recurrence in the operated segment.

In 1.1% of cases, endoscopic microdiscectomy resulted in asymptomatic damage to the dura mater. According to C. Koebbe et al. [4], dural tears were observed in 2% of cases.

Analysis of the technical capabilities of endoscopic microdiscectomy demonstrated that all standard microsurgical instruments can be used during the surgery, without compromising the visibility in the operating field. This method allows one to use the approach space much more effectively.

Taking into account the low-impact nature of the approach, less pronounced intraoperative bleeding was reported. However, the convenience of using standard bipolar coagulation was poorer than that in microsurgery due to the limited possibility of changing the angle of coagulator branches. We find other hemostasis methods, such as a using hemostatic gauze and SurgiFlo, more effective than bipolar coagulation.

Conclusion

The study demonstrated that the effectiveness of endoscopic discectomy is comparable with that of microsurgical technique. Since this method is comparable with microdiscectomy in its technical characteristics and capabilities, this technology can be used to remove disc herniations. In some cases, the technical capabilities of the method make it possible to perform decompression of neural structures, which can be used to treat non-discogenic spinal stenoses.

REFERENCES

The article focuses on an acute problem: surgical treatment of disc herniations in the lumbosacral spine. As we accumulate more data on spine dynamics, we understand more and more clearly the importance of retaining the supportive structures of the spine and surrounding muscles. Advances in neurosurgery over the past decade have been inextricably linked with the development of endoscopic techniques, because among all minimally invasive techniques, endoscopy the highest visualizing power and is therefore the most promising method.

In this article the authors scrutinize their extensive experience of using portal endoscopic techniques. The MacNab criteria for surgical treatment outcomes were used for reliable comparison with other minimally invasive techniques described in foreign literature. The article by C. Koebbe et al. was selected from the variety of publications comparing minimally invasive techniques; it compared and described the methods used by different authors. Therefore, the authors of this article compare endoscopic techniques with a whole range of minimally invasive procedures.

The article carefully and meticulously describes the technique of portal endoscopic resection of disc herniations. The descriptive part focuses on the technical aspects of the technology, which makes it possible to use it as a teaching aid in adopting this method.

The article is of undoubted scientific and practical interest for practicing neurosurgeons. The results obtained can be used for further development and application of endoscopic techniques in spinal surgery.

There is a potential for developing endoscopy application in surgery of lumbar disc herniations using the transforaminal or intralaminar approach using thin endoscopes about 7 mm in diameter. This type of intervention is less traumatic and can be performed under local anesthesia.

N.A. Konovalov (Moscow, Russia)
Factors Affecting the Outcome of Surgical Management for Extramedullary Spinal Cord Tumors: a Multicenter Study

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Extramedullary spinal cord tumors (ESCTs) are relatively rare neoplasms that require surgical treatment. This paper presents a study of outcomes in patients with ESCTs treated at Irkutsk region hospitals with different facilities. **Objective.** To identify factors affecting the outcome of surgical treatment of ESCTs. **Material and Methods.** The disease stage before surgery was evaluated according to the I.Ya. Razdol’skiy and McCormick classifications. Particular features and the scale of the approach, blood loss volume, surgery duration, and the equipment used were analyzed. Treatment outcomes were assessed according to the MacNab and McCormick neurological outcome scales. **Results.** ESCTs were removed totally in 84 (95%) and subtotally in 4 (5%) patients. Tumor recurrence was reported for 8 patients. No deaths were observed. No correlation was found between the treatment outcome, according to the McCormick scale, and such factors as gender, tumor location, histological type, tumor grade, disease duration, and type of a surgical approach and equipment used. Factors with average and strong correlation to the disease outcome are a neurological disease phase and initial neurological deficit: sensory deficit, r=0.32; motor deficit, r=0.33; pelvic disturbances, r=0.35; McCormick grade before surgery, r=0.74; disease phase r=0.41 (p<0.05). **Conclusion.** The disease phase is the most significant factor affecting the outcome of surgical treatment in patients with ESCTs. However, such factors as the choice of the approach that is adequate to the tumor size and localization, as well as combination of different surgical techniques, are important in surgical treatment of ESCTs.

**Keywords:** extramedullary tumor, surgical treatment, McCormick.

Extramedullary spinal cord tumors (ESCT) form a broad category that includes relatively rare neoplasms derived from lesions surrounding the spinal cord, its roots, vessels, sheaths, and epidural tissue [10].

According to I.Ya. Razdol’skiy [6], the incidence of ESCTs is 1.96%, while A.P. Romodanov et al. (1976) believe it to be 2.2% of all tumors of the central nervous system (CNS). The ESCTs constitute 80—90% of all spinal cord neoplasms. Most of these tumors are highly differentiated and benign. For example, the largest portion of ESCTs, which amounts to up to 95% [28], is comprised of nerve sheath tumors (schwannomas and neurofibromas), meningiomas, and myxopapillary ependymomas of the filum terminale.

It is necessary to emphasize the importance of accurate and timely diagnosis, since clinical presentation of spinal tumors is similar to that of other pathological processes.

Surgery plays the pivotal role in treatment of ESCTs patients. Recent advances in neuroimaging and intraoperative neurophysiological monitoring ensure safety of a surgery as well as the high rate of positive outcomes [19].

The development of minimally invasive technologies allows a neurosurgeon to minimize the approach size and preserve orthopedic stability of the functional spinal units during a course of a surgery, while performing a radical intervention, which takes into account both anatomical and physiological limitations, as required by the principles of oncology.

In recent years, numerous studies [19, 24, 31, 41] have examined the outcomes of ESCT surgeries performed using different approaches and techniques. This fact and the differences in facilities available in neurosurgical operating rooms had been the incentive for this study.

Our objective was to evaluate the tactics and effectiveness of surgical management of patients with ESCTs at neurosurgical hospitals in the Irkutsk region and to identify factors affecting the outcome.

**Objectives:**
1. To assess surgical approaches to treating ESCTs at Irkutsk regional hospitals.
2. To evaluate the clinical and neurological status of patients with ESCTs before and after surgery.
3. To identify factors affecting the outcome of a surgery.

**Material and Methods**

The Irkutsk region is located in the southeastern part of the Siberian Federal District. The population of the area, as of January 2013, is 2,422,026. The regional center, Irkutsk, has the population of 606,100 (data of 2013). Three out of five Irkutsk neurosurgical hospitals participated in the study. The study did not include the Children’s Hospital and the City Hospital, which serves as an emergency station. The study included a total of 88 patients who were operated on between 2004 and 2012 at the Irkutsk Railway Clinical Hospital, the Scientific Center of Reconstructive and Restorative Surgery, and the Irkutsk Regional Clinical Hospital. The study is based on retrospective evaluation of prospectively collected data.

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All patients underwent a comprehensive clinical and neurological examination, contrast-enhanced MRI (1.5 T and above), and, if necessary, multislice helical computed tomography.

The following parameters were examined: duration of symptoms manifestation prior to the diagnosis, dynamics of sensory, motor, and pelvic disturbances (Nurick grade of functional outcomes and MacNab subjective criteria, before and after the surgery), phase of the disease (I.Ya. Razdol’skiy [6] classification and McCormick scale [31]), and length of stay.

The following parameters of a surgery were also evaluated: approach type, volume of blood loss, surgical duration, and the equipment used. The list of the equipment included Olympus and Zeiss operating microscopes; microsurgical instruments by Aesculap, Ulrich, and Mizuho; a Sonoca ultrasonic dissector-aspirator (Soring GmbH), which combines a high-frequency generator and a piezoelectric converter for dissection with a surgical vacuum aspirator for irrigation and aspiration; infrared CO\textsubscript{2} Nidek Unipulse Col-1040 laser (average beam power 1.0–20 W, power density up to 6000 W/cm\textsuperscript{2}). In some cases the microsurgery was supplemented with intraoperative endoscopy carried out with Aesculap and Karl Storz rigid endoscopes with 0°, 30° and 45° field of view.

Tumor localization was examined in axial and vertical projections. The histopathological assessment of tumors was performed according to the 2007 WHO histological classification [15].

Patients with a newly diagnosed ESCT amounted to 93% of the total number of patients. 7% of cases required reoperation due to the continued tumor growth.

Tumors were removed totally in 84 (95%) patients and subtotally in 4 (5%) patients. The relative incidence rate of various pathomorphological types of ESCTs is shown in Fig. 1. Tumor recurrence was reported for 8 patients. No deaths were observed.

Statistical analysis was performed using Statistica 8.0 software. The data are presented as medians and interquartile ranges, as Me (25; 75). P-values<0.05 were considered to be significant.

**Assessment of surgery tactics**

One- or two-level hemilaminectomy was performed in case of lateral and ventrolateral localization of a tumor in the thoracic, lumbar and lower cervical spine.

In case of ventral localization in the thoracic spine both hemilaminectomy and laminectomy were accompanied by resection of transverse process and the adjacent collum costae. Tumor size larger than half the diameter of the dural sac, as determined by contrast-enhanced MRI, was an indication for laminectomy in the projection of the tumor, accompanied by partial resection of arches at the adjacent intact levels [5].

One patient with a craniovertebral ESCT underwent laminectomy combined with suboccipital craniotomy. The parenchymal component required an anterolateral access as either the only or the second stage of the surgery; the retroperitoneal access was used in case of lumbar spine tumors, while tumors at the level of the thoracolumbar junctional region required minithoracophrenotomy and application of microsurgical techniques.

![Fig. 1. The relative incidence rate of various pathomorphological types of extramedullary spinal cord tumors.](image-url)
The ventral access was used in case of extravertebral tumor growth. In one case, the shape of the tumor (primarily extravertebral and located in the intervertebral foramen) allowed performing its total resection in a single step using the retroperitoneal approach. The extravertebral part of the tumor and its fragments in the intervertebral foramen were resected after microdissection. The intervertebral foramen was then expanded under ×8 optical magnification using high-speed drills and Kerrison rongeur forceps. The dura mater and the remaining fragments of the tumor were mobilized in a newly formed bone window using microsurgical techniques. Ablation of the tumor and its matrix by laser radiation under visual (endoscopic and microsurgical) control was performed in order to ensure the ablastics principle and reduce the volume of the tumor tissue.

The distribution of patients based on the access used is presented in Table. The most common approach was the posterior one (n=86), which included one or two-level hemilaminectomy, one-, two-, or multilevel laminectomy, supplemented, if necessary, by partial medial facetectomy. In two cases anatomic and topographic features of the tumors were indications for anterior retroperitoneal approach (1 case) and thoracophrenotomy, which was required to access the anterolateral surface of the L1 vertebra (1 case).

The resection of the intradural portion of the tumor was performed as follows: the epidural tissue was removed and epidural veins were coagulated and sectioned along the approach line using ×8—12 optical magnification for control. During laminectomy the dura matter was dissected medially in case of dorsal or dorsolateral localization of the tumor. During hemilaminectomy the dissection of the dura mater was performed paramedially. The arachnoid sheath was dissected and the subarachnoid space was examined to detect the tumor. For lumbar spine tumors the examination included pulling the roots of the cauda equina away from the proposed location of tumor growth. In case of cervical and thoracic localization, one or more odontoids were dissected to improve the field of view. An endoscope with angle optics was used in addition to a microscope in order to visualize the invisible regions (n=14). To isolate the tumor nodule microdissection of arachnoid lesion was performed and feeding vessels were isolated and coagulated. The tumor was then freed from neural structures and dura mater all the through to its origin. If tumor size exceeded the length of the dura mater incision by less than 1.2:1, a tumor node was resected as one unit. If the size of a tumor exceeded that of the approach more than 1.2-fold and in cases of tumor petrification or presence of multiple lesions to the adjacent tissues, the tumor volume was reduced using ultrasound (US) destructive aspiration (n=37) or laser radiation (n=29). Intrasellar decompression using the US aspirator was used both in combination with laser treatment and without it, and was followed by dissection and removal of the neoplasm.

**Assessment of surgical treatment outcomes**

Upon admission to the hospital the first phase of the disease (according to I. Ya. Razdol’sky [6] classification) was diagnosed in 23% of the patients, the second stage, in 49%, and the third, in 28% of patients.

The tumors were predominantly neuromas (49%) and meningiomas (37%) (Fig. 1).

In most cases (66%) the tumors were located in the dorsal, lateral and dorsolateral positions relative to the cross section of the spinal cord, which defined planning and the access of choice. The relative incidence rate of various localizations of ESCTs relative to the spinal cord cross section is shown in Fig. 2.

The length of time from the first manifestation of the symptoms until the surgery ranged from few days to 18 months, with a median of 5 months (2; 8). The significant differences in preoperative period duration were observed: men (8 months (1; 10)) vs. women (4 months (3; 5)) (pU < 0.001). The average hospital length of stay was 15.5 months, with a median of 5 months (2; 8).

### Distribution of patients based on the approach

<table>
<thead>
<tr>
<th>Approach</th>
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<th>Number of patients</th>
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<td></td>
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<td>Absolute</td>
<td>Relative (%)</td>
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<tr>
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<td>Hemilaminectomy</td>
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<td>2</td>
<td>5</td>
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<tr>
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<td>Thoracophrenoldubotomy</td>
<td>1</td>
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<td>Retroperitoneal approach</td>
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**Number of patients**

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<td>Laminectomy</td>
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**Absolute**

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radiosurgical treatment of ESCTs is also possible. According to S. Sachdev et al. [36], a decrease in tumor size was observed in 40% of cases if this method was used. The potential of radiosurgical treatment of ESCTs requires further investigation.

Modern approaches to surgical treatment of spinal cord tumors are aimed at increasing the use of minimally invasive techniques, precise diagnostic methods and modern equipment and tools. The use of minimally invasive approaches to resection of spinal cord tumors has recently been the subject of many papers [2, 8, 24, 33, 42]. For example, F. Haji et al. [22] used a METRx MAST QUADRANT retractor system in the treatment of both extramedullary and intramedullary spinal cord tumors and reported good results of minimally invasive resection with no increase in risk of adverse neurological outcomes.

According to Y. Yu et al. [41], minimization of bone resection to access ESCTs (hemilaminectomy) has several advantages: the best preservation of orthopedic stability, reduction in intraoperative blood loss, muscle dissection, surgical duration and, as a consequence, reduction in postoperative pain syndrome and fast physical rehabilitation. According to Y. Yu et al. [41], surgical duration was reduced from 3±0.39 to 2.5±0.3 h. In our study, the average duration of laminectomy ($n=80$) was 3.7 h and that of hemilaminectomy was 4.1 h ($n=6, p>0.05$). The average volume of blood loss, according to Y. Yu et al. [41], has decreased significantly from 123 to 88 mL. According to our data, the volume of blood loss had not changed significantly (357 mL for laminectomy, 383 mL for hemilaminectomy, p-value>0.05). This disparity can be due to different approaches to blood loss evaluation.

According to M. Iacoangeli et al. [24], the hemilaminectomy approach permits total removal of the tumor and restoration of the dura mater integrity, thereby ensuring better course of postoperative period than the one reported for the control group, which underwent a laminectomy. The original transspinal posterior approach was proposed by D. Lu et al. [28a] as an alternative to hemilaminectomy. The necessity of using minimally invasive surgical approaches to preserve orthopedic stability was demonstrated by S. Furtado et al. [20] on the basis of estimated incidence rate of postoperative kyphosis in children following cervical spine laminectomy.

According to M. Iacoangeli et al. [24], disruptions of orthopedic stability are more common in thoracic spine of middle-aged women. The authors note that clinical manifestations of instability are often non-specific and symptoms may precede the elucidation of the final clinical diagnosis by several months or even years, especially in the elderly, for whom related chronic diseases may mask the symptoms for a long time. The aim of ESCTs treatment is the total surgical removal of the tumor and the best possible preservation of orthopedic stability. Therefore, the issue of selecting a proper surgical approach is very important.

Ventral localization of ESCTs is a challenge for neurosurgeons. In some cases, their total removal requires using the anterior approach [11]. In case of ventral and ventrolateral localization of thoracic spine tumors, some authors [25, 38] suggest endoscopic techniques.
The use of endoscopy and endoscopic assistance in resection of ESCTs is a relatively new trend in spinal neuro-oncology. For example, in 1992 G. Landerenau and, independently from him, W. Werder [40] confirmed the feasibility of using the thorascoscopic access to remove spinal cord tumours, neurofibromas and hourglass schwannomas.

Thorascoscopic technology can provide full direct access to ventral surface of the thoracic spine. Its use improves patient’s quality of life and reduces the recovery time compared to open surgery and has a good cosmetic effect [2]. The successful application of thorascoscopic techniques in resection of thoracic spine tumours has been demonstrated in many studies [2, 4, 12, 17, 41]. Several authors suggest possible expansion of indications for endoscopic techniques. V.V. Krivetsky et al. [4] report on video-endoscopic removal of a spinal cord tumor using the posterior transligamentous approach. A number of authors [12, 14, 39, 40] also reported successful application of combined approaches, such as the use of posterior and thorascoscopic approaches in case of intraforaminal tumor growth. In particular, these tumors can be removed through a minimally invasive hemilaminectomical approach and then thorascopically without the need for large thoracotomy approaches [4]. In our study video assistance was used only when it was required to control the degrees of tumor removal or the adequacy of hemostasis.

There is also an alternative opinion in favor of the posterior approach in case of spinal cord neuromas, rather than the anterior transthoracic approach [36]. In case of contraindications for transthoracic surgeries, such as ventral and ventrolateral localization of intradural extramedullary tumors, the use of posterior approach was proposed, featuring dissection of odontoid ligaments and spinal rotation around its axis [26].

Surgical laser is used to perform ablations. According to M. Desgeorges et al. [16], the use of carbon dioxide and neodymium lasers to treat hard-to-reach ESCTs increases the amount of number of total removal of meningiomas. Many authors [1, 8, 9, 16] have also remarked on decrease in neural structures traction, reduced surgical duration and intraoperative blood loss. In our study a CO₂ laser was used. We have found that irradiation of tumor matrix with laser was the most useful in the following cases:

1. highly vascular and dense neoplasms that spread over 1—3 vertebrae with predominantly lateral localization.
2. meningo-vascular tumours with infiltrating growth.

After the tumor and the surrounding matrix had been removed, the dura mater was irradiated with an unfocused CO₂-laser beam (beam diameter less than 3 mm, beam power 6—8 W) for 2 min. At the first stage the intact dura mater at the periphery of the tumor was irradiated from a distance of 0.5—1.0 cm and then the matrix itself, from the periphery to the center [1].

Two relapses were reported for patients who received laser treatment during the surgery (n=29). Nevertheless, the difference in the number of relapses with and without additional laser treatment was not statistically significant (p=0.94). Therefore, the study design does not allow us to draw any conclusions on the efficacy of laser radiation.

Intraoperative ultrasound imaging (IOUS) allows a surgeon to cut open the dura mater exactly over the tumor. Dislocation of intradural tumor occurs during the formation of the approach which includes bone resection. Intraoperative ultrasound imaging helps to plan the dura mater incision and adjust the approach based on tumor location and size. H. Zhou et al. [42] emphasized the importance of IOUS for reducing the risk of neurological complications associated with expansive dissection of the dura mater. Some IOUS features can be used for differential diagnosis of intradural tumors. In addition, IOUS allows evaluation of the relationship between the neoplasm and the spinal cord, as well as estimation of residual tumor size after excision. It seems reasonable to employ IOUS during the surgical removal of ESCTs, although this technique was used in our studies in only 7 cases at one neurosurgery department.

Navigational systems are important for establishing the exact tumor location in order to make decision on the size of surgical wound and degree of bone structures resection. W. Campos et al. [13] reported on the application of navigational systems and thorascoscopy. Open surgery at the thoracic spine level is fraught with risk of errors in level selection. The search for tumor located close to the spinal cord and its nerve roots and vessels can lead to various complications and postoperative pain. Verification of the level requires radiological control (X-ray machines or C-arm), which in some cases had been used excessively, especially in obese patients. Therefore, according to W. Campos et al. [13], the combination of thoracoscopy and a navigational system allowed exact positioning and execution of total excision of tumors through the minimally invasive approach without compromising spine stability.

In our studies, C-arm was used before and during the surgery.

Introduction of electrophysiological monitoring was beneficial for neuro-oncology as it allowed one to estimate what amount of tumor resection would be safe. Intraoperative electrophysiological monitoring is mandatory in many spinal neurosurgical clinics, especially in case of intradural localization of the tumor. The resection of ESCT tumors is not possible without intraoperative monitoring. M. Forster et al. [18] reported intraoperative application of sensory- and motor-evoked potentials for removal of intradural tumors. The study showed that neurophysiological monitoring during tumor resection is essential for identification of the critical stages of surgical procedures and timely prevention of potential complications. In our study neurophysiological monitoring was used only in 37 cases. The design of our study does not allow us to draw any conclusions about the feasibility of using neurophysiological monitoring in surgical treatment of ESCTs.

A similar study of the surgical treatment outcomes in case of intradural ESCTs was conducted by M. Nambiari and B. Kavar [33]. According to their data, the incidence rate of total resection was 72.3%. The low ratio of premorbid clinical phase was the most significant positive predictor of outcome in case of dispensary observation (OR=9.498, 95% CI 2.780—32.451; p<0.001). The authors conclude that surgical outcome depends on premorbid, preoperative or postoperative clinical phase, degree of tumor resection as well as tumor localization.
and histological phase. Our study confirms these data. However, we found no significant correlation between histological phase of the tumor and the outcome.

Minimally invasive ESCT surgery provides such advantages as reduction in postoperative pain, early rehabilitation and prevention of orthopedic spine instability. R. Mannion et al. [29] raised concerns about the feasibility of safe and efficient tumor resection in case of minimally invasive approaches. By comparing advantages and disadvantages of minimally invasive methods with those of the standard ones, R. Mannion et al. [29] pointed out failures of the minimally invasive approach in 2 (15.4%) clinical cases, one of which required conversion. In this case 1 (7.7%) patient experienced postoperative complications (liquorhea and infection) that required reoperation. In conclusion, R. Mannion et al. [29] reported that safe and effective resection of ESCTs using minimally invasive techniques is possible. However, the researchers fail to provide the definitive answer, leaving the question of “pros and cons” of minimally invasive surgery open. A. Goel [21] is even more critical in his comments. He points that it is irrational to use high-tech equipment because of associated high costs, and mentions potential damage to the edges of a surgical wound when tubular retractors are used. There is no doubt that the minimally invasive approach makes manipulations more difficult and increases the duration of the intervention and risk of complications.

In our opinion, it is necessary to achieve a balance between the approach size and the complete removal of the tumor. Limited bone resection increases the risk of damage to neural structures which results in aggravated neurological deficit. We believe that minimally invasive neurosurgery should primarily be minimally invasive with respect to neural structures. For example, numerous studies [4, 9, 33, 42] have proved that the use of modern surgery technologies allows a surgeon to maintain orthopedic stability of the spine, reduce surgery wound, risk of infectious complications, postoperative pain intensity, volume of intraoperative blood loss, and tumor recurrence rate by ablation and total resection of the tumor.

**Conclusion**

1. Neurosurgical hospitals in the Irkutsk region use modern approaches and different combinations of surgery techniques (due to different facilities available in hospitals and diverse traditions in selecting surgical approaches) for surgical treatment of ESCTs.
2. The clinical and neurological status of the patients with ESCTs has been significantly improved after the surgery based on MacNab and McCormick criteria.
3. The analysis of the data revealed no correlation between treatment outcomes according to the McCormick scale and such factors as disease duration, type of the approach and equipment used, volume of blood loss, and tumor grade. Factors correlating with the outcome of the disease included sensory deficit, \( r=0.32 \), motor deficit, \( r=0.33 \), pelvic disturbances, \( r=0.35 \), McCormick grade before surgery, \( r=0.74 \), and disease phase \( r=0.41 (p<0.05) \).

The disease phase is the most significant predictor of the outcome of surgical treatment in patients with ESCTs. However, the choice of an approach that would be adequate to tumor size and location, as well as the use of different operating techniques, remains an essential component of surgical treatment of ESCTs.

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

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The volume of surgical activity involving spinal cord tumors has increased severalfold over the last few years. Identification of factors affecting the outcome of surgical treatment of the most common spinal cord tumors, the extradural tumors, is certainly a pressing issue. In this paper, the authors examined the outcomes of surgical treatment of 88 patients with extradural tumors of the spinal cord. The multicenter study was conducted in three neurosurgical hospitals in Irkutsk, where modern surgery techniques were used for surgical treatment of tumors. The patients evaluated the outcomes of treatment by using MacNab subjective criteria, while the McCormick scale was used to assess their functional capabilities. Based on these criteria the authors report improvement in the clinical and neurological status of the patients after surgeries. Unfortunately, these scales do not reflect a degree of manifestation of one of the most important extradural tumor syndromes, the pain syndrome, whose intensity was not analyzed in the study. The analysis of the data revealed no correlations between treatment outcomes on McCormick scale and such factors as disease duration, type of the approach, equipment used, volume of blood loss, and tumor grade. The factors that correlated with treatment outcome in patients with extradural tumors included sensory deficit (r=0.32), motor deficit (r=0.33), pelvic disturbances (r=0.35), and McCormick grade before surgery (r=0.74). All these factors are interlinked and presented as phases of the disease, which is the most important predictor of the surgical treatment outcome. In their work, G.Yu. Evzikov et al. (2000) also listed a number of factors that significantly increase the risk of poor treatment outcome for extradural meningiomas. These factors include the phase of the disease, patient’s age over 60 years, ventral location of the tumor and its complete petrification. Yu. A. Zozulya et al. (2004) reported in the increased risk of poor outcomes if a large extradural tumor has to be removed. The study reports the high rate of total removal of the tumors. Total removal was achieved in 84 (95%) patients, and subtotal, in 4 (5%). All clinical results presented in the study are comparable with those of other published papers.

Therefore, the present article is devoted to an important problem and reports on the efficiency of modern technology in surgical treatment of extradural tumors of the spinal cord.

Commentary

N.A. Konovalov, R.A. Onoprienko (Moscow, Russia)
The Use of Minimally Invasive Approaches to Resect Intradural Extramedullary Spinal Cord Tumors


Burdenko Neurosurgical Institute, Moscow, Russia

The aim of the study was to conduct a comparative analysis of outcomes in patients with extramedullary tumors operated on using a minimally invasive approach and traditional laminectomy. Material and methods. The study included 40 patients (13 males and 27 females) who underwent surgical treatment at the Department of Spinal Neurosurgery of the Burdenko Neurosurgical Institute. The mean age of patients was 47 years (range: 41—60 years). Tumors were located in the cervical, thoracic, and lumbar spine. All patients were divided into two equal groups. In the control group, 20 patients underwent traditional laminectomy using a yard retractor or a Egorov—Freidin neurosurgical retractor. In the study group, 20 patients underwent hemilaminectomy using a retractor for minimally invasive surgery (Casper and MAST Quadrant). The outcomes were evaluated 3, 6, and 12 months after surgery. The McCormik and VAS scales were used for the evaluation. MRI data were also evaluated. Results. Total tumor resection was reached in all cases. The mean surgery duration was 134.75 min (range: 60—200 min) for the first group and 105.25 min (range: 60—190 min) for the second group. The volume of blood loss was 297 mL (range: 100—600 mL) for the first group and 210 mL (50 to 400 mL) for the second group. The histological nature of the tumors was as follows: neurona, meningioma, and ependymomas of the cauda equina. The evaluation of the pain syndrome in the early postoperative period revealed that pain syndrome intensity according to the VAS was reduced in the second group of patients compared to that in the first group. The evaluation using the McCormik scale revealed no obvious difference in the results between the study and control groups. MRI studies performed in the postoperative period showed no tumor recurrence. Conclusion. Surgical treatment of patients with intradural extramedullary tumors can be safely and effectively performed using minimally invasive approaches. Potential reduction in surgery duration, intraoperative blood loss, amount of anesthetic drugs, and reduction in pain syndrome during the early postoperative period allows us to conclude that, when performed by an experienced surgeon, the method of minimally invasive surgery may be an alternative to the traditional removal method for extramedullary tumors.

Keywords: intradural extramedullary tumor, minimally invasive surgery, Caspar retractor, MAST Quadrant retractor.

Intradural extramedullary tumors are the most common type of primary spinal cord tumors. The most common histological types of extramedullary tumors are meningiomas (29%), neuromas (24%) and ependymomas (23%) [1]. Timely diagnosis and surgical treatment provide for the most effective treatment of patients. Laminectomy is a traditional approach providing access to a tumor [2—6]. However, despite satisfactory results, in some cases patients developed an unstable vertebral segment at the laminctomy site in the long-term period [7—9]. Advances in microsurgical techniques introduced the practice of minimally invasive hemilaminectomy [10—13].

Minimally invasive spine surgery is a set of special techniques (using magnifying techniques: a microscope or an endoscope, proper planning of the approach, the use of special retractors, including tubular ones), allowing one to perform the desired manipulation of the spinal cord and nervous structures using special tools with the minimal access and traumatization in muscle tissue.

The minimally invasive approach to spinal tumors involves the use of retractors, which allow shortening the length of skin incision and reducing injury muscles, and hemilaminectomy, making it possible to avoid complete resection of vertebral arches and parts of the facet joints on both sides. Studies of spine biomechanics demonstrated that the minimally invasive approach preserves the structural integrity of the spine and minimizes changes in the structure of spinal cord segments [10—12]. Different studies [13, 14] of minimally invasive spine surgery have been recently performed. Since the detectability of extramedullary tumors has been improved, surgical activities requiring better quality and treatment outcomes have also increased. In the present study, we demonstrated the possibility of using modern minimally invasive techniques (approaches) for surgical treatment of intradural extramedullary tumors at different levels compared to the conventionally used methods. Determination of indications and contraindications for surgery and the introduction of minimally invasive approaches into the clinical practice of surgical treatment of patients with intradural extramedullary tumors are important tasks.

Material and Methods

The study included 40 patients (13 men and 27 women), aged 22—76 years (median age of 47.4 years) with a verified diagnosis of benign intradural extramedullary tumors who had been operated on at the Burdenko Neurosurgical Institute during the period from January 2012 to May 2014. More detailed characteristics of patients are shown in Table 1. Clinical presen-
The functional status was graded according to the McCormick scale prior to the operation, during the early postoperative period and during the follow-up period (3, 6, and 12 months after the surgery) (Table 2).

The completeness of tumor resection was assessed by T1, T2, STIR and T1-weighted contrast-enhanced MRI using a Philips 1.5 T MRI system and Magnevist and Omniscan contrast agents (Fig. 1). All patients underwent MRI examination before surgery and 3, 6, and 12 months after surgery. According to the MRI data, tumors were verified as benign intradural extramedullary tumors. Neoplasms were located in the cervical (10 patients), thoracic (11 patients), and lumbosacral (12 patients) spine. The tumor length varied from one to two segments. The exclusion criteria for study enrollment were as follows: large size (over than two segments long) and the ventral location of the tumor. Standard laminectomy was used in cases when it the presence of inclusion of radicula in the stroma or ossifying tumor was suspected.

All patients were divided into two groups: group 1 (control) and group 2 (study group). In the control group, 20 patients underwent conventional laminectomy using a yard retractor or a Egorov-Freidin retractor. This technique has been described by Russian and foreign authors.

The study group included 20 patients who underwent minimally invasive approaches to resect intradural extramedullary spinal cord tumors. This method included hemilaminectomy using a retractor for minimally invasive surgery, a Caspar (B Braun-Aesculap AG), and a MAST Quadrant (Medtronic) retractors.

**Surgical technique**

Patient’s position on the operating table was the standard one used for the posterior approach; the operation was performed under combined endotracheal anesthesia. Tumor localization was determined using direct radiography. An electron-optical converter was used; lateral and frontal images were taken. In cases when tumor location (the shoulder girdle) made it inaccessible, an intraoperative CT O-arm (Medtronic) was used to determine tumor location (Fig. 2). Caspar and MAST Quadrant (Medtronic) retractors were used to access the tumor (Figs. 3, 4).

The median or paramedian skin incision length was 3—3.5 cm. Hemilaminectomy or the approach was performed using a high-speed Legenda burr (Medtronic) or a Zimmer burr.

### Table 1. Characterization of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Laminectomy + yard retractor (group 1, n=20)</th>
<th>Hemilaminectomy + minimally invasive retractor (group 2, n=20)</th>
<th>Total (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of men</td>
<td>7 (35%)</td>
<td>6 (30%)</td>
<td>13</td>
</tr>
<tr>
<td>Number of women</td>
<td>13 (65%)</td>
<td>14 (70%)</td>
<td>27</td>
</tr>
<tr>
<td>Age (mean age), years</td>
<td>26—76 (51)</td>
<td>22—75 (43)</td>
<td></td>
</tr>
<tr>
<td>Tumor localization:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cervical spine</td>
<td>6 (30%)</td>
<td>4 (20%)</td>
<td>10</td>
</tr>
<tr>
<td>thoracic spine</td>
<td>6 (30%)</td>
<td>5 (25%)</td>
<td>11</td>
</tr>
<tr>
<td>lumbar spine</td>
<td>8 (40%)</td>
<td>11 (55%)</td>
<td>19</td>
</tr>
<tr>
<td>Histology:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>meningioma</td>
<td>10 (50%)</td>
<td>5 (25%)</td>
<td>15</td>
</tr>
<tr>
<td>neuroma</td>
<td>6 (30%)</td>
<td>12 (60%)</td>
<td>18</td>
</tr>
<tr>
<td>ependymomas</td>
<td>4 (20%)</td>
<td>3 (15%)</td>
<td>7</td>
</tr>
</tbody>
</table>

### Table 2. Evaluation of patients’ neurological status according to the McCormick modified scale before and after surgery treatment in groups 1 and 2

<table>
<thead>
<tr>
<th>McCormick scale, before the surgery</th>
<th>Control group (n=20)</th>
<th>Study group (n=20)</th>
<th>Total (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 (25%)</td>
<td>12 (60%)</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>14 (70%)</td>
<td>8 (40%)</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>1 (5%)</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>
Fig. 1. a, b — intradural extramedullary tumor (neuroma) located at the T10—T11 vertebral level on the right side (contrast-enhanced T1-weighted MRI (Omniscan)); c — image of a 2×1.2 cm removed neuroma.

Fig. 2. Intraoperative CT scan of the cervicothoracic spine in the scanning 3D-mode using an O-arm.
burr (Fig. 4a–c); a 3 mm burr with diamond-coated rotary point head was used for the approach. Hemostatic materials (Surgicel gauze, standard Spogostan sponge and Surgiflo hemostatic matrix (Ethicon)) were used to control epidural bleeding. The next step was durotomy. A linear or arcuate incision of the dura mater (DM) was performed (Fig. 4d). The DM was sutured to the muscle. Then tumor poles were visualized and allotted. A cotton swab blocking the cerebrospinal fluid flow and helping to visualize the tumor pole was placed on the cranial tumor pole. The tumor was usually removed as a single unit and much rarer as several fragments using microsurgical instruments (Fig. 4e). Debulking with a Sonoca 300 ultrasonic aspirator (Soring) was performed after separating the tumor from the arachnoid sheath for meningiomas. Such manipulation was performed to reduce tumor volume and spinal cord traction. The cyst content was evacuated using an aspirator in case of neartomas and myxopapillary ependymoma with a cystic component. Such aspiration also allowed tumor volume reduction. After tumor resection the DM was sutured with a braided, absorbable thread PGA HR 17 (Resorba) (Fig. 4f). A Tachocomb hemostatic sponge (Nycomed) with a corresponding size was placed on the suture. Tissucol fibrin glue (Baxter) was applied on top to prevent the formation of liquor cysts, whereupon layer suturing of the incision was performed. Subcuticular suture for skin closure was then performed.

**Follow-up study and processing of surgical intervention data**

The outcomes were evaluated during the early postoperative period 3, 6, and 12 months after surgery. The complex examination included contrast-enhanced MRI performed to control tumor growth. After the study, all patients were examined by a neurologist and a neurosurgeon. The neurological status and quality of life were graded according to the McCormik scale. The intensity and severity of pain were analyzed.
Fig. 4. Intraoperative photograph of the performed approach using a MAST Quadrant minimally invasive retractor, hemilaminectomy and removal of extramedullary neuroma.

Fig. 5. Evaluation of the neurological status of the patient according to the modern McCormick scale before and after surgical treatment in groups 1 and 2.

Using the VAS scale. All data were recorded in a specially created database. The data were analyzed using Microsoft Excel 2007 and Statistica 10 software.

**Results**

The histologic nature of the tumors was as follows: for the first group meningioma — 10 patients, neuroma — 6 patients, ependymoma — 4 patients; for the second group — 5, 12 and 3 patients, respectively (Table 1).

Mean tumor size for the first group was 2.2×1.5 cm (ranging from 1×0.5 to 5×3 cm), for the second group, 2.5×1.5 cm (ranging from 1.5×1.0 to 4.5×2.0 cm (Fig. 1).

The following results were obtained after surgical treatment: total tumor resection was achieved for patients of both groups, mean surgery duration for the first group was 134.75 min (60—200 min), the mean surgery duration for the second group was 105.25 min (60—190 min), the average amount of blood loss was 297 mL (100—600 mL) and 210 mL (50—400 mL), respectively.

All patients were mobile not later than 24 h (range: 2 to 24 h) after the surgical treatment.

Significant reduction of the pain syndrome occurred before the operation and neurological symptoms were improved after surgical treatment in both groups of patients (Table 2, Fig. 5). The evaluation of pain syndrome before the operation was done on the first day after surgery and again at discharge. Already on the first day after surgery, 17 patients of the study group and 13 patients of the control group noted the regression of pain syndrome compared with the preoperative period; i.e., pain syndrome intensity according to the VAS was reduced by more than 3 points. For the study group, the median VAS score on the first day after surgery was 4.3 versus 5.65 in the patients...
of the control group. Upon hospital discharge, median VAS score in patients of the second group was 2 and in patients of the first group it was 3.3.

It should also be noted that all patients were available for monitoring of the long-term treatment outcomes. The fact of episodes of moderate pain syndrome in 3 patients of the control group in the surgical treatment area is of particular importance. Pain syndrome intensity was 1—2 according to the VAS scale. This result was interpreted as being post-laminectomy syndrome.

Tumor recurrence was detected in neither control nor study group during the follow-up period (from 3 to 16 months, mean period being 7.5 months) (Fig. 6). One case of complications, liquorrhea, was reported in the study group. Additional stitches were applied and lumbar drainage was installed after examination of the patient. On day 7, the patient was discharged from the hospital in a satisfactory condition based on the positive dynamics and MRI data. No other complications in early and postoperative periods were detected.

**Discussion**

In our study, the outcomes were compared for the study and the control groups; the characteristics of all patients in the control group (tumor morphology, size, location, etc.) were close to those in the first group.

During the study, indications and contraindications for surgery using different approach methods were developed.

Indications and contraindications for minimally invasive approaches include the following aspects:

— radiologically verified benign tumor, intradural extramedullary localization;
— tumor size should not exceed two spinal units;
— assumed ossifying tumor or the presence of inclusions of radicula in the stroma is a contraindication for the minimally
Invasive approach; expansion of manipulation space is required. In such cases, we used the standard laminectomy; — bilateral tumor localization is also a contradiction for using the minimally invasive approach.

Certain indications and limitations for minimally invasive approach have been reported in some earlier studies. Thus, R. Mannion et al. [13] suggested the following indications for the use of the minimally invasive approach to remove spinal cord tumors: dorsal or lateral tumor location, the size not exceeding three spinal units. Based on the results obtained on 40 patients with intradural tumors by hemilaminectomy, Sarioğlu et al. [15] suggested the use of this approach for all intradural extramedullary tumors, except bilateral neoplasms. In the study by R. Gu et al. [16], all neoplasms had a small size and were located laterally. It should be noted that it was difficult to remove large tumors through a window created by hemilaminectomy with resecting the base of the spinous process due to the limited visual angle and small space for manipulation in the wound. Based on the results of the study, the authors [16] concluded that the indications for this type of approach were as follows: lateral tumor location, tumor diameter not greater than 2 cm, tumor size not greater than two spinal units.

An intraoperative study of patients was performed in 2D mode directly in the operating room to determine tumor location. In some cases, if the tumor was located in an anatomically inaccessible region (the shoulder girdle), which was not visualized on two-dimensional images, 3D scanning increasing approach accuracy and reducing the number of mapping errors was performed using an O-arm. This technique was described by I.N. Shevelev [17].

Currently, the use of a modern retractor has opened up new possibilities for minimally invasive surgery of spinal degenerative diseases. In our study we have described the use of re retractors and hemilaminectomy in surgical treatment of spinal tumors.

To remove intradural tumors, we used a median or ipsilateral paramedian skin incision 2.5 cm from the midline. The length of skin incision was equal to tumor size (measured from the tumor pole) using a Caspar soft tissue retractor system. Visualization of the wound surface can be increased up to 3 times when using a Quadrant retractor system with blade toeing (Fig. 7).

This allows reducing the load on soft tissues during distraction and reducing incision length. The Quadrant retractor is effective for removing tumors with lengths of two spinal units. In addition, the installation of such a retractor requires at least a 3.5 cm incision, while a 2.5—3 cm incision is needed for a Caspar distractor. The Caspar distractor does not require an increased wound surface, since its shape allows installation via a smaller incision. We found some advantages for both retractors, but in our opinion the Quadrant retractor is the best choice, since the surgeon does not need an assistant to use it.

G. Yu. Evzikov and V.G. Fomichev [18] suggested using hemilaminectomy only for lateralized meningiomas and neuromas. The use of minimally invasive techniques, according to their opinion and the opinion of most authors, narrows the operative field, causing problems in the separation of the medial part of the neoplasm from the spinal cord.

In our study, the problem of approach to the spinal canal was solved by resecting the base of the spinous process using micro-instruments and a high-speed burr performing decompression over the top (Fig. 8) used for degenerative diseases. This technique allows visualization of the opposite side of the dural sac. In addition to the expansion of the visual field, the operation table was rotated to the opposite side of the surgeon at an angle of 45°. Thus, 4 tumors with medial locations were successfully removed in our study.

One of the major difficulties of minimally invasive approaches was suturing of the DM after the tumor had been removed. That is why the first surgeries using minimally invasive approaches took a long time. However, during the study and application of approaches in clinic routine practice, a trend toward decreased operation duration was observed. The use of TachoComb and Tissucol glue also played an important role in preventing complications associated with dural sac integrity after suturing.

Resection of the spinous process, vertebral arches, and supraspinal and interspinous ligaments and yellow ligaments can reduce spine stability. In the postoperative period, instability most often develops in the cervical and lumbosacral spine and is associated with the topographic anatomical features of these regions. The absence of posterior spinal structures promotes pronounced cicatricial adhesions in the laminectomy.

**Fig. 8.** Schematic and intraoperative image of performinge over-the-top decompression.
<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>Number of patients*</th>
<th>Tumor type</th>
<th>Tumor histology (number of patients)</th>
<th>Tumor localization (number of patients)</th>
<th>Radicality of tumor removal, %</th>
<th>Operation duration, min</th>
<th>Blood loss, mL</th>
<th>Time of patient activation, days</th>
<th>Length of stay, patient days</th>
<th>Complications (number of patients)</th>
<th>Spinal instability</th>
<th>Catamnesis duration, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Nzokou et al. [24], 2013</td>
<td>13 (7/6)</td>
<td>Extramedullary, extradural</td>
<td>Neuroma (6), meningioma (5), plasmacytoma (1), MTS(1)</td>
<td>Th (9), L (4)</td>
<td>90</td>
<td>189 (75—540)</td>
<td>219 (25—500)</td>
<td>1</td>
<td>2,75 (1—6)</td>
<td>Leg weakness augmentation (1)</td>
<td>—</td>
<td>21 (2—68)</td>
</tr>
<tr>
<td>T. Tredway et al. [25], 2006</td>
<td>6 (4/2)</td>
<td>Extramedullary, intradural</td>
<td>Neuroma (5), mycopapillary ependymoma (1)</td>
<td>C (1), Th+ L (5)</td>
<td>100</td>
<td>247 (180—320)</td>
<td>56 (40—75)</td>
<td>1</td>
<td>2,375 (2—3,3)</td>
<td>Not detected</td>
<td>—</td>
<td>11,3 (3—18)</td>
</tr>
<tr>
<td>R. Mannion et al. [13], 2011</td>
<td>11 (4/7)</td>
<td>The same</td>
<td>Neuroma (7), ependymoma (2), meningioma (2)</td>
<td>C (1) Th (4) L (6)</td>
<td>92,3</td>
<td>150 (90—252)</td>
<td>155 (50—600)</td>
<td>1</td>
<td>3,1 (1—5)</td>
<td>Liquor cyst(2)</td>
<td>—</td>
<td>16 (12—24)</td>
</tr>
<tr>
<td>F. Haji et al. [26], 2011</td>
<td>20 (10/10)</td>
<td>Extramedullary, extradural, intradural, extradural</td>
<td>Meningioma (6), neuroma (9), PNET (2), teratoma (1), myxopapillary ependymoma (2)</td>
<td>C (2), Th (6), L (12)</td>
<td>68</td>
<td>210 (120—285)</td>
<td>428 (60—1250)</td>
<td>1</td>
<td>3 (1—9)</td>
<td>Liquor cyst (1), leg weakness augmentation and ischuria (1)</td>
<td>—</td>
<td>24 (2—48)</td>
</tr>
<tr>
<td>A. Pompili [27], 2004</td>
<td>10 (5/5)</td>
<td>The same</td>
<td>Neuroma (10)</td>
<td>Th (2), L (8)</td>
<td>70</td>
<td>140 (100—210)</td>
<td>—</td>
<td>2</td>
<td>4,5 (4—5)</td>
<td>Not detected</td>
<td>Not detected</td>
<td>16 (6—24)</td>
</tr>
<tr>
<td>C. Sun et al. [28], 2011</td>
<td>45 (19/26)</td>
<td>The same</td>
<td>—</td>
<td>C (21), Th (12), L (12)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>The same</td>
<td>Not detected during 26 months</td>
<td>26 (4—94)</td>
</tr>
<tr>
<td>R. Gu et al. [29], 2008</td>
<td>16 (7/9)</td>
<td>Extramedullary, extradural</td>
<td>Neuroma (12), meningioma (4)</td>
<td>C (3), Th (4), L (9)</td>
<td>100</td>
<td>140 (90—200)</td>
<td>300 (150—500)</td>
<td>—</td>
<td>—</td>
<td>The same</td>
<td>Not detected during 23,7 months</td>
<td>23,7 (6—40)</td>
</tr>
<tr>
<td>J. Sim et al. [30], 2008</td>
<td>7 (4/3)</td>
<td>The same</td>
<td>Neuroma (6), meningioma (1)</td>
<td>C (3), Th (3), L (1)</td>
<td>100</td>
<td>—</td>
<td>—</td>
<td>1</td>
<td>3</td>
<td>The same</td>
<td>Not detected during 18 months</td>
<td>12 (3—18)</td>
</tr>
</tbody>
</table>

Footnote. *Number of men/number of women.
area. M. Seppälä et al. [19] reported a series of 187 patients diagnosed with intradural neuromas. All tumors were removed through the traditional approach — laminectomy. The authors were able to perform total resection in 90% of cases. Postoperative complications, such as pain, instability, and liquor cysts were detected in 10% of patients; the mortality rate was 1.5%. The occurrence of such complications as instability after laminectomy was detected in 20% of adults [12] and <45% of children [13]. Due to complications after laminectomy, M. Seppälä et al. [19] proposed to use hemilaminectomy to remove extramedullary tumors. I. Oktem et al. [20] published the experience of treating 20 patients with intradural tumors using hemilaminectomy in 2000. No development of instability of functional spine units was detected during the two-year of follow-up.

S. Chiou et al. [21] published data demonstrating that patients who had undergone microsurgical removal of intradural tumors through a window created by hemilaminectomy, had lower number of postoperative complications and shorter hospitalization compared to those who had undergone standard laminectomy. M. Yasargil et al. [22] recommend using hemilaminectomy to treat intradural tumors. A group of authors led by Dr. Y. Yu [23] reported that hemilaminectomy reduces operation duration and blood loss as opposed to the conventional laminectomy. T. Naganawa et al. [14] report that hemilaminectomy can increase the speed of neurological recovery of patients without affecting spine stability. These conclusions were based on the evaluation of surgical treatment outcomes in 20 patients with intradural extramedullary spinal cord tumors.

Evaluation of treatment outcomes

To evaluate treatment outcomes, we compared the results obtained in the two groups of patients. In both groups, similar treatment outcomes with respect to radicality of tumor removal and the absence of spine instability. Unfortunately, it is not possible to draw any conclusions about spine stability based on short-term observations.

The mean operative time in the study group was 30 min shorter and the mean blood loss was 80 mL less, which may be insignificant, but patients in the second group were discharged from the hospital on average 3 days earlier than the control group and had earlier refused to take analgesics due to the rapid regression of pain.

Evaluation of the neurological status using the McCormick scale before and after surgical treatment did not show any significant difference in treatment outcomes between the first and the second groups. Thus, 10 patients in the control group moved from one functional class to the higher class. In the study group, only two patients moved to the higher class; in spite of this fact, we cannot draw a conclusion about the better outcomes of the first group, since the number of patients with I functional class in the study group was initially higher.

We did not separate patients based on localization of pain syndromes, since local pain syndromes prevailed over radicular syndromes in both groups of patients. In a series of the patients under study, an analysis of pain syndrome intensity using the VAS score showed no significant difference between of both groups of patients due to the fact that the pain reported before surgical treatment regressed in the majority of cases in both groups, but the patients in the first group were more concerned about pain in the surgical wound. Clinical results obtained in the study group are comparable with those reported in previously published studies analyzing the use of minimally invasive approaches to remove intradural extramedullary tumors (Table 3).

Our study had several limitations, including the small sample size (40 patients); sample heterogeneity (the small differences between the original class of the functional state of the patients); insufficient catamnestic data, since the assimilation of the method occurred in the course of the study; lack of experience with tumor removal via minimized approach during the first operation also took place. All these restrictions were associated with objective reasons. In the future we plan to eliminate these limitations during an expansion of the study.

Thus, the data of our clinical study suggest that minimally invasive techniques in our series of patients are beneficial.

Conclusion

Surgical treatment of patients with intradural extramedullary tumors can be safely and effectively performed using minimally invasive approaches. In this study, we were able to demonstrate the advantage of minimally invasive approaches over the conventional ones based on 20 cases. A potential reduction in surgery duration, intraoperative blood loss, the amount of anesthesia, and the reduction in pain syndrome during the early postoperative period allows us to conclude that, when performed by an experienced surgeon, the method of minimally invasive surgery may be an alternative to the traditional resection of an extramedullary tumor. Certainly, minimization of surgical approaches is a step in evolution of surgery and provides an opportunity to reduce the costs of treatment and prevent patients’ disability. Despite these findings and the better treatment outcomes in the study group, the is it is up to surgeon to decide what approach to use.
REFERENCES


Commentary

In this study a comparative evaluation of the effectiveness of removing extradural tumors by hemilaminectomy and traditional laminectomy was performed. The minimally invasive approach was used to treat 40 patients with tumors of different histological nature. Retractors for minimally invasive surgery were used for hemilaminectomy. The results of interventions were evaluated by repeated examinations of the dynamics over a 1-year follow up study using the modern rating scales. Taking into consideration the relative rarity of spinal tumors, a group of 40 patients is convincing enough for evaluating the safety and potential benefits of the minimally invasive approach. The authors noted that the use of the minimally invasive approach employing modern technical equipment of operating rooms did not deteriorate the functional outcomes of operations, since full view of the surgical area is achieved by using an operating microscope and varying the viewing angle of the wound by tilting the operating table. The use of minimally invasive approaches allowed reducing operation duration and blood loss and achieving a good functional outcome of operations. The study described by the authors allowed selecting optimal indications for using this approach in clinical practice. The article is of great practical importance for spine surgeons.

G.Yu. Evzikov (Moscow, Russia)
Intramedullary spinal cord tumors (IMSCTs) are a rare neurosurgical disease. There are a lot of controversies in their epidemiology. Most references were published in the 1980s—90s. The authors describe and analyze the largest contemporary clinical series of IMSCTs treated by one surgeon (YK). Material and Methods. 201 patients (aged 2 months — 18 years) with IMSCT operated on during the past 12 years. Results. A slight predominance of male patients was discovered. Astrocytomas account for 74% of all pediatric IMSCTs. Classic ependymomas are rare (5.5%). Pediatric spinal cord hemangioblastomas (HABs) are highly suspicious for von Hippel-Lindau disease. Conclusion. Benign histological variants of astrocytomas are the most common type of pediatric IMSCTs. Neither gender nor age differences in the incidence of most tumors (except for HABs) have been observed. Results

A slight predominance of male patients was noted in the analyzed group: there were 113 (56.2%) males and 88 females (43.8%). This trend was observed in all age groups older than 3 years. There was a slight predominance of females among the patients younger than 3 years old (Table 1). The median age of patients was 9.7±0.7 years. There was no gender-related difference in the median age. Notably, there was also no clear predominance of any age group among the patients with IMSCTs. However, there were two moderate peaks of age distribution at 2—3 years and 11—13 years (Fig. 1).

Tumor length was estimated as the number of vertebrae it affected. It is a sufficiently objective criterion for tumor size assessment, since it shows the number of fragments involved in the process. The average tumor length in the clinical series is 5.4±0.5 vertebrae/segments. No gender difference was noted (Fig. 2). Multivariate analysis revealed several correlations between tumor length and other epidemiological (biological) factors. The younger age had an independent effect on greater tumor length with a correlation coefficient of −0.143 (−0.232, −0.054). Histological diagnoses "ependymoma" and "anaplastic ependymoma" influenced tumor length with positive correlation coefficients of 2.558 (0.712, 4.404) and 2.199 (0.052, 4.347), respectively. The functional status of a patient during the operation demonstrated the same relation: the patients with the higher degree of disability had disseminated tumors.

Table 1. Gender structure for different age groups of pediatric patients with intramedullary tumors

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older than 16</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>From 13 to 16</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>From 11 to 13</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>From 6 to 11</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>From 3 to 6</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>3 years and younger</td>
<td>19</td>
<td>18</td>
</tr>
</tbody>
</table>

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Tumor distribution among the main segments of the spinal cord is shown in Fig. 3. The study of a possible predisposition of certain histological types of tumors to a particular region of the spinal cord revealed such relation only for conus and epiconus, which are considered to be rare locations for IMSCT. Our series contained 3 (1.5%) tumors isolated from conus and epiconus of the spinal cord: dermoid, epidermoid and teratoma. Meanwhile, low location of the conus was noted with no obvious signs of spinal dysraphism.

IMSCRTs of unique distribution are found in children. These IMSCTs affect all spinal cord regions and are known as holocord tumors. The first successfully operated clinical series of such patients were reported by F. Epstein in 1981 [10]. In our series, there were 7 (3%) of these patients. All the resected tumors were either piloid astrocytomas or ependymomas by their nature (Table 2).

Of most interest is to analyze the incidence of various pediatric histological groups of tumors and the observed patterns. The summarized data are presented in Table 3. As expected, astrocytomas were dominant among pediatric IMSCT pathologies and constituted 73.2% of all the removed tumors. Piloid astrocytomas turned out to be the most abundant type of tumors (38.3%), followed by astrocytomas (14.9%) and glioblastomas (GBMs) (9.5%). Ependiomas that are typical of adults accounted only for 5.5%. Meanwhile, children demonstrated high incidence of anaplastic ependymomas (8.5%; the 4th place among all tumors) similar to posterior cranial fossa tumors in biological behavior and prognosis. Only a total of 7 (3.5%) patients were diagnosed with hemangioblastomas (HABs) in our clinical series, with 5 (70%) of them being associated with von Hippel-Lindau disease. Relatively high incidence of epidermoids (4.5%), not related to clear manifestations of spinal dysraphism, probably serves as a proof of their prenatal origin. A single case of cavernoma in our clinical series suggests the rare nature of the pathology and that it is more common among adult population. Rare malignancies of the spinal cord (teratoma, schwannoma, neuroblastoma, metastatic medulloblastoma, primitive neuroectodermal tumor, dermoid) were found in single cases and together accounted for 5% of overall IMSCTs in the analyzed series.

An analysis of the age dependence of tumor incidence demonstrated such relation only for GBMs and HABs. These malignances were shown to be typical of patients older than
the median age in the series (Fig. 4, 5). GBMs were not found in children <3 years old, and the youngest patient with HAB was 12 years old. Other tumors were observed in all age groups.

After the most frequent IMSCTs in our series were divided into two groups (benign or malignant tumors), the multivariate analysis revealed no significant correlations. Pediatric malignant IMSCTs constituted 25% in our clinical series.

**Discussion**

IMSCT is a rare pathology. Population studies of rare cases are infeasible. Analyzing large clinical series remains the only source of data. Unique prospective clinical series including more than 440 patients operated on for IMSCT by a surgeon have been collected over the past 12 years in the Burdenko Neurosurgical Institute. Prospective registration of the main clinical and epidemiological data on each patient makes the analysis maximally objective for such type of research. This paper was based on the data on the subgroup of pediatric patients in these series.

It is worth noting that no similar works registered on the Medline search engine have been found in the world literature. Hence, we will conduct a comparative analysis of our findings with the results represent more or less significant series of pediatric patients that include a detailed description of the histological diagnosis and accurate specification of patients’ age [3, 5, 6]. Only one relevant publication was found, which included 164 pediatric patients (<21 years old) from the series by F. Epstein [3]. Analysis of the data of this series has been presented in many articles by different authors, which is quite disorienting [3, 5, 7]. The patients were operated on by F. Epstein in 1980—1994. The series is considered to be old according to the modern standards, especially taking into account of the fact the current advance in MRI visualization and pathomorphology over the past 20 years. The data we obtained fundamentally agree with the main conclusion of the cited authors: astrocytic gliomas are the predominant type of tumors in pediatric patients. However, the details of the results differ. The concept of intramedullary anaplastic ependymoma has not been discussed in the literature. Nevertheless, this tumor type is the fourth most common one (8.5%), being most common among non-astrocytic neuroectodermal tumors. It is important to mention that some experts believe that patients under 3 years of age do not have ependymomas [6].

Patients with von Hippel-Lindau disease are considered to constitute approximately 25% of spinal cord HAB cases [8]. These data were obtained from mixed and adult series. According to our data, pediatric HAB is an extremely rare pathology that is considered to be a genetic disease with high probability (70%). Therefore, any child with single spinal cord HAB should be examined for von Hippel-Lindau disease, while the parents should have a consultation regarding the disease features.
The main issue of any cohort study is how well the research objects reflect the overall population statistics. The only paper analyzing the incidence of spinal cord tumors was published in 1989; it showed the situation in Norway and reported an annual incidence of 0.1 per 100,000 of pediatric population aged 1—14 years and 0.3 per 100,000 of children older than 14 years (here we are talking about intradural tumors of the spinal cord and roots) [1]. For this proportion, the average annual incidence rate is 0.15 per 100,000 in patients aged between 0 and 18 years. Taking into account the fact that the Norwegian population is biologically similar to Russian, we have about 30 novel cases of pediatric intradural spinal cord tumors per year. In our series, the annual average of 17 children with IMSCTs have been operated on. It suggests that the analyzed series is a cross-section of at least 75% of all pediatric IMSCTs diagnosed annually in Russia and is quite representative.

The prevalence of pediatric IMSCTs has been widely described in the English-language literature [2, 4, 6] and constitutes 4—6% of overall CNS tumors. In this regard the authors refer to the paper by A. DeSouza et al. [9] or secondary sources [9]. Careful examination of the paper does not enable one to infer this parameter even indirectly, even not mentioning the fact that it has not been presented among the data. The collected material enables only deriving the "upper limit" of this parameter. Thus, one of the authors of the current paper (Yu.V. Kushel) operated on 201 children with IMSCTs over the past 12 years. He has also operated on approximately 1200 children with various CNS tumors over the same period. In this case, the incidence of IMSCTs constituted 14% of pediatric CNS tumors in an actual surgical practice.

**Conclusion**

Pediatric intramedullary tumors are represented mainly by benign histological variants of astrocytomas. Neither gender nor age differences in the incidence of most tumors (except for HABs) have been observed.

The presence of hemangioblastoma of the spinal cord in children is highly suspicious for von Hippel-Lindau disease and is an indication for screening. Most of the previously cited data on the epidemiology of IMSCTs are biased. The only evident conclusion is that intramedullary tumor is a rare pathology. Even taking into account specialized pediatric neurosurgical clinical data, the incidence of such tumors among pediatric neurooncology does not exceed 14% and constitutes a smaller percentage in the general population.
The current paper is a unique study of the epidemiology of pediatric intramedullary spinal cord tumors carried out in the Burdenko Neurosurgical Institute. The author's conclusion on the absence of reliable statistical data on pediatric tumor incidence is questionable. Moreover, the results obtained by S. Chatterjee (Carolina State Univ), indicating the 4—10% incidence of spinal cord tumor development in pediatric cases among all CNS tumors, are available. The incidence of intramedullary malignancies among all intraspinal tumors is twofold higher in children compared with adults and comprises 40%, which differs from the data obtained by the author.

The validity of the presented data is rather evident. However, the incidence of pediatric intramedullary tumors (30 per year) is questionable, since this parameter was determined based on the study of the Norwegian population. On referring to Zachary D. Guss (Cancer Center Johns Hopkins Univ.) we assume that the number of children with intramedullary malignancies is much greater: 120—150 in Russia, based on populational characteristics (150—200 per year in the USA).

Histological analysis of the operated tumors is of undoubted interest, considering the extent of the material to study, where piloid astrocytomas have always been the prevailing type among the pediatric population, followed by fibrillar astrocytomas (WHO II — World Health Organization classifier), although this tumor type is much less frequent. In fact, it would be appropriate to mention more representative classifiers in the section describing the histological forms of intramedullary tumors in order to identify and justify further treatment strategy. The fact of 100% surgical activity in such clinical cases within pediatric population is not fully supported by a number of researchers (I. Sandalcioglu, E. Essen, Germany), especially with regard to high-grade astrocytomas. Radiotherapy as the treatment method of choice for this histological type of neoplasm is certainly rare, but still accepted.

In general, this work is a very compact representation of the collected data, including further substantiation of the age, histopathological and anato-morphological spread patterns of pediatric intramedullary tumors. Taking into account the authors’ opinion on the series of papers devoted to this topic, one should expect that a comprehensive analysis of the data from the perspective of both clinical and diagnostic aspects and all surgical aspects of this problem (studying the catamnestic data and other issues) will be performed in subsequent publications.

A.O. Gushcha (Moscow, Russia)
The Use of Intraoperative Electrophysiological Monitoring in Patients Who Undergo Decompression of the Ulnar Nerve near the Elbow Joint

A.G. FEDYAKOV1, O.N. DUBROVINA1, O.N. DREVÁL2, A.V. GOROZHANIN1,2, E.N. PLASTUNENKO

1S.P. Botkin City Clinical Hospital; 2Russian Medical Academy of Postgraduate Education, Moscow, Russia

Near the elbow joint, the ulnar nerve can be compressed in the retroepicondylar groove, at the cubital tunnel, or by the Osborne’s hand. Optimal surgical therapy should be directed to the specific site of involvement. It is more difficult to identify the level of ulnar nerve compression. Anatomical variations can make it difficult to identify the causes of ulnar neuropathy at the elbow. The data provided by medical inspection, neurological presentation, or electroneuromyography do not allow one to reliably determine the compression level. Intraoperative electroneuromyography performed in 14 patients with ulnar nerve neuropathy allowed localizing the precise compression site in 12 cases. Intraoperative studies allowed identifying compression by Osborne’s hand in 8 patients. We believe that, in most cases, intraoperative electroneuromyography allows identifying compression level of the ulnar nerve more accurately than the conventional examination methods.

Keywords: intraoperative electroneuromyography, cubital tunnel syndrome, ulnar nerve compression, peripheral nerve surgery.

Ulnar nerve compression within the cubital tunnel is a common pathology among compression-ischemic injuries of the peripheral nerves of the upper extremities and the second most frequent pathology after the carpal tunnel syndrome [6]. According to the National Program of Outpatient Surgery for Studying Trends in Treatment of the Ulnar Nerve Tunnel Syndrome (1994—2006), a total of 52,133 surgeries for this disease were carried out in the US in 2006. This shows that the frequency of surgical interventions has increased compared to 1994 (26,283) and 1996 (35,406). The total number of surgeries for ulnar nerve decompression has increased by 47% within 11 years (from 1996 to 2006) [12]. According to several authors [11], conservative treatment of compression neuropathy of the ulnar nerve can be effective only in the cases of mild electrophysiological disorders of nerve impulse conduction, while surgical intervention is required in the case of moderate or severe disorders. These data demonstrate the high relevance of surgical treatment of compression-ischemic neuropathy of the ulnar nerve at the present time.

Historical background. In 1878, ulnar neuropathy at the elbow joint caused by an elbow injury was first reported by Panas. The term “tardy ulnar nerve palsy” that occurs after an old bone fracture or elbow joint dislocation was later suggested. Soon afterwards this term began to be used for any non-specific ulnar nerve injury, based on unsubstantiated assumptions that the injury probably occurred, but the patient did not remember about it. [5] Description of aponeurosis between the heads of flexor carpi ulnaris as the cause of ulnar nerve compression was first proposed by British neurologist Dr F. Buzard and his colleague, surgeon Mr P. Sargent in 1916. This observation was lost and then re-discovered in 1950 by several researchers. G. Osborne [10] described this pathology as a spontaneous ulnar nerve paresis. W. Feindel and J. Stratford [8] coined the term “cubital tunnel syndrome” to describe ulnar nerve compression by intermuscular membrane. These scientists tried to identify the patients who had compression caused by intermuscular ligament only among all the patients with cubital syndrome. They suggested that only intramuscular membrane dissection should be performed instead of nerve transposition in these cases.

Anatomy of the ulnar nerve at the elbow joint. The most common site of ulnar nerve compression is the elbow joint level, where the anatomical factors contribute to its compression-ischemic injury [9]. At the level of the lower third part of the brachium, the ulnar nerve exits the caput mediale, spreads on its surface and runs subcutaneously, entering the retroepicondylar groove. The area located immediately distal to the retroepicondylar groove is called the cubital tunnel. This groove is a curved bony canal between the medial epicondyle of the humerus (epicondylus medialis), lying anteriorly and medially, and the olecranon located posteriorly and laterally, where the nerve is covered with fascia and skin. The number of aponeuroses covering the retroepicondylar groove may be different or even absent, allowing the ulnar nerve to slide or “fall on” on the medial epicondyle during the forearm flexion [4]. In this region, the ulnar nerve ramifies towards the elbow joint capsule. After exiting this region, the ulnar nerve passes under the aponeurotic membrane located 1.0 to 2.5 cm distal to the medial epicondyle and representing the aponeurosis between the heads of the flexor carpi ulnaris [9]. In 75% of cases, the aforementioned intermuscular aponeurosis is very dense, thickened, and is called the Osborne’s fascia (membrane). During elbow flexion, the humeral and ulnar heads of the flexor carpi ulnaris move apart, thereby causing stretching of the intermuscular membrane, compressing the ulnar nerve (nerve trunk pressure rises by 19 mm Hg) [13]. Upon elbow flexion the ulnar nerve is under unfavorable conditions: being located in a flat canal, the nerve is tortuous and constricted.
with the aponeurotic membrane. Upon full flexion, the ulnar nerve often leaves the ulnar nerve sulcus of the humerus (sulcus nervi ulnaris humeri), either partially or completely, in healthy individuals [13]. Therefore, at the elbow joint there are several anatomical reasons contributing to ulnar nerve compression at this level: compression in the retroepicondylar groove and nerve compression by the Osborne’s membrane near the nerve entrance between the heads of flexor carpi ulnaris [5]. Therefore, the general concept of the “cubital tunnel syndrome” (ulnar neuropathy at the elbow joint) can reflect not only the ulnar nerve compression at the retroepicondylar groove, but also injury of its more distal portion caused by tendinous Osborne’s membrane, as well as combination of these factors. Preoperative diagnosis allowing for reliable differentiation of the local cause of the ulnar nerve compression at the elbow joint is often extremely difficult, which may lead to inadequate surgical intervention and, as a result, preserved ulnar nerve compression by Osborne’s membrane at the distal level. This fact spurred the search for optimization of surgical techniques for decompression of the ulnar nerve at the elbow joint.

Clinical presentation and diagnosis of the compression-ischemic ulnar neuropathy. Diagnosis of the compression-ischemic ulnar neuropathy includes evaluating complaints, medical history, neurological disorders, electroneuromyographic study, and ultrasonography (US) to confirm the nerve trunk compression.

Clinical presentation. In most cases, the initial symptoms of ulnar nerve injury at the elbow joint include periodic numbness and paresthesias in the ulnar nerve innervation area (the medial third portion of the hand near the minimus and ring finger). Sensory disturbances worsen upon elbow flexion, at night and morning time (patients often associate these states with uncomfortable position of the extremities or the cervical spine during sleep). These symptoms can occur for several months, or even years, due to the fact that many patients become accustomed to these sensory disorders and stop paying attention to them. Pain syndrome is extremely rare in this period (except for the cases of traumatic injuries and elbow joint arthritis), unlike the carpal syndrome (when pain is the leading symptom, while paresthesia and hypoesthesia are less pronounced). As the pathological process progresses, patients begin to complain of more pronounced and permanent numbness. Patients also complain of elbow pain radiating from the medial surface of the forearm to the hand. Sensory disorders observed in patients with ulnar neuropathy are not always strictly consistent with the expected dermatomes due to the anatomical variability of the nerve structure, in particular the sensory innervation of the ring finger. Motor impairment can remain unnoticed by patients for months and sometimes even years [13]. The ulnar nerve innervates the muscles located in the forearm and hand. Movement disorders in patients with ulnar neuropathy are predominantly associated with disorders of fine coordinated motor activity of hand and fingers. Motor function disorders result in decreased strength of the wrist flexion at the radiocarpal joint, weakness of flexion of the distal phalanges of the ring finger and, especially, the minimus; paresis of intrinsic hand muscles (except for thenar) takes place. Muscle wasting will eventually occur, including the hypothenar and dorsal interosseous muscles (in particular at the first interdigital space). Finally, the so-called “claw” forms are formed [1, 4]. Thus, the clinical presentation of the ulnar nerve injury at the elbow joint is primarily characterized by sensory and motor deficits. Due to the absence of pain syndrome these disorders occur gradually and their progression is often unnoticed by a patient. For this reason the patient seeks medical help when there is already severe muscular atrophy and, as a result, severe motor deficit. In these cases, surgical intervention aimed at ulnar nerve decompression is required (if the diagnosis was confirmed electrophysiologically and ultrasonically), omitting the conservative treatment stage in order to prevent further progression of the hand muscle atrophy and “claw” formation.

Electroneuromyographic examination is the most important aspect of objective assessment of functional impairment of the peripheral nerves. In the case of peripheral neuropathy, the M-response amplitude is reduced, which is an objective marker of functional impairment of nerve impulse conduction. Electroneuromyographic examination allows determining the level of ulnar nerve compression: the axillary, brachial, or cubital regions, Guyon’s canal (wrist). This diagnostic method also allows assessing the state of effector muscles innervated by a certain nerve (the presence and magnitude of spontaneous excitation activity of innervated muscle fibers), which provides an indication of severity of hypotrophy or atrophy of muscular tissue and allows making a decision on the appropriateness of surgery aimed at muscle reinnervation.

Ultrasound of the nerve trunk allows determining its anatomical structure, location, type and level of impairment. Ultrasound plays an important role in determining the cause and location of nerve trunk compression. The ultrasound picture of nerve compression includes thickening (edema), disalignment (tortuosity) of the nerve trunk, and significant reduction or absence of nerve fiber differentiation. These symptoms are usually observed proximal to the nerve compression level. At the elbow joint, thickening of the ulnar nerve can be detected proximal to the cubital tunnel (near the medial epicondyle of the humerus), which is indicative of nerve compression at its entrance to the cubital tunnel. Swelling of the nerve, as well as its spreading in the region of the cubital tunnel is indicative of nerve compression by connective tissue roof of the tunnel, “shallow” cubital tunnel syndrome or compression by Osborne’s fascia located more distally. In some cases, nerve disalignment (S-shaped tortuosity), as well as its deformation by surrounding tissues as a result of cicatrical and adhesive processes, can be observed. However, in some cases, it is difficult to find out the exact causes of ulnar nerve compression in the cubital tunnel by ultrasound due to the large number of possible compressing factors: nerve compression at the canal entrance, hypertrophied tendinous roof, presence or absence the Osborne’s fascia, cicatrical adhesions localized at any segment of the cubital tunnel or spreading along its entire length.

The complex of patient’s complaints, medical history, neurological disorders, electrophysiological parameters, and
ultrasound data allows formulating indications for surgical treatment, selecting the optimal timing of surgery and identifying surgical intervention options. However, in some cases, despite the available clinical and instrumental data, the extent of surgery can be determined only during the operation, due to the variety of possible ulnar nerve compressing factors at the elbow joint, which often requires intraoperative verification of adequate decompression of the nerve trunk. We propose one of intraoperative monitoring methods, recording the change in nerve impulse conduction upon ulnar nerve decompression at the elbow joint, to solve this problem [7].

**Material and Methods**

A total of 14 surgical interventions for ulnar nerve decompression at the elbow in patients with compression-ischemic neuropathy were carried out (post-traumatic lesions are not included in this review). Microsurgical intervention technique was used during the surgical treatment (OPMI Pentero and OPMI Vario 700 surgical microscopes (Carl Zeiss), and microsurgical instruments), intraoperative electromyography was performed, and preventive measures against cicatricial and adhesive processes in the postoperative period were taken (wrapping the nerve trunk with ElastoPOB biodegradable membrane after decompression [2, 3]). Electrophysiological control was carried out on IOM XLTEK Protector system (Natus, Canada), the response was recorded using the m.ADM needle electrodes; stimulation was carried out using a bipolar electrode with repeated pulses of 0.2 ms, frequency of 4.7 Hz and strength of current up to 4 mA. The stimulating electrode was placed proximal to the level of ulnar nerve compression. The increase in M-response amplitude was assessed during staged ulnar nerve decompression.

Patients were predominantly males (12) aged 41 to 62 years and two females aged 64 and 62 years. Cubital tunnel syndrome was detected in 4 cases on the right side, and in 10 cases, on the left side. All patients underwent electroneuromyography and ultrasonography of the ulnar nerve, which revealed impaired nerve impulse conduction and compression of the nerve trunk. The standard microsurgical intervention aimed at ulnar nerve decompression at the cubital tunnel was carried out. All operations were performed under local anesthesia (S. novocaini 0.5% or S. lidocaini 1%). The approach to the ulnar nerve and fixation of needle electrodes for electrophysiological monitoring (at hypothenar) are shown in Fig. 1.

After layered dissection of soft tissue, the proximal fragment of the ulnar nerve was separated to its entry into the cubital tunnel and intra-trunk injection of local anesthetic was performed (in the proximal direction). Electrophysiological monitoring was then performed with installing the stimulating electrode distal to the area of anesthetic administration. It this way, we recorded the initial value of the nerve impulse response prior to nerve decompression (Fig. 2).

The next step included decompression, neurolysis of the ulnar nerve at the cubital tunnel followed by electrophysiological control (Fig. 3).

**Fig. 1.** Approach to the left ulnar nerve at the cubital tunnel and fixation of needle electrodes for intraoperative electrophysiological monitoring.

1 — ulnar nerve projection; 2 — skin incision line; 3 — needle and grounding electrodes.

**Fig. 2.** Intraoperative stimulation of the proximal fragment of the ulnar nerve near its entrance into the cubital tunnel.

1 — the site of local anesthetic administration; 2 — ulnar nerve; 3 — the entry point of the ulnar nerve into the cubital tunnel; 4 — stimulating electrode.

**Fig. 3.** Electrophysiological monitoring of the ulnar nerve after neurolysis.

1 — ulnar nerve; 2 — stimulating electrode (arrows).

Osborne’s fascia, compressing the ulnar nerve at the distal part of the cubital tunnel (Fig. 4) was intraoperatively detected in 9 patients. Fascia was dissected and control electrophysiological monitoring was performed. Completeness of the
ulnar nerve decompression was assessed based on the monitoring data.

After complete nerve decompression, the nerve trunk was covered with ElastoPOB membrane to prevent cicatrical and adhesive complications in the postoperative period (Fig. 5). Layered wound closing was then performed and aseptic dressing was applied.

Nonparametric paired-comparison Wilcoxon test and Biostat program (BIOSTAT for IBM PC) were used for the statistical analysis of the results.

Results

Baseline values of M-response amplitude during stimulation of the proximal fragment of the ulnar nerve prior to its decompression ranged 40—120 (83±25) μV. After complete decompression of the ulnar nerve at the elbow joint, including dissection of the cubital tunnel roof followed by neurolysis, and dissection of Osborne’s membrane (if present), the value of M-response increased by 138—290% (except for 2 cases) (Fig. 6). Statistically significant difference between M-response amplitudes before and after ulnar nerve decompression was obtained (p<0.02). Intraoperative dynamics of increase in M-response varied depending on the presence or absence of Osborne’s membrane. When it was absent, M-response increased by 138—246% after dissection of the cubital tunnel roof and subsequent neurolysis of the ulnar nerve in this region (4 cases). In the presence of Osborne’s membrane, an increase in M-response after dissection of the tunnel roof and neu-

Fig. 4. Osborne’s fascia at the distal portion of cubital tunnel.
1 — ulnar nerve; 2 — Osborne’s fascia; 3 — head of the flexor carpi ulnaris (arrows).

Fig. 5. Prevention of cicatrical and adhesive processes at the surgical treatment area by wrapping the nerve trunk with ElastoPOB membrane.
1 — ElastoPOB membrane (arrow).

Fig. 6. M-response values before decompression of the ulnar nerve (μV).
1 — free-run ENMG (spontaneous neuromuscular activity); 2 — trigger ENMG (stimulated neuromuscular activity) before nerve decompression; 3 — trigger ENMG (stimulated neuromuscular activity) after nerve decompression.
Changes in the nerve impulse conduction (µV), as a function of surgical procedure stage (in the parentheses — an increase in M-response)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial conduction</th>
<th>Dissection of the cubital tunnel roof, %</th>
<th>Dissection of the Osborne’s fascia, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>100 (43)</td>
<td>205 (193)</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>85 (70)</td>
<td>170 (240)</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>230 (130)</td>
<td>390 (290)</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>65 (63)</td>
<td>130 (225)</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>200 (100)</td>
<td>380 (280)</td>
</tr>
<tr>
<td>6</td>
<td>120</td>
<td>210 (75)</td>
<td>420 (250)</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>90 (50)</td>
<td>220 (267)</td>
</tr>
<tr>
<td>8</td>
<td>80</td>
<td>150 (86)</td>
<td>280 (250)</td>
</tr>
<tr>
<td>9</td>
<td>80</td>
<td>80 (6)</td>
<td>80 (13)</td>
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<tr>
<td>10</td>
<td>80</td>
<td>190 (138)</td>
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<td>11</td>
<td>120</td>
<td>400 (233)</td>
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<td>110</td>
<td>380 (246)</td>
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<td>230 (156)</td>
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</tr>
<tr>
<td>14</td>
<td>60</td>
<td>70 (17)</td>
<td>—</td>
</tr>
</tbody>
</table>

Dissection of the nerve trunk was only 43—130%, while increasing up to 193—290% after resection of the membrane (in 8 cases). In 2 cases (the membrane was present in one case and absent in the other one) no significant dynamics of M-response was observed during the surgery (M-response increased by 13 and 17%) (Table).

An analysis of two cases with no intraoperative increase in M-response showed that one patient suffered from cubital nerve compression for 5 years (Osborne’s membrane wasn’t found), and the other patient had a severe suppurative arthrosis of the elbow joint with several drainage operations (heterotrophied Osborne’s membrane was revealed). In both cases, endoneural administration of local anesthetic solution revealed severe intra-trunk cicatrices. We assume that in these cases the disorder of the ulnar nerve conduction was primarily due to intra-trunk changes formed by the time of surgery due to prolonged compression and inflammatory changes, rather than due to direct impact of compression-ischemic factors that were removed during surgery. Therefore, we can assume that visually adequate external decompression of the nerve trunk does not lead to intraoperative increase in M-response in those cases, where there is significant injury of internal structure of the nerve trunk in addition to the existing external compression. These facts lead to a preliminary conclusion that the intraoperative electrophysiological diagnosis not only helps to control the success of peripheral nerve decompression, but also provides important information about the prevalence of one or another cause of the nervous conduction disorder (external — compression-ischemic, internal — intra-trunk cicatrical changes, or their combination). These data are an important factor for predicting the recovery of nerve fiber conduction and functional recovery.

**Conclusion**

Intraoperative electrophysiological monitoring is a technically uncomplicated manipulation and does not significantly increase the duration of operation and its preparation. This method provides objective information on the adequacy of decompression of the ulnar nerve trunk, allows determining location, extent and causes of functionally significant compression directly during the surgery (compression and cicatrical adhesive process directly in the cubital tunnel, Osborne’s fascia, internal injury of the nerve trunk, or combination of these factors). In addition, this diagnostic method can help in predicting the results of surgical treatment of tunnel neuropathy of the ulnar nerve at the elbow joint.

**REFERENCES**


**Commentary**

Detectability of compression-ischemic tunnel syndromes has recently been significantly improved due to the development of diagnostic facilities and the possibility of adequate differential diagnosis. The surgical treatment of this type of peripheral nerve disease is therefore a very important issue. The more so, because the working-age population is susceptible to this disease.

The historical aspects of the problem are discussed, the modern survey methods used in this pathology are described in detail, and their comparative evaluation is given.

The intraoperative electrophysiological monitoring method during decompression of the ulnar nerve in the cubital tunnel proposed by authors provides highly informative intraoperative assessment of the quality of ulnar nerve decompression.

The authors propose and describe in detail the technique of intraoperative monitoring of the ulnar nerve using direct stimulating needle electromyography. Steps of the surgery are also described and illustrated in detail. In the final part of the paper, the analysis of the dynamics of the M-response values at different stages of surgery is provided. The reliability of the obtained data is demonstrated. The results are compared to preoperative examination data. The technique proposed by the authors seems to be promising in practice to evaluate the effectiveness of surgical intervention. It also seems to be important for assessing the pathogenesis of ulnar neuropathy in each specific case, predicting postoperative course of the disease, and choice of further rehabilitation methods.

*A.V. Shtok (Moscow, Russia)*
The Use of Botulinum Toxin Type A in the Acute Phase of Facial Nerve Injury after Neurosurgical Surgery

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Aim. To evaluate the role of botulinum toxin type A in the acute phase of facial nerve injury after neurosurgical surgery. Material and Methods. The study involved 55 patients with acute facial muscle paralysis caused by facial nerve injury during surgery of posterior cranial fossa and cerebellopontine angle (CPA). Group 1 consisted of 35 patients (mean age, 48.14±1.26 years) who were injected with botulinum toxin type A (Xeomin) at a dose of 2—3 U per point in muscles of the intact face side. The control group included 20 patients (mean age, 49.85±1.4 years) who underwent standard rehabilitation treatment of this pathology. The treatment efficacy was evaluated using the House—Brackmann Scale, the Yanagihara facial nerve grading system, the Facial Disability Index (FDI), and the Sunnybrook Facial Grading (SFG) Scale. Results. Before treatment, patients in both groups experienced severe dysfunction according to the House—Brackmann Scale. A month after the botulinium toxin type A therapy had been started, a significant improvement in the group of patients who received botulinum toxin was observed at all scales (p<0.05), whereas improvement in the facial nerve function in the second group was observed only by the 3rd month of rehabilitation treatment (p<0.05). The number of synkineses in the patients who did not receive botulinum toxin was 46% higher than that in Group 1 (p=0.019) one year after the surgery, and it was higher by 91% after 2 years (p<0.001). Conclusions. The use of botulinum toxin type A is reasonable in acute facial nerve injury and should be mandatory in combination therapy of these patients.

Keywords: facial nerve injury, botulinum toxin, synkinesis.

Facial nerve injury is among the most frequent postoperative complications in surgical treatment of posterior cranial fossa and cerebellopontine angle tumors [1]. This type of neuropathy is associated with numerous persistent structural and functional facial muscle disorders [2, 3].

Patients have unilateral paresis or paralysis of mimic muscles accompanied by such dysfunctions as lagophthalmos with the risk of developing keratopathy; eating and drinking difficulties, and speech disorders [4]. In addition to dysfunction and marked facial asymmetry, there are severe mental implications including low self-esteem, anxiety and depressive disorders, as well as social isolation [5, 6].

The methods for treating facial nerve neuropathy vary according to the views on disease etiology and pathogenesis, as well as the current “state of the art” of pharmacology and physical therapy [7, 8]. All treatment methods can be subdivided into conservative (drugs and physiotherapy) and surgical ones. The therapeutic methods usually focus on activation of facial muscles on the affected side. The recent trend is to use long-lasting facial relaxation of the intact side by locally injecting modern myorelaxant, botulinum toxin type A [9, 10]. In the acute phase of facial nerve neuropathy, it is recommended that botulinum toxin agent is injected into facial muscles on the intact side to reduce mimic muscle contracture on the affected side, to reduce mimic hypertonia on the intact side, to affect the muscular antagonism, and to perform esthetic correction [11].

The benefits of this technique include injection simplicity, flexibility of the injection site, prompt and long-lasting effect, and almost complete absence of adverse effects [12].

Injection of botulinum toxin into the intact facial side in patients with persistent facial nerve paralysis is the minimally invasive technique improving facial symmetry at rest and during facial movements [13, 14]. Furthermore, the resulting temporary muscle weakness on the intact side strengthens the paralyzed structures and improves their functionality [15]. The experience of using botulinum toxin suggests that it can be successfully used in patients with acute paralysis of mimic muscles, which can result in short-term reduction of facial asymmetry and reduce the rate of later complications of synkineses and contractures.

The objective of this study was to evaluate the role of local injection of botulinum toxin type A into muscles on the intact side in the acute phase of facial nerve injury after neurosurgical interventions.

Material and Methods

Fifty-five patients with acute facial nerve neuropathy caused by surgical treatment of posterior cranial fossa (PCF) and cerebellopontine angle (CPA) tumors were examined. Group 1 included 35 patients (19 (54.3%) males and 16 (45.7%) females aged 34—63 (median age, 48.14±1.26 years). Group 2 (control group) consisted of 20 patients [10 (50.0%) males and 10 (50.0%) females aged 42—63 (median age, 49.85±1.4 years)].

Group 1 patients received botulinum toxin type A (Xeomin) injection 24—48 h after the emergence of facial paresis or paralysis. Botulinum toxin was injected at a dose of...
2—3 U per point of muscles on the intact side of the face (Fig. 1).

Group 2 patients (control) were prescribed an adhesive bandage to ensure tension from the intact side to the injured one oriented against the muscular traction on the intact side. Corrective bandage made of adhesive tape (1—2 cm wide) was placed as strips on the region of the contracted muscles in such a way as to use fixation of tape at bone prominences (temple, zygoma, and mandible). Skin and muscles of the affected side were pulled by strips upwards and laterally, thereby preventing stretching of paretic muscles. The patients were recommended to receive treatment in daytime during 30—60 min, mostly during active facial movements (food intake or communication). The treatment duration was subsequently increased to 2—6 h per day.

The physical rehabilitation program, same for both groups, included a set of differentiated therapeutic exercises that made allowance for the specificity of clinical and functional changes, facial massage, exercises for mimic muscles under objective control in front of a mirror; articulation exercises in front of a mirror with pronouncing sounds, words and tongue twisters.

Treatment efficiency was assessed clinically taking into account the characteristics of functional activity of the neuromuscular apparatus. The severity of facial paresis was evaluated using the House—Brackmann Scale and the Yanagihara facial grading system. The Facial Disability Index (FDI) questionnaire was self-completed by patients. Facial symmetry and synkineses were assessed using the Sunnybrook Facial Grading (SFG) Scale.

Table 1. The rate of clinical symptoms in the examined patients, abs. (%)

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>Group 1 (n=35)</th>
<th>Group 2 (n=20)</th>
<th>Total (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial muscle weakness</td>
<td>35 (100)</td>
<td>20 (100)</td>
<td>55 (100)</td>
</tr>
<tr>
<td>Mastoid discomfort</td>
<td>19 (54.3)</td>
<td>11 (55.0)</td>
<td>30 (54.5)</td>
</tr>
<tr>
<td>Epiphora</td>
<td>12 (34.3)</td>
<td>6 (30.0)</td>
<td>18 (32.7)</td>
</tr>
<tr>
<td>Dry eye syndrome</td>
<td>7 (20.0)</td>
<td>4 (20.0)</td>
<td>11 (20.0)</td>
</tr>
<tr>
<td>Facial hypoesthesia</td>
<td>4 (11.4)</td>
<td>2 (10.0)</td>
<td>6 (10.9)</td>
</tr>
<tr>
<td>Hypacusia</td>
<td>33 (94.3)</td>
<td>19 (95.0)</td>
<td>52 (94.5)</td>
</tr>
</tbody>
</table>
Results

Among all patients examined, 37 (67.3%) individuals had undergone removal of acoustic neuroma: 24 (68.6%) patients from group 1 and 13 (65.0%) from the control group. Eighteen (32.7%) patients had petroclival meningioma: 11 (31.4%) group 1 patients and 7 (35.0%) group 2 patients (Fig. 2).

The main clinical symptoms included facial muscle weakness (100%) and hypacusia (94.5%). Dry eye syndrome (20.0%) and epiphora (32.7%) were the rarest ones (Table 1).

Both group 1 and 2 patients had severe dysfunction according to the House—Brackmann Scale: score 3.26±0.16 and 2.65±0.23, respectively. Moderate facial nerve dysfunction (score 3) was significantly more common for patients in both groups (p<0.05) (Fig. 3). The average Yanagihara System score was 20.06±6.99 (range: 11—31) in group 1 and 19.85±5.3 (range: 10—32) in group 2.

Significant improvement was observed a month after the botulinum toxin type A therapy had been started: the facial nerve dysfunction rate decreased by 41% (p<0.05). Furthermore, facial asymmetry scores were better by 28.1% compared with those of patients in group 2 (p<0.05). In group 2, significant improvement in facial nerve function was observed only by the 3rd month of rehabilitation treatment: by 35% compared with the scores prior to treatment (p<0.05). In group 1, this parameter improved by 48% by the 3rd month of follow-up, but no significant difference compared with group 2 was detected (Table 2).

According to the Yanagihara System, the status of group 1 patients one month after treatment was improved by 73% (the average score of 34.72±7.25; p<0.05), while being improved only by 19.5% (the average score of 23.74±5.76) in group 2. Significant improvement in group 2 was observed by the 3rd month of treatment: by 77% compared with the scores before treatment (the average score of 35.22±7.81; p<0.05).

Thus, the use of botulinum toxin type A in early postoperative treatment of facial nerve neuropathy has a more rapid effect compared with the conventional treatment approaches.

The catamnestic assessment yielded the following data. Synkineses were observed in 16 (45.7%) and 12 (60.0%) group 1 and 2 patients, respectively, six months after surgery. Group 1 patients showed a trend towards lower synkinesis rates, but no significant difference was detected. Group 1 patients continued to receive treatment with botulinum toxin type A, which was injected on the side of facial nerve injury, in the synkinesis area, at a dose of 2—3 U per point.

One year after surgery, the synkinesis rates in patients who had not received botulinum toxin were 36.4% higher than those in group 1 patients (p=0.019); 2 years later, by 65.7% (p<0.001) (Table 3).

The average SFG scores 6 months later were 71.1±9.38 and 59.4±7.21 in group 1 and 2 patients, respectively. Significant improvement (by 46%) was observed one year after surgery in patients who received botulinum toxin injections according to the SFG compared to those who performed therapeutic exercises only (score 80.03±10.14 in group 1 and 54.9±8.25 scores in group 2; p<0.05). One year later, the average score was 87.25±11.07 and 49.34±7.92 in group 1 and 2 patients, respectively (p<0.05).

The average FDI score 6 months after surgery was 122.35±16.37 in group 1 and 104.19±19.72 in group 2 patients. One year later these figures were 139±18.64 and 94.87±21.19, respectively (p<0.05), and 2 years later patients’ status in group 1 was 91% higher (the average score of 164.21±23.18 and 86.15±12.34, respectively; p<0.05).

Conclusion

The development of efficient methods for treating acute peripheral facial nerve neuropathies is a topical issue, especially considering that this pathology is observed in patients of all age groups and holds leading prominent place among diseases of the peripheral nervous system. Motor impairment of facial muscles impedes speech, eyelid closure, food intake, while cosmetic defect attracts patient’s own and others’ attention, thus significantly decreasing patient’s quality of life. Inappropriate management of facial nerve neuropathy leads to gross impairment in mimic expression. Therefore, prevention of facial contractures is of special significance.
The primary tasks of rehabilitation measures for treating facial nerve neuropathy include establishing conditions for regenerative processes and preservation of denervated muscular tissue; prevention of shortening of contralateral paralyzed muscles (“contracture of antagonists”) and mastication muscles; attempts for gradual recovery of involuntary movements to become voluntary by involving them in various synergistic reactions (propioreceptive facilitation and stimulation); appropriate exercises to increase muscle strength, prevention of substitutive movements (in case of minimal voluntary activity); and recovery of isolated volitional muscle contractions [16].

In this study, patients with facial nerve neuropathy after the removal of PCF and CPA tumors received botulinum toxin type A in the course of rehabilitation therapy. The botulinum toxin was shown to provide more prominent therapeutic effect: the more rapid recovery of the injured nerve and facial muscle functions.

The use of botulinum toxin in patients with acute facial nerve injury is reasonable. Dosed and proper prescription of botulinum toxin and instructing patients to do special exercises to recover facial functions should be obligatory in multimodal treatment of such group of patients.

REFERENCES


Commentary

The relevance of this study is determined by high frequency of facial nerve injury after removal of acoustic neuroma and petroclival meningioma and development of ipsilateral facial paralysis and hypertonia of contralateral facial muscles. Local injection of myorelaxant botulinum toxin type A into tensed muscles is one of the most advanced and effective methods for treating muscular hypertonia. Safety and high efficiency of botulinum toxin therapy have been confirmed in a number of clinical trials. The authors assessed the role of local injections of botulinum toxin type A into facial muscles on the intact side in the acute phase of facial nerve injury after neurosurgical interventions for the first time, which made it possible to reduce facial asymmetry and speed up the recovery of muscle activity on the side of facial nerve injury.

The relevance of the study is determined by the need for early treatment of this pathology in patients after neurosurgical treatment in order to render effective medical care.

The reliability of the results is proved by sufficient amount of analyzed data, by the use of methods that are reasonable for the assigned tasks and by the use of modern statistical analysis procedures. The results obtained by authors using modern investigation methods suggest that the assigned tasks have been successfully solved.

V.L. Golubev (Moscow, Russia)
Intradural Extramedullary Myxoma at the L1 Level


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Myxoma of the peripheral nerve sheath is a rare benign tumor with the predominant localization in the upper extremities, head, neck, and chest. In this study, we reported a clinical case of a patient with intradural myxoma at the L1 level. Much attention was given to histological characterization of the tumor and differential diagnosis of histological types of benign extramedullary tumors. A conclusion was drawn that patients with myxoma need further thorough examination as there is a risk of generalization of the tumor process.

Keywords: intradural extramedullary tumor, myxoma, radiological characterization, histological characterization.

Myxoma of the peripheral nerve sheath is a rare benign tumor with the predominant localization in the upper extremities, head, neck, and chest. A growth origin is often localized in the dermal layer of the skin. In the literature, this tumor was first described in 1969. J. Harkin and R. Reed [1] called the detected tumor as myxoma of the peripheral nerve sheath, but later, R. Gallager and E. Helwig [2] found a myxoma-like histological type of the tumor that was called neurothekeoma. In this paper, we present a rather rare case of the intradural localization of the tumor in the area of the cauda equina nerve roots.

Case study

A 52-year-old female patient E. was admitted to the Burdenko Neurosurgical Institute on 06.02.14 with complaints of severe pain in the lumbar spine, with pain spreading over the anterior surface of both legs. According to the disease history, the patient had been bothered by these symptoms for the past 2 years. In the past year, the pain intensified and became persistent, which was the reason to perform magnetic resonance imaging (MRI) of the lumbar spine in May 2013. MRI revealed two intradural tumors located at the L1 level, in the area of the cauda equina nerve roots and medullary cone. The lesions intensively accumulated a contrast agent (Fig. 1b, c).

According to the radiological pattern, the tumors corresponded to neuromas and were located laterally, on both sides of the spinal canal. The patient consulted a neurosurgeon but, for some reason, abstained proposed surgery at that time. The pain syndrome progressed for 1 year, a leg weakness developed, which was the reason to perform control MRI. MRI of the lumbosacral spine (Fig. 1), conducted in January 2014, revealed growth of the intradural lesions. 10.02.14, surgery for removal of the intradural extramedullary tumors at the T12—L1 level was performed. A yard retractor was used to perform an approach, traditional laminectomy was performed, the T12 and L1 vertebral arches were partially resected. A linear incision of the dura mater along the midline was carried out.

Two tumor nodes were visualized on both sides of the cauda equina nerve roots located in the center of the laminectomy window. The tumors were located along the walls of the dural sac and compressed the cone and roots of the spinal cord (Fig. 2a—c). The tumors were of pale yellow color and had an elongated oval shape. Their size was 20×5 mm and 10× 10 mm. The tumor growth zones were identified during isolation from the arachnoid mater. At the resection stage, it seemed that the tumors grew from the denticulate ligaments and had a cystic component (Fig. 2b, c). Based on microsurgical removal, coagulation, and transection of the denticulate ligaments, total resection of the tumors was achieved (Fig. 2d). After completion of the surgery, hemostasis was performed. The dura mater was sutured with a continuous suture. The wound was closed according to the standard procedure.

Histological diagnosis: myxoma

Regression of the preoperative pain syndrome and an increase in the leg strength were observed in the postoperative period. The patient was aroused on the 1st day after the operation and then underwent a course of remedial treatment. The patient was discharged home in a satisfactory condition 8 days after the operation. During the postoperative period, the patient underwent MRI 3 months after the operation that confirmed complete removal of the tumor (Fig. 3).

Discussion

Myxoma of the peripheral nerve sheath is usually a multinodular benign tumor with different severity of myxomatosis of the stroma. According to the literature [1], the tumor is typically localized in the upper extremities, head, neck and chest. The maximum of morbidity of myxoma occurs in the fourth decade of life. The tumor localization in the CNS is a rare phenomenon in world practice. In this case, it is necessary to clearly differentiate this histological tumor type from neuroma and neurothekeoma.

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Fig. 1. Intradural extramedullary tumors at the L1 level.

a — MRI in the T2 mode, sagittal projection; b, c — T1 mode with contrast enhancement; b — frontal projection; c — axial projection.

Fig. 2. Intraoperative pictures of the removal stages of intradural myxoma at the L1 level.

See the text for explanation.

Fig. 3. Control MRI 3 months after surgery.

a — T2 mode, sagittal projection; b, c — T1 mode with contrast enhancement; b — sagittal projection, c — axial projection.
During histological examination, very severe myxomatosis of the stroma was observed, the tumor was covered with a thin fibrous capsule for almost the entire length. Elongated spindle-shaped cells with the eosinophilic cytoplasm and small nuclei were located relatively rarely in the myxomatous extracellular matrix, the nuclei had the distinct chromatin, no mitotic division figures were observed. No structures, typical for neuroma, such as the Verocay bodies and the Antoni A and B patterns, were not detected. An immunohistochemical analysis revealed the expression of S100 protein, type IV collagen and Vim in tumor cells, and CD34 mainly in the vessels. The expression of smooth muscle actin, Des, and EMA was negative (Fig. 4, 5).

Based on the performed analysis, the morphological pattern was evaluated as myxoma of the nerve sheath.

Single multinucleated giant cells and mitotic division figures were detected rarely enough. The tumor cellularity was variable. The differential diagnosis of myxoma and neuroma with myxomatosis of the stroma was required during the examination. The distinctive feature of neuroma is the presence of their typical structures — Verocay bodies. Unlike myxoma, neurothekeoma is a moderately cellular tumor with a less severe myxoid component. Cells are round or oval, more polymorphic. Among them, multinucleated giant cells are more predominant. At the microscopic level, they have pronounced lobularity. The immunohistochemical features of myxoma, like neuroma, are presented by the expression of S100 protein. Neurothekeoma, unlike myxoma and neuroma, does not express this protein. The epithelial membrane antigen EMA may focally be present in myxoma of the nerve sheath, while it is lost in neurothekeoma. The same applies to the expression of type IV collagen and laminin. Vimentin (Vim) is rather highly expressed in both tumors.

M. Yamato et al. [3] used Schwann/2E monoclonal antibodies. The feature of these antibodies is their ability to interact with the nuclei and cytoplasm of Schwann cells and myelin of the peripheral nervous system and to remain intact during the interaction with cells of the central nervous system. Therefore, the authors, in the course of identification of foci of the interaction between the antibodies and the target in the tumor, believed that the tumor starts from the peripheral nerves. This fact, apart from histological and immunohistochemical analyses confirmed that the tumor was myxoma of the peripheral nerves [3].

Despite the fact that myxoma is a tumor of the dermal origin, there are reported cases of the tumor localization in the spinal canal [3, 4]. The spinal nerve root compression was caused by the tumor capsule. The clinical picture depended on the topographic anatomical location of the tumor. For example, the tumor often manifested with a pain syndrome, sensory and motor disorders [5]. Differential diagnosis, based on the MRI data, is complicated due to the fact that the radiological pattern is similar to that for meningiomas, neuromas, neurofibromas, and neurothekeomas [6]. Therefore, the definitive diagnosis is possible only after the biopsy.

**Conclusion**

Patients with the verified diagnosis of myxoma need a further careful examination, because this tumor is characterized by generalization of the process with the development of nodes of different localization as well as a relapsing course.
REFERENCES


Commentary

In the article, the authors describe a clinical case of treatment for myxoma of the intradural localization. It is worth noting that similar publications in the literature are very rare, which certainly emphasizes the uniqueness and value of this publication. The detailed medical history, data of clinical and instrumental analyses, and features of the surgery with illustrations are provided in details. Next, the literature data on the progression features of myxomas of the central nervous system are presented. The authors together with pathologists conducted the histological and immunohistochemical analysis of the material. Issues of the differential diagnosis are discussed. In this work, the authors demonstrated a successful example of surgical treatment with a good long-term outcome for myxoma of a rare localization. It should be noted that this article introduces myxomas of the central nervous system, which are rare pathology, in terms of the differential diagnosis of extramedullary tumors of the spinal cord and recommends a plan of further procedures for the neurosurgeon upon detection of this disease.

E.R. Musaev (Moscow, Russia)
A Recommended Protocol for Treating Acute Complicated and Uncomplicated Spinal Injuries in Adult Patients (Association of Neurosurgeons of Russia). Part 1

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Keywords: traumatic injury, spine, spinal cord.

Spinal injuries amount to 3—5% of all closed trauma and to 5.5—17.8% of injuries affecting the musculoskeletal system. Patients with acute spine and spinal cord injuries (SCI) constitute 2—3% of all patients admitted to neurosurgery departments. In 40—60% of patients, SCI are coupled with damage to other organs and tissues.

1. Classification of injuries to the spine, spinal cord and other neurovascular structures of the spinal canal

There are three types of injuries: 1) uncomplicated spinal cord injuries (with no injury to neurovascular structures of the spinal canal); 2) spinal cord injuries (with no injury to the spine); 3) spine and spinal cord injuries (a combination of injuries to the structures of the spine and neurovascular structures of the spinal canal). The classification outlined below includes all types of injuries to the spine and spinal cord.

Classification of spine and spinal cord injuries

According to the injury type:
1. Isolated SCI
2. Complex SCI
3. Combined SCI

According to the period:
1. The acute period (the first 3 days)
2. The early period (from 3 days to 1 month)
3. The late period (after 1 month)

According to the degree of penetration into skin and dura mater:
1. Closed
2. Open
3. Penetrating

According to nature of the spine injury:
1. Stable
2. Unstable

Injuries to the spinal column, classified according to the injury mechanism:
1. Compression (type A)
2. Distraction (type B)
3. Rotation (type C)
4. Stab (type K)
5. Gunshot and blast (type O)

According to the type of spinal injury:
1. Spine contusion
2. Fractures of vertebral bodies
3. Dislocation of vertebral bodies
4. Self-fixing dislocation of a vertebral body
5. Damage to the capsular-ligament system of the functional spinal unit
6. Rupture of an intervertebral disc

According to presence of an injury to neurovascular structures of the spinal canal:
1. Uncomplicated (with no injury to the spinal cord and spinal nerves)
2. Complicated (with an injury to spinal cord and/or spinal nerves)

According to the type of injury to neural structures:
1. Spinal cord concussion
2. Contusion of the spinal cord and/or nerve roots
3. Compression of the spinal cord and/or nerve roots
4. Partial rupture of the spinal cord and/or spinal nerves
5. Full anatomical rupture of the spinal cord and/or spinal nerves

According to the nature of compressing substrate:
1. Bones or bone fragments
2. Subdural hematoma
3. Epidural hematoma
4. Intracerebral hematoma
5. Traumatic disc herniation

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Spinal injury grades

<table>
<thead>
<tr>
<th>Injury grade</th>
<th>Number of affected columns</th>
<th>Vertebral dislocation</th>
<th>Angular deformity of the spine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Less than 25%</td>
<td>&lt;11° cervical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;40° thoracic</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;25° lumbar</td>
</tr>
<tr>
<td>3</td>
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<td>&gt;40° thoracic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;25° lumbar</td>
</tr>
</tbody>
</table>

6. Foreign body

According to the localization:
1. Cervical spine injuries
2. Thoracic spine injuries
3. Lumbar spine injuries
4. Lumbosacral spine injuries
5. Multiple spinal injuries
6. Multi-level spinal injuries
7. Multiple multi-level injuries to the spinal column.

Nosological diagnosis is more important for selecting a proper treatment strategy than evaluation of the functional status of the spinal cord. Some types of spinal cord injuries are treated conservatively, while others (such as compression of the spinal cord, its major vessels and roots) are treated operatively.

The type of spinal cord injury can often be determined only retrospectively due to spinal shock experienced by a patient in the acute period. The compression of the spinal cord and its major vessels and nerve roots can be subdivided into acute, early and late ones.

Acute compression occurs at the time of injury as bone fragments, traumatic disc herniations, damaged ligamentum flavum, dislocated vertebral structures (in case of dislocations and fractures), and foreign bodies (knife fragment, bullet, etc.) penetrate into the spinal canal.

Early compression, which occurs within 30 days after the injury, can be caused by an epidural or intracerebral hematoma, progressing uncontrolled brain edema, secondary displacement or worsening displacement of vertebrae, bone or cartilage fragments, subdural hygroma.

Late compression can develop several weeks, months or even years after the injury as a result of osteochondral accretion or cicatricial adhesions in the spinal canal and formation of tension cysts.

An injury to two or more adjacent vertebral bodies and/or intervertebral discs is classified as a multiple injury to the spinal column. An injury to two or more non-adjacent vertebral bodies and/or intervertebral discs is classified as a multi-level injury to the spinal column. Multiple vertebral fractures at one level can occur simultaneously with multiple injuries at another level. This type of injury is referred to as a multiple multi-level injury of the spinal column. This distinction has important practical implications. An injury to two or three adjacent vertebrae requires different volume of surgery to be performed in the affected region and may affect the choice of fixation methods and approach options. An injury to vertebral bodies at different levels, even within the same section of the spine, requires a completely different approach to treatment.

The classification scheme for thoracic and lumbar spine injuries is based on pathomorphological criteria and the injury mechanism [47]. There are three types of injuries: A, B and C. Each type is further divided into three groups and each of those contains three subgroups with specific types of damage to vertebral bodies. The injury severity progresses both from the type A to type C and within each type and subgroup. The types of injuries depend on the fundamental mechanisms acting on the spine: compression, distraction (tear of the anterior or posterior segments of the spine as a result of pressure applied to the opposite side of a vertebra) and axial torque.

Type A injuries accompany compression traumas resulting in stable wedge compression fractures (A1), stable and unstable split fractures (A2) and unstable burst fractures of vertebral bodies (A3).

Type B injuries result from a combination of compression and violent distraction (rupture) of the anterior or posterior region of a vertebral body; they may include flexor or extensor fracture-dislocations that can be accompanied by spinal cord compression.

Type C injuries result from a combination of violent torsion (rotation) with compression and distraction of vertebral elements. These most severe spinal injuries are accompanied by rupture of all three vertebral columns and varying degrees (from C1 to C3) of spinal canal deformation (Appendix 1).

We have amended the classification scheme proposed by F. Magerl et al. (1994) to include two other types of injuries to the spinal column: stab (type K) and gunshot and blast (type O) injuries. gunshot injuries to the spine are usually classified according to Kosinskaya (5 types). In peacetime, the incidence of gunshot and stab injuries (caused by knives, sharp objects, crossbows, and other rarer tools, as well as wounds caused by combat and the so-called non-lethal weapons (“Osa”, “Makarych”, etc.) varies from 5 to 8% of all SCI.

Injuries to C1 and C2 vertebrae are to be classified separately. For example, injuries to C2 odontoid process are divided into three types (according to L. Anderson and R. D’Alonzo, 1974) [30] (Appendix 2) (Fig. 2). Type 1 fractures do not require surgical treatment. Type 2 and 3 fractures are usually treated operatively. There are fracture-dislocations of C2 (so-called hangman’s fracture), which involve fracture of C2 pars interarticularis on both sides and a rupture of C2—C3 disk with anterior dislocation of C2. Such fractures require surgical treatment. Appendix 3 (Fig. 1, 3) lists possible fractures and dislocations of C1 vertebra.
The Subaxial Injury Classification (SLI) proposed by A. Vaccaro et al. [51] is the most appropriate classification scheme for injuries to the cervical spine on subaxial level. This scale allows elucidation of treatment strategy based on the type of the injury to vertebral bodies and disco-ligamentous complex and the neurological examination data: less than 4 points, conservative treatment; 4 points, at the discretion of an attending physician; more than 4 points, operative treatment (Appendix 3).

The classification system proposed by F. Dennis [35] is based on the concept of three mechanical columns and is used to assess injury stability. The anterior column includes the anterior longitudinal ligament, the anterior two-thirds of a vertebral body, annulus fibrosus and disc. The middle column consists of the posterior one-third of a vertebral body, annulus fibrosus, disc, and posterior longitudinal ligament. The posterior column consists of pedicles, arches, articular, transverse and spinous processes, supraspinous and interspinous ligaments, ligamentum flavum and intervertebral joint capsule. An injury to the middle column or 2—3 columns is considered to be unstable and requires mandatory stabilization.

P. Mayer et al. (1996) developed an algorithm for surgical treatment of vertebral fractures and spinal cord injuries (see Table) which is based on the classification schemes earlier proposed by F. Magerl and F. Denis and take into account: (a) the number of injured columns; (b) degree of vertebral displacement relative to each other; (c) injury to the anterior section of the spine and degree of angular deformation; (d) loss of vertebral body height by more than 50% (in the late period there is a high risk of onset of neurological disorders); (e) compression of the spinal canal (narrowing over 15—25% is an indication for decompression).

If at least one grade 3 criterion is met, decompression of the spinal cord and rigid stabilization of the vertebrae are compulsory.

If no grade 3 criteria are met, but at least one grade 2 criterion is met, such spinal injuries require stabilization and, in some cases, decompression of the spinal cord.

If the spinal injury does not meet any grade 2 or 3 criteria, the conservative treatment is indicated.
Appendix 1

Types of vertebral injuries (according to the classification scheme proposed by F. Magerl et al., 1994) [47]
Appendix 2

Types of the upper cervical vertebral injuries

Fig. 1. Schematic representation of a burst (Jefferson) fracture.
The arrows indicate the direction of traumatic impact rupturing of the atlas ring under axial load (a, b). The sideways separation of the atlas halves (c, d) provides conditions for insertion of the odontoid process into the foramen magnum.

Fig. 2. Possible fractures of axis odontoid process (L. Anderson and R. D’Alonzo) [30].
a — apex, type 1; b — cervix, type 2, c — through the body of the axis, type 3.

Fig. 3. Possible atlas dislocations.
a, b — anterior through ligaments; c — anterior through odontoid; d — posterior through odontoid.
Appendix 3

Sub-axial injury classification of surgery tactics [51]

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injury to vertebral body:</strong></td>
<td></td>
</tr>
<tr>
<td>no damage</td>
<td>0</td>
</tr>
<tr>
<td>compression fracture of a vertebral body</td>
<td>1</td>
</tr>
<tr>
<td>compression-splintered (burst) fracture of a vertebral body</td>
<td>+1=2</td>
</tr>
<tr>
<td>distraction injury (subluxation, hyperextension)</td>
<td>3</td>
</tr>
<tr>
<td>rotation and/or translation injury (dislocation, fracture-dislocation, unstable comminuted fracture of the vertebral body and other more severe types of compression-flexion injury)</td>
<td>4</td>
</tr>
<tr>
<td><strong>Injury to the intervertebral disc and ligamentous apparatus:</strong></td>
<td></td>
</tr>
<tr>
<td>no injury</td>
<td>0</td>
</tr>
<tr>
<td>indirect signs of injury (increased interspinous gap, signal changes on MRI)</td>
<td>1</td>
</tr>
<tr>
<td>disruptions (expansion of a intervertebral disc, subluxations and dislocations in the intervertebral joints, kyphosis)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Neurological status:</strong></td>
<td></td>
</tr>
<tr>
<td>normal</td>
<td>0</td>
</tr>
<tr>
<td>root injury</td>
<td>1</td>
</tr>
<tr>
<td>complete cord injury</td>
<td>2</td>
</tr>
<tr>
<td>incomplete cord injury</td>
<td>3</td>
</tr>
<tr>
<td>continuous cord compression</td>
<td>+1</td>
</tr>
</tbody>
</table>

Interpretation of the SLIC scale data

<table>
<thead>
<tr>
<th>Recommended treatment strategy</th>
<th>Total points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative (stiff collar, halo-machine, etc.).</td>
<td>&lt;4</td>
</tr>
<tr>
<td>At the discretion of a surgeon</td>
<td>4</td>
</tr>
<tr>
<td>Surgery (decompression and stabilization)</td>
<td>&gt;4</td>
</tr>
</tbody>
</table>

Explanatory drawings for SLIC scale

Fig. 1. a — simple compression fracture is identified by a loss of the vertebral height at the level of the anterior column; b — compression fracture may be accompanied by disruption of the disco-ligamentous complex; c — laminar fractures; d — undisplaced lateral mass and facet fractures are classified as compression injuries; e — axial view of lateral mass fracture with vertical fracture line.
Fig. 2. a — burst injuries result from more severe compression impact and are characterized by fracturing through the entire vertebral body; b — midsagittal cervical spine view of a burst fracture.

Fig. 3. a — distraction fracture is identified by anatomic dissociation in the vertical axis, which may affect both anterior and posterior structures of the spine; b — are often accompanied by bilateral vertebral dislocation; c — hyperextension may lead to rupture of intervertebral disk and posterior fractures; d — distraction with flexion will result in posterior ligamentous tearing.

Fig. 4. a — translation/rotation fracture is identified by horizontal displacement of the superadjacent vertebra relative to the subadjacent vertebra; b — translation in the sagittal plane with complete discoligamentous disruption; c — translation with a pedicle fracture or facet fracture; d — rotation is best illustrated with an axial projection.
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Clinical Reasoning of a Neurosurgeon

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Keywords: neurosurgery, philosophy, reasoning.

Modern methods of non-invasive neuroimaging allow us to see almost everything that happens in the brain from anatomical and, in many ways, functional perspectives [1, 8]. Impressive technological progress has led to a breakthrough in study and diagnostics of the central nervous system disorders.

The technologization of neurosurgery provides great advantage for the specialists and, more importantly, their patients. However, successful introduction of non-invasive imaging and minimally invasive neurosurgery into daily practice has revealed their inherent dangers [2]. These dangers cannot be ignored and must be confronted. Negative aspects of the technologization of neurodiagnostics manifest in the threats of:

1) atrophy of clinical reasoning and addiction to technology;
2) loss of neurological examination skills (hyposkillia), medical incompetence and complete reliance on “pictures” for diagnostics;
3) disengagement between a physician and a patient and disregard for the patient’s personality.

Neurosurgery is experiencing a technological boom and a crisis of clinical reasoning and ethics. The problem is global, affecting all branches of medicine, and is certainly not limited to Russia [4, 9, 11]. A cardiologist B. Lown named his book “Lost Art of Healing” [11]. He is echoed by a neurosurgeon L. Kessler [9] in “In a High Tech Age, is Clinical Judgment a Lost Art Form?”

We hope to be understood correctly. The authors are not reactionary. State-of-art technologies are absolutely essential for modern neurosurgery and modern diagnostics is unthinkable without neuroimaging. However, indiscriminate application of such logic as “there is no need to think about it since a picture will reveal everything” is fraught with dangerous consequences.

The only reliable antidote to destructive processes in modern neurosurgery is neurosurgeon’s clinical reasoning, i.e. systematic approach to resolving issues of diagnosis and therapy.

Definition

What is clinical reasoning? This term is used very often, but its exact definition is not normally provided. There is neither formal nor descriptive definition of “clinical reasoning” in the Big or the Small Medical Encyclopedia, the Encyclopedic Dictionary of Medical Terms or in any other Russian or foreign publication. As if the term represents a well-known and self-evident notion. We will try to fill this gap.

It is obvious that clinical reasoning essentially follows the same rules as regular thought process by a man. It implements the highest form of reflective activity of the brain and human cognition: thought operations, such analysis and synthesis, comparison and discernment, judgments and inferences, abstraction, generalization, etc., but they are fundamentally based on specific medical knowledge and are aimed at solving problems associated with diagnostics, prognosis and choice of treatment strategy.

Taking this into account, we believe that physician’s clinical reasoning is his ability to capture, analyze and synthesize all the available data on a patient, which are obtained by various means, while simultaneously comparing them with earlier observations, book knowledge and intuition (experience) in order to establish an individual diagnosis and prognosis and select proper treatment strategy [4].

Clinical reasoning and diagnosis

A physician will always choose the shortest and the safest path to a diagnosis (primarily in the best interests of a patient) and this path will, undoubtedly, include non-invasive imaging techniques. Does this imply that technicism represents a threat to clinical reasoning? Yes, if it replaces the reasoning with pictures. No, if it enriches the reasoning in visualization of a pathology and adequate interpretation of the images.

The problem boils down not to the replacement of clinical reasoning with instrumental findings, but to opening clinical reasoning to adequate use of such data in the interests of diagnosis and treatment and, ultimately, a patient.

Despite the impressive advances in instrumental methods of research, clinical examination remains the enduring fundamental principle of diagnosis. And any technology can only be subordinate to it.

In a significant number of observations the apparent contrast between certainty, visual brightness and high precision of neuroimaging and vagueness, ambiguity and subjectivity of clinical data is staggering.

Yet for all its outstanding achievements no instrumental method can fully encompass an individual diagnosis. For ex-
amplify, we can observe an indubitable evidence of a tumor by using magnetic resonance imaging or CT scanning and discern all its features from the images, but we still cannot confirm indications or contraindications for any type of surgery without taking into account such basic truths as patient’s age, history of complications, status of his internal organs, degree of mental disturbance and disorders of vision, speech and other functions, and, finally, the clinical phase of the disease.

In contrast to instrumental techniques which successfully address extremely important aspects of diagnosis, clinical examination deals with a unique individual pathology of the organism as a whole, with peculiar features of its compensatory processes; so a clinician does not deal with the disease only, but also with a man who copes with the disease in his own way. Diagnostics is always a creative process.

It may seem that mastering clinical examination, which is based on such routine methods as questioning and examining a patient, is much easier than mastering sophisticated instrumental techniques. However, it is not the case. Despite easy technical availability of neurological examination, one needs many years of practical experience to become an experienced doctor with fully developed clinical reasoning.

The illusion that techniques and technologies are self-sufficient in recognition of nervous system pathologies is both erroneous and dangerous.

Nowadays many doctors proclaim the superiority of technology over clinical examination. After all it is much easier to switch a CT or MRI machine on and see a tumor or a hematoma rather than to spend time talking to a patient, performing a thorough neurological examination and drawing intellectual comparisons. However, only clinical reasoning can impart the relevant meaning to these magnificent pictures. Here are some examples.

Despite the use of all modalities of a 3T magnetic resonance instrument, it was only possible to identify the nature of a pathology and the cause of temporal paroxysms by noticing that a 23-year-old patient had congenital varicose veins on his left wrist and left calf and, therefore, he had a rare form of brain pathology, basal veins varicose of the left temporal lobe (Fig. 1).

In another case a differential diagnosis of a 30-year-old patient indicated either an intracerebral tumor or a late suppuration of cerebral cicatrix; the truth was revealed by collecting his history: 17 years ago the patient sustained a penetrating wound from a barrel of a self-made weapon (Fig. 2).

Clinical reasoning and treatment strategy

Clinical reasoning is as important for selecting a treatment strategy as it is for elucidating the diagnosis. Clinical reasoning is based primarily on scientific knowledge and takes into account pathogenesis and sanogenesis of a pathology; it resolves difficulties in choosing an adequate method of treatment.

For example, a normotensive hydrocephaly with progressing disorders of cognitive and memory processes is an indication for shunting of the enlarged lateral ventricles in order to drain the CSF out of the craniovertebral space. However, without understanding the etiology and pathogenesis of the normotensive hydrocephaly this seemingly correct treatment strategy might fail to help and also harm a patient. If the hydrocephaly with ventriculomegaly is active, i.e. due to impaired resorption of cerebrospinal fluid (in particular as a result of a traumatic brain injury) shunting is life-saving. However, if the same normotensive hydrocephaly with ventriculomegaly is passive, i.e. due to CSF compensating for decreasing volume of the brain matter caused by its atrophy (as a result of age or pathology), shunting is, at best, pointless.

Clinical reasoning that takes into account all the circumstances helps to avoid such formally indicated, but in fact contraindicated surgeries. Here is an example.

A 20-year-old girl had been operated on for growing hydrocephalus as a child; ventriculoperitoneal shunting had been performed. She grew up normally afterwards and was successful at school. An MRI scan performed 3 years ago “just in case” revealed bilateral chronic subdural hematomas. A closed external drainage was performed at the Burdenko Neurosurgical Institute. However, one year later an MRI scan revealed the recurrence of hematomas in their original positions (Fig. 3). The girl’s mother asked for a surgery. The patient herself, however, had no complaints. She was one of the best students in a drama school, in which she enrolled after her graduation.

Neurological examination revealed no symptoms. The only abnormal measurement was the circumference of the head, 64 cm, but it has been the case since she was a child. The MRI, however, clearly showed two chronic subdural hematomas.

The pictures “asked” and even “shouted” for the hematomas to be removed. The family history and clinical examination suggested that it must not be done. Why? An active shunt prevents the brain from completely filling its cranial cavity, which has been expanded as a result of hydrocephaly. Nature abhors a vacuum. Therefore, the chronic subdural hematomas were formed by the ex vacuo mechanism to fill the void and they “peacefully” coexist with brain hemispheres, without interfering with their normal function or causing any pain. A steady balanced symbiosis has been achieved between the...
shunt, the hematomas and the brain. To touch the shunt or
the hematomas was to initiate pathological reactions, which
would be difficult to manage. Therefore, follow up was pre-
ferred to a surgery.

Another example of clinical reasoning is given below.

Patient B., 29 years of age. In 2011 he underwent a surgery
to remove a glioblastoma in the right frontal lobe. He then
received a course of radiation therapy. One and a half years
later the overall level of his health was satisfactory with under-
lying rare epileptic seizures. However, a spiral computed to-
mography (CT) check-up revealed a hyperdense tumor; the
tumor’s broad side was adjacent to a bone in the area of the
former surgery theater (Fig. 4). A radiologist diagnosed a ra-
diation-induced meningioma, while a neurosurgeon took a
seemingly reasonable decision to postpone the surgery. How-
ever, this decision did not take into account the fact that con-
tinued growth of a glioblastoma can proceed in the cortical
direction through postoperative and postradiation scarring.
Therefore, neither the surface localization of the tumor nor its
hyperdensity on SCT scans can be decisive arguments in favor
of a radiation-induced meningioma. The surgery confirmed
the neurologist’s opinion of the glioblastoma relapse.

Clinical reasoning is necessary to select a proper treatment
strategy even in case of indisputable diagnosis, because one
has to take into account not only direct indications for a sur-
gery, but also potential changes in patient’s quality of life af-
Afterwards.

Let us take for example a benign intramedullary extended
tumor of the cervical-thoracic spinal cord in a 40-year-old
woman with a past history of very moderate blackouts, which
were a nuisance, but did not prohibit full employment and
normal family life. The diagnosis was confirmed by MRI. What
should be done? A tumor was detected. There is material to be
cut out and therefore it is necessary to performed a surgery,
and the sooner, the better. One certainly should not wait until
the patient is incapable of walking... However, based on the
characteristic features of the tumor’s spread the patient’s quali-
ity of life was bound to get worse even in case of a successful
surgery, because in this particular case even an electrophysi-
ologically controlled surgery could result in limb paresis. So,
should we dramatically speed up what may occur spontane-
ously many years into the future? Is not it better to observe,
thereby preserving the patient’s quality of life at a satisfactory
level?

**Fig. 2.** MRI of 30-year-old patient Sh., epileptic and cephalgic syndromes.

Late suppuration of cerebral cicatrix (a, b).

**Fig. 3.** MRI of 20-year-old patient B., clinically asymptomatic bilateral chronic subdural hematoma after ventriculoperitoneal shunting (a, b, c).
Evaluation of all parameters of the diagnosis and prognosis of patient’s quality of life, his profession, his family and social status, his personality and all other factors may help to choose an appropriate treatment strategy. In this mesmerizing masquerade of pictures any image can only reveal its true meaning through clinical reasoning.

Clinical reasoning and prognosis

The incidence of particular disease symptoms has previously been characterized as “more often” or “less often”, “more” or “less”, etc. Now a clinician is armed with reliable statistics. It is good news. A figure is always more exact than a word. And yet statistical data — a quantitative characteristic — on an isolated clinical manifestation cannot replace collection of clinical data on a disease as a whole, which is a qualitative synthetic notion. This applies not only to the diagnosis, but also to prognosis.

Even the most flawless statistics can lead to absurdity if it prevails over clinical reasoning. Here are some examples.

The $r$ and $p$ values are used to evaluate forecast reliability and are calculated based on the incidence of a trait. The more often a trait occurs, the more significant it is. Taking this, seemingly indisputable, notion into account a serious study was conducted on chiasm-sellar region tumors. One of the parameter used in the study was the “state of alertness”. Examination of the results revealed significant difference between “stunned” and “comatose” state for prediction of an outcome. “Stunned” had a much greater weight for poor prognosis than “comatose”. Yet, a formal application of statistics indicated exactly the opposite.

Authors of a published article found that lack of “headache” complains in patients with chronic subdural hematomas was associated with more frequent recurrence of hematomas during the postoperative period. They did, therefore, concluded that complains of “headache” in patients with chronic subdural hematomas are associated with more positive prognosis, since it allows predicting a recurrence-free postoperative period with greater confidence. Clinical reasoning would have never allowed such a blind obedience to statistics.

Ask any neurosurgeon: in case of acute intracranial hematoma, is “lucid interval” a good or a bad sign for prognosis and the quality of life outlook? The answer would be the same: it is “undoubtedly a good sign, since it indicates that besides hematomas there are no other concomitant severe brain damage.”
A scientist from St. Petersburg performed a statistical analysis of extensive data on mortality in patients with epidural and subdural hematomas. The numbers proved that those patients who had experienced a lucid interval were significantly more likely to die that those who did not have a lucid interval after a traumatic brain injury. Therefore, the conclusion states, a lucid interval in acute and subacute meningeal hematomas is associated with poor prognosis. It is not difficult to imagine what had actually happened during the research: patients with intracranial hematomas in critical condition were operated on immediately upon admission to city hospitals, while those with lucid intervals had been put under observation until they fell into a coma; valuable time had been lost and such delayed surgeries naturally had higher mortality rate.

It would have been possible to easily avoid the errors presented here as well as many other dangerous and absurd predictions had clinical reasoning been employed.

Undoubtedly, the statistics is necessary and important for making prognosis. However, we should always remember that in case of, in particular, severe traumatic brain injuries any mathematical calculations can only provide a highly satisfactory overall prognosis. Any individual prognosis is impossible without clinical reasoning.

Clinical reasoning and preventive neurosurgery

Neuroimaging made it possible to accidentally discover congenital and acquired pathologies of the brain and spinal cord in living patients and it started to happen quite often. Nowadays you can no longer simply declare the presence of such pathologies posthumously; you need to find solutions, some of which may turn out to be life-saving, while others may become disastrous.

Only clinical reasoning allows you to see through a picture of a pathology to find a non-suffering patient behind it and to use your medical expertise to imagine future threats and to decide whether to help him or not and how and when to do it. When performing a surgery on asymptomatic brain pathology a neurosurgeon should question what his action would do for, I emphasize, a non-suffering patients. Actions that ensure healthy future are good, while those that make a man suffer are evil, which has been actively, albeit reluctantly, inflicted on him by preventive surgery. Some examples are presented below.

One of the authors gave a consultation to one of our greatest chess players, who was accompanied by a sports doctor. The player had been preparing for the upcoming World Chess Championship and a MRI made on the occasion of a headache revealed significant cerebrospinal fluid cyst in the left temporal region (Fig. 5). The patient had been sent to the Burdenko Neurosurgical Institute for surgery. However, after examining the patient, we have concluded that “while a substrate for surgery is present, the cyst is congenital and clinically non-aggressive. The brain “has got used” to it. There is complete compensation. Therefore, there is no need for any action, since an action is incomparably more dangerous than inaction.” We explained it to the chess player and wished him victory in the upcoming match. Our patient with the brain cyst became a World Chess Champion.

The situation does, however, become more complicated when accidental findings reveal acquired pathological processes, first of all tumors. In this case one must consider not only the degree of clinical compensation, but also the nature and localization of focal lesion and should decide on the feasibility (to the benefit of a non-suffering patient) of dynamic follow-up (for example, in case of small meningeomas or asymptomatic diffuse benign gliomas) or on the necessity of a planned surgery, in such cases as large tumors of pellucid septum shown in Fig. 6, when a possibility of quick deterioration of clinical compensation has been obvious.

Arguably, even a more difficult decision has to be made when accidental screening discovers an arterial aneurysm or an arteriovenous malformation of cerebral vessels. The patient feels no pain, displays no symptoms and leads an absolutely normal life. However, an aneurysm is a “bomb” that can explode at any moment and result in a critical condition. Does one have to perform a preventive surgery or is it more prudent to wait for the “explosion” to happen? It is not a clear-cut
issue, for the “explosion” may not take place at all and a surgery is always fraught with complications.

One day a young woman, a college teacher from St. Petersburg, was admitted to our hospital. Her sister, an identical twin, suddenly developed a severe subarachnoid-parenchymal hemorrhage due to, as it turned out, a rupture of saccular aneurysms. All attempts to save her life failed. The other sister thought that she had the same aneurysm. Indeed, angiography revealed an aneurysm in the same vessel, which had been affected in her sister (Fig. 7, upper images). The patient insisted on a surgery.

The “bomb” has been successfully disarmed (Fig. 7, bottom images).

However, for all the indisputable benefits of performing a surgery on an organism that had not been weakened by a disease, there are still potential risks of various complications. The staff of the Burdenko Neurosurgical Institute have performed preventive surgeries on more than 500 patients with saccular arterial brain aneurysms discovered by chance. All patients signed informed consent forms. They were saved from a very real danger of life-threatening rupture of the aneurysm. However, 3% cases resulted in incapacitating complications [6]. These figures are consistent with literature data on both direct [7, 14, 17] and endovascular [12] interventions in case of unruptured aneurysms. The percentage is low, but behind it there are human lives. There is a similar story for arteriovenous malformations.

Let us take for example pronounced stenosis of internal carotid artery, confirmed by duplex scanning, with asymptomatic clinical presentation and fully compensated cerebral circulation. Should one wait for signs of trouble or anticipate them by performing preventive stenting? In his review H. Steiger [15] points out that the average incidence rate of benign intracranial tumors, aneurysms and carotid stenosis in the European and North American populations is ca. 1% for each of these types of pathology. In Japan the incidence rate of arterial intracranial aneurysms is even higher [16]. The incidence rate of asymptomatic CNS pathologies increases with age [13, 18]. Large-scale screening using non-invasive imaging techniques to detect asymptomatic intracranial aneurysms and carotid stenosis and subsequent preventive surgeries may be justified, provided that the risk of associated disability is very low.

Preventive neurosurgery, just like any other preventive surgery, should be guaranteed. A clear rationale is a must.
In particular, certain features of localization of an aneurysm or an arteriovenous malformation, their size, patient’s family history and neurosurgeon’s experience are very important. We emphasize that preventive surgery should be performed by high-level specialists. And, undoubtedly, in addition to neurological considerations the decisive factor in favor of a surgery must be the patient’s consent, his understanding and will.

Preventive surgery on an asymptomatic pathology is even greater responsibility than treatment of a clinically manifested disease.

In case of preventive neurosurgery the diagnosis is indeed “pictorial”; however, the decision on treatment strategy should be both clinical and philosophical.

**Clinical reasoning and contradictions of modern neurosurgery**

Technological advances in modern neurosurgery have given rise to new contradictions within the field [3]. Here are some of them:

— the sanctity of life vs. the quality of life;
— professional duty of a doctor vs. commercial temptations;
— fetishization of pictures and disregard for patient’s history vs. clinical examination;
— logic of common sense vs. logic of scientific knowledge;
— saving lives vs. organ transplantation;
— extensive technical capabilities vs. limited financial resources.

We will explain how clinical reasoning helps to resolve these and other contradictions by using one of them as an example: common sense vs. scientific knowledge.

The notion of “common sense” is clear to everyone. To act according to “common sense” is to carry out an obvious, proven and effective action aimed at removing of an adverse event. In clinical practice doctors are often guided by “common sense”, which is, of course, grounded in their professional knowledge.

However, it is not uncommon for “common sense” in medicine to be dangerous. The fact is that “common sense”, scientifically speaking, is a linear solution to a problem. And a doctor often deals with tasks that require nonlinear solutions. Paths to a goal that follow the logic of knowledge can provide better results than those following the logic of “common sense.” Here are some examples to back my words.

Chronic subdural hematomas are growing benign encapsulated lesions (Fig. 8), which, unless removed, could result in patient’s death due to compression of the brain and entrapment of its stem. There is a radical solution to the problem: one-stage complete removal of a “blood bag” along with its contents and its capsule by a wide trepanation. This approach had been used for many decades.

However, the brain that has been compressed by a chronic hematoma for a long time cannot quickly recover its former volume, in particular in elderly patients. It creates a serious threat of severe collapse of the brain and various complications, from tense pneumocephalus to recurring bleedings. The radiocative treatment of chronic subdural hematomas has the mortality rate of up to 12—18%. However, the patients who have survived the difficult postoperative period are cured.

Meanwhile, some studies, including those carried out in the Burdenko Neurosurgical Institute, have proven that the main cause of the existence and periodic expansion of chronic subdural hematomas is hyperfibrinolysis of their contents. It is caused by accumulation of fibrin degradation products in the hematoma cavity, at an amount exceeding those observed in the peripheral blood of the same patients by 6—60 times, according to our data. Under hyperfibrinolysis conditions various minor external and internal factors can easily result in macro- and/or microbleeds from defective vessels of a chronic hematoma capsule (Fig. 9).

If this mechanism plays a crucial role in pathogenesis of volume fluctuations of an encysted meningeal hematoma,
then a change in the intrahematoma environment, such as removal of fibrin degradation products, is enough to start sanogenesis.

If that is the case, a minimally invasive approach can be used instead of an open surgery. A hematoma capsule can be punctured through a mini-hole and its content can be washed away with saline.

A closed external drainage system is then installed for a short period of time (1—2 days).

The results exceeded expectations: the mortality rate dropped to 1% (mainly due to extracranial causes in the elderly patients), complications were mostly absent and a significant improvement in patient’s condition and alleviation of focal neurological symptoms normally occurred the next day after the installation of the drainage, which also ensured controlled internal decompression [5]. According to MRI and CT data (427 cases) subdural hematomas and their capsules have been resorbed within 1.5—3 months (Fig. 10).

Long-term post-traumatic basal liquorrhrea is another example. The “common sense” suggests to simply seal the leak. However, this approach has resulted in a huge number of relapses as the ongoing overproduction of the cerebrospinal fluid caused intracranial hypertension and simply “popped” the plug out. The logic of scientific knowledge suggested that it was necessary to create conditions for changing the cerebrospinal fluid flow from an open to a closed circuit simultaneously with a plastic surgery at the skull base. This has been achieved by a temporary drainage of the cerebrospinal fluid for 1.5—2 weeks via lumbar drainage. Over this period, the CSF system had time to regroup; therefore, the effect of an endoscopic or intracranial surgery persisted.

It is obvious that in the upcoming decades medicine will undergo radical changes as a result of elucidation of genetic and molecular mechanisms of disease pathogenesis and sanogenesis using nanotechnology and other innovations. Fundamentally different approaches to treatment and, most importantly, to healing of various diseases will follow. However, the entrenched traditional notions that have become “common sense” will become a paradigm: on the one hand, they will become a protection against hasty, not time-tested techniques and practices, while on the other hand being an obstacle to practical implementation of new evidence-based treatment technologies, which will have passed all the tests. The elimination of these natural contradictions in the development of knowledge should include both the educational process at medical schools, as well as the entire system of postgraduate education and self-education of medical specialists.

The Hippocratic principle of “First do no harm” remains in force and, depending on the situation, it either sides with

Fig. 10. MRI dynamics in bilateral chronic subdural hematoma (CSH).

a—c — upon admission; d—f — 2 months after bilateral closed external drainage; on one side — complete resorption of HSG, on the other — little remnants of HSG.
“common sense” or with the logic of knowledge. This is the art of science-based healing.

**Clinical reasoning and neurosurgeon’s ethics**

The clinical way of seeing to a patient as a suffering human being should be an antidote to the technological approach, in which diseases are treated on their own with no regard to individual characteristics of a person suffering from them, even though those characteristics define features of clinical manifestations of diseases and compensatory processes associated with them. The fact is that a sick person cannot be reduced to his disease, no matter how significant or even fatal it may be for him.

It is natural that visualization of nervous system pathology has become the most important tool for a neurosurgeon, since it offers much stronger evidence for diagnosis than communication with a patient. However, not only does it often ignore personal traits of a patient but also lessens both clinical and psychological attention paid to him, thus leading to a dangerous syndrome of disengagement between a doctor and a patient.

Medical science mainly focuses on the study of signs of a disease and substrates, achieving tremendous success in this field. As a result, a patient is artificially “divided” into a carrier of a disease and an individual, and the latter receives almost no attention. We should always remember that surgery is performed on a patient, not on a picture. The development of high technology should make the role of humanistic principles in a neurosurgeon’s activities more, rather than less, important. Clinical reasoning helps neurosurgeon to develop moral qualities.

**Clinical reasoning and philosophy of neurosurgery**

Philosophy of neurosurgery is its general theory both as a clinical discipline and a neuroscience; it defines the professional outlook of a neurosurgeon and provides the systematic approach and the holistic overview of any neurosurgical situation and any neurosurgical patient. However, according to D. Long [10], the philosophy of neurosurgery has not been formulated so far.

We believe that the philosophy of neurosurgery is implemented in practice through clinical reasoning and conceptual solutions (Fig. 11).

Clinical reasoning of a neurosurgeon, which is based on neuroscience, empathy and technology, allows for individual diagnosis, prognosis and choice of treatment strategy, while conceptual solutions of surgical interventions are based on disease pathogenesis and sanogenesis and define surgery goals, methods and results.

**Conclusion**

Just like any other doctor, a neurosurgeon must be educated in philosophy, methodology and ideology and be fully capable of clinical reasoning in order to avoid becoming a “cog” in the modern medical machine and in order to remain a humane and thoughtful doctor.

We cannot allow neurosurgery to become dehumanized. The founder of cybernetics Norbert Wiener stressed: “render unto man the things which are man’s, render unto computer the things which are computer’s”. Clinical reasoning is a man’s thing, but it knows how to make full use of computer’s and, we would add, technology’s.

A neurosurgeon, just like any other physician, must be not only Homo sapiens, but Homo moralis. Along with clinical reasoning and high technology it is the main condition of humanization of neurosurgery in the XXI century.

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**Fig. 11. Philosophy of neurosurgery tree.**
The readers of our journal are undoubtedly familiar with the scientific work of Professor L.B. Likhterman and with his numerous literary works.

L.B. Likhterman is a skilled writer; his works are characterized by their brilliance, polemical nature and adherence to certain philosophical notions. Even though the article “Clinical reasoning of a neurosurgeon” is written with co-authors, it reflects the thoughts of Leonid Boleslavovich and is written by his hand.

“The role of clinical reasoning” is one of his favorite topics for presentations at conferences and congresses. The “Clinical reasoning of a neurosurgeon” is, to a certain extent, the result of the author’s reflections on this, undoubtedly, very important issue.

The main theme of the article is a fight against “negative consequences of technologization of neurodiagnostics”, which, according to Leonid Boleslavovich, lead to “atrophy of clinical reasoning and addiction to technology, loss of neurological examination skills, medical incompetence and utter reliance on pictures for diagnosis.”

It is certainly a very bold turn of phrase; “utter reliance on pictures for diagnosis” is particularly memorable. Leonid Boleslavovich defines clinical reasoning as “capture, analysis and synthesis of all the data on the patient (history, clinical, instrumental and laboratory data) and its comparison with one’s own, collegiate and book knowledge, based on personal experience and intuition which result in elucidation of individual diagnosis, prognosis and treatment strategies based on systematic approach.” It is challenging, but correct. However, the text of the article makes it clear that L.B. Likhterman equates clinical reasoning to neurological assessment data only.

His numerous comments on the importance of modern imaging diagnosis support this reading. They are, as already mentioned, “addiction to technology”, “pictorial diagnostics” and later “mesmerizing masquerade of pictures”, “fetishization of images”, etc.

A doctor elucidating patient’s diagnosis and indications for surgery must certainly take into account all features of a disease, its clinical manifestations and particular traits of the patient as a person. These are the truths known to every physician and there is no room for debate here.

However, the authors’ disdain for “pictures”, CT, MRI, PET etc. is rather puzzling. One gets an impression that the analysis of “pictures” and incorporation of very important data that these studies provide are outside of the scope of “clinical reasoning.” The examples presented in the article also favor such interpretation.

According to Leonid Boleslavovich, in the first case the proper diagnosis — varicose brain damage — was made only on the basis of the fact that the patient had congenital varicose veins in his wrist and calf. Unfortunately, the example is not convincing because no verification was presented and Leonid Boleslavovich does not mention whether MRI (SW) modes were used, which are specifically designed for the diagnosis of vascular lesions.

The two other cases featuring patients with post-traumatic abscess and continued glioblastoma growth only tell us that an accurate diagnosis by CT or MRI has not been an objective at all. Had such an objective been set, special MRI modes (including spectrography) would have allowed clarifying the nature of the disease with almost 100% accuracy.

All what these examples teaches us is that a doctor (neurosurgeon) must have solid understanding of capabilities of modern diagnostic methods (CT, MRI, PET, etc.) and be able to properly employ them when indicated.
Therefore, it is useful to recall the X-ray diagnostics virtuosi of the past such as M.B. Kopylov and A.B. Kun. M.B. Kopylov, relying only on certain changes in a craniogram, had in many cases been able not only to detect a brain tumor, but also to predict its localization and histology.

The bottom line of the debate is the following: the data provided by modern diagnostic methods should not be treated as mere “pictures”, but as a part of research, which requires equally serious and competent assessment, as does the study of disease history and particular features of neurological symptoms.

In his polemical fervor Leonid Boleslavovich is looking for contradictions in places, where, in fact, none exists.

In the case of the outstanding chess player and accidental discovery of congenital arachnoid cysts, the decision not to operate on a person who is normal in all respects is not an illustration of the power of “clinical reasoning”, but a common strategy of any physician in case of discovery of such pathology. The strategy that has been developed as a result of enormous clinical experience is not to interfere in the absence of clinical manifestations. Almost identical arguments can be applied to the case of treating chronic subdural hematomas.

The preference of hematoma puncturing over removal of hematoma and its capsule is not based on the all-conquering power of “clinical reasoning”, but on the vast neurological and neurosurgical clinical experience.

In my opinion “contradictions between the logic of common sense and logic of scientific knowledge” look strange and far-fetched.

Common sense cannot be very sensible unless it is based on knowledge and experience. I am sure that a layman, even a highly educated person capable of logical thinking, cannot and should not be an expert in such a distant scientific field as medicine. Such attempts are called amateurism rather than common sense.

Despite my disagreement with Leonid Boleslavovich on a number of issues and my critique presented here, I consider his article to be provocative, but important, because it forces us to reflect once again on such issues as the doctor—patient relationship, physician’s ability to use scientific achievements and his own experience in diagnostics and selection of appropriate treatment.

A neurosurgeon is a clinician and therefore he must think clinically or to put it even simpler: a doctor should know a lot and be skilled in using this knowledge.

A.N. Konovalov (Moscow, Russia)
Scoliotic Spinal Deformity in Combination with Craniovertebral Junction Pathology in Children and Adolescents

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This literature review focuses on the clinical and pathogenetic aspects of the relationship between Chiari I malformation (CM1) and scoliosis. The concept of development of clinical presentation of CM1 that occurs concomitantly with scoliosis is considered from the viewpoint of both CSF circulation disorders and vascular pathology of the craniovertebral junction. The role of the posterior atlantooccipital membrane is evaluated. Case reports demonstrating the risk factors for scoliosis progression in patients with CM1 are presented.

Keywords: Chiari I malformation, scoliosis, decompression of the posterior cranial fossa, posterior atlantooccipital membrane.

Epidemiological studies of spinal deformity show that the prevalence of scoliosis in children ranges from 3.4 to 15%. According to different authors [1], progression to severe scoliosis is observed in 10—20% of cases. The prevalence of scoliosis is 0.04 per 10,000 population according to appealability data. According to medical screening data, this number rises to 18.2 [2].

The etiology and pathogenesis issues of idiopathic scoliosis still remain the subject of lively debate. However, the term “neuromyogenic” is increasingly frequently used instead of “myogenic”, which is indicative of the increased role of the nervous system in the genesis of idiopathic scoliosis [3].

Several questions have been posed when planning this review: 1. Are there any data on the relationship between scoliosis, Chiari I malformation (CM1), syringomyelia, and symptoms of hemodynamic instability at the craniovertebral junction (CVJ) in the available literature? What diagnostic protocols exist in this context? 2. Whether the role of the posterior atlantooccipital membrane (PAOM) in formation of scoliosis and pathological processes at the CVJ was studied? Is there any surgical significance of the anatomical changes in PAOM? 3. What treatment protocols are used in children with scoliosis that occurs concomitantly with CVJ pathology and syringomyelia? Has comparative evaluation of the effectiveness of various combinations of these protocols been performed? This question was spurred by our personal observations related to the stabilization or regression of scoliosis after suboccipital decompression for Chiari I anomalies and syringomyelia, on the one hand, and regression of neurological symptoms, such as headache and dizziness, as a result of suboccipital decompression in children with the same diseases, on the other hand. Publications that either directly or indirectly confirm our observations [4—7] were another motivating factor.

Among the works dealing with diagnosis and treatment of scoliosis, we have selected studies based on investigation of the influence of CVJ pathology, including birth trauma, on the development or clinical course of scoliosis, especially in childhood [8—12].

It should be noted that publications discussing specific features of diagnosis and treatment of CVJ malformations, and CM1 in particular, were the most numerous ones [13—17].

In these studies, the authors mostly investigated the anatomical and biomechanical relationships between bone and brain structures and their impact on cerebrospinal fluid (CSF) circulation in norm and pathology. The literature data on the role of vertebral arteries and veins at the CVJ in the development of cerebral symptoms, especially in childhood, are scarce; this fact was mentioned in studies carried out in different periods [18—20]. Publications based on the study of neurological and neurosurgical CVJ pathology usually mention scoliotic spinal deformity is usually mentioned as comorbidity without studying the causal relationships [21—23]. According to the studies based on the MRI examination of patients with idiopathic scoliosis, neurological abnormalities, such as syringomyelia and CM1, were observed in 4—26% of cases [24—27]. MRI reveals CM1 and syringomyelia in 13% of cases in patients who had a positive family history of idiopathic scoliosis. The authors of this study believe that MRI needs to be conducted prior to treating scoliosis [28].

Syringomyelia in patients with idiopathic scoliosis is often asymptomatic and can be found only during preoperative examination [29]. It is clear that the epidemiology of asymptomatic CM1 is also unknown due to the lack of characteristic symptoms of the disease. The malformation in these patients is detected coincidentally during MRI for other indications. A retrospective analysis of MRI data for the biennium was performed in order to detect asymptomatic syringomyelia of the cervical spine. The analysis has shown a large number of coincidentally detectable CVJ pathologies, including CM1 [30]. On the other hand, there is a report that scoliosis was found in 28% of patients with isolated CM1 and in 49% of patients with CM1 and concomitant syringomyelia [31]. Children with early manifestations of scoliosis suffer from back pain and various neurological deficits, and MRI reveals neurosurgical anomalies in 45% of cases. [32]
There is currently no doubt that there exists a relationship between CM1, syringomyelia and scoliosis [33, 34]. In the literature, the relationship between syringomyelia and CM1 is mainly considered from the viewpoint of the Gardner’s CSF circulation theory or its various modifications [35—37]. We found no studies on vascular pathology at the CVJ in children with scoliosis and syringomyelia. MRI of the spine is the most commonly recommended examination method in patients with scoliosis in recent publications [38]. We also found no information on feasibility of MRI of the head and other examinations of the CNS, such as Doppler sonography of blood vessels of the head and neck in children with scoliosis.

2. The problem of vascular pathology of the vertebrobasilar system is being studied quite intensively in adult patients, mainly in degenerative and atherosclerotic processes [39, 40].

The condition of craniovertebral venous drainage and arterial blood flow in pathology at this important anatomical level has been poorly studied [41—43]. Most studies focus on the investigation of Kimerle’s abnormality [44, 45]. Given that the vertebral arteries in the third segment pierce the posterior atlantooccipital membrane, the connective tissue formation susceptibility to morphological changes, which may have an impact on the state of the vessels passing through the membrane, we searched for the phrase “posterior atlantooccipital membrane”. A total of 22 studies have been retrieved, 18 of them were devoted to anatomy and morphology. Only several publications assigned some clinical role to this formation. Thus, a case was reported, where the authors suggested that it was thickened atlantooccipital membrane that caused compression of the vertebral artery in its groove and thus played a role of the mechanism of syncopal syndrome. Decompression of the vertebral artery had a positive effect. Improved blood flow was confirmed by postoperative angiography [46].

Contradictory descriptions of the relationship between the posterior atlantooccipital membrane at the cervical spine level and nearby tissues as well as further search for the etiology of vertebragenous headaches have impelled clinicians to conduct a number of neurophysiological and anatomical studies. One of these studies was conducted in 9 embalmed bodies using identical slices. The study has revealed a connection between the PAOM and nuchal ligament in the atlantooccipital and atlantoaxial intervals along the midline. No connection was found below the C2 arch. Connective tissue bridges between the deep portion of the small posterior rectus muscle of the head and transverse fibers of the PAOM that laterally adhered to perivascular tissues of the vertebral artery were found [47]. Another study of the anatomical relationship between the dura mater (DM) and the rectus capitis posterior minor revealed connective tissue bridges between the muscle and the DM characterized by the transverse direction of the fibers. According to [48], this can affect the roots of C1—C3 and cause the vertebrogenic headache in pathological situations. Connective tissue bridges between the rectus capitis posterior minor and PAOM, having a transverse direction of the fibers, restrict the mobility of the DM with respect to the brain, which may be important for preservation of the DM during surgery [49, 50]. In the study conducted in 75 cadavers, the rectus capitis posterior minor was gradually separated from the upper attachment point to the point where it connected to PAOM. The discovered connective tissue bridges between the membrane and the muscle were visually identified as: 1) muscular; 2) tendinous; 3) fascial; and 4) no attachment. No differences in the occurrence rate of these bridges were observed for men and women [51]. There are studies of the relationship between the occipital bone periosteum and rectus capitis posterior minor. The occipital bone periosteum is connected to the anterior fascia of the rectus capitis posterior minor at the posterior atlantooccipital space, and runs in front of the posterior arch of the atlas towards the DM. In the atlantoaxial interval, the same takes place with the anterior fascia of the rectus capitis posterior major muscle and the inferior oblique muscle, which is connected to the periosteum of the posterior arch of the atlas [52].

Therefore, there are close anatomical and functional relationships between flexible bone, connective tissue and vascular structures at the CVJ, which can be either directly or indirectly involved in various pathological processes, both congenital and traumatic. However, we found no evidence to support or refute our viewpoint about the role of PAOM and vertebral vessels in pathogenesis of scoliosis in children. In addition, we found no evidence of possible involvement of the posterior atlantooccipital membrane in pathogenesis of craniovertebral vascular disorders described in our previous studies [53].

3. There are two effective types of treatment for idiopathic scoliosis in the world: corset treatment and surgery [54—57].

A number of factors should be taken into account when determining indications for surgical treatment, including patient’s age, deformity prognosis, degree and form of scoliosis, as well as comorbid conditions. Depending on the age when idiopathic scoliosis was diagnosed for the first time, the Scoliosis Research Society distinguishes [58]:

1) infantile scoliosis (from birth to 3 years);
2) juvenile scoliosis (from 4 to 10 years);
3) adolescent scoliosis (from 10 to 20 years).

In the world practice, the degree of scoliosis is determined in accordance with the method for measuring the angle of frontal spinal deformity described by J. Cobb [59] in 1948.

Deformities of the cervicothoracic and thoracic spine are an unfavorable prognostic factor [60]. Deformities of the thoracolumbar and lumbar spine are more stable in terms of their progression. It was noted that the risk of progression of scoliosis angle increases when Cobb’s spinal deformity angle is at least 30° [61]. However, we found no prospective studies in this direction.

Early signs of progressive scoliosis may include the emergence of neurological symptoms presenting as motor or sensory disorders. Neurological microsymptoms and signs of the dysraphic status, which are indicative of myelodysplasia, are unfavorable prognostic factors [62, 63].

There are different ways of surgical correction of scoliosis using transpedicular screws, laminar hooks and the combined methods. Techniques and tools are being constantly modified, but still no method is available that would meet all the neces-
sary requirements to treat this multifacted and complex disease [64—66].

Surgical treatment of CM1 is primarily aimed at reducing the neurological symptoms [67]. Decompressive trepanation of the posterior cranial fossa (PCF) is the primary surgical method, which has various modifications. Some authors use dissection and plastic reconstruction of the DM [68], while others perform DM-preserving surgery limited only to its superficial layer [69, 70]. It is believed that in the absence of CSF circulation pathology in CM1 patients, clinically proved vascular pathology at the CVJ and adequate PAOM excision, it is possible to achieve a stable clinical effect using only dissection of DM superficial layer (Patent no. 2380042 granted on January 27, 2010) [71].

In the world literature, we found studies discussing the effect of decompressive trepanation of the PCF in patients with CM1 and syringomyelia on the postoperative course of concomitant scoliosis. In these studies, the authors often provided the results of individual cases of surgical treatment of adults and children [72, 73]. Investigations of large series of patients are scarce, and there is no analysis of causal relationships between scoliosis and CM1 in available studies. Thus, a total of 442 cases of CM1 were discussed in a retrospective series over twelve years; scoliosis was detected in 65% of them. All the patients underwent surgical treatment in the form of CVJ decompression. The authors of this study noted that improvement was observed only in 95% of CM1 cases, and progression of scoliosis either stopped or improved in 44% [74]. We found no literature data on the time schedule of surgical intervention in patients with concomitant scoliosis, CM1 and syringomyelia and sequence of surgical interventions in cases when metal wire fixation was required. There is evidence that the average age of patients who had progression of scoliosis after decompression of the posterior cranial fossa was 14.5 years. Children under 8 years of age showed either stabilization or reduction of the Cobb angle after PCF decompression. The authors of this study believe that decompression alone improves or stabilizes spinal deformity in patients with CM1, syringomyelia and scoliosis if it was performed at an earlier age [75]. In this regard, there are interesting data demonstrating improve-

ment of scoliosis after PCF decompression in children under 10 years with syringomyelia, while there was no improvement when only a cyst was drained in patients with syringomyelia [76].

There have previously been attempts to predict the course of scoliotic deformity after surgical treatment of CM1. Thus, a 2-year follow-up of 15 patients with scoliosis who had undergone surgical treatment for CM1 revealed a number of risk factors for scoliosis progression, including older age at the time of neurosurgical intervention, a double scoliotic curve, more pronounced kyphosis, rotation and size of the initial curve. The authors confirm the relationship between CM1 and scoliotic spine deformity. They believe that early neurosurgical treatment of CM1 is a preventive measure aimed at preventing or inhibiting deformity progression [77].

In conclusion, it should be noted that the neurological component in the development of scoliosis is undisputed. Implementation of modern diagnostic techniques has allowed one to reveal the hidden neurological causes of scoliosis (CM1 and syringomyelia) and made it possible to establish the previously unknown pathogenetic links. In this regard, understanding of etiological mechanisms, pathogenesis and relationship between spinal deformity and neurological disorders has improved in such patients. Surgical treatment protocols of children with scoliosis combined with CM1 and syringomyelia were designed. However, there are no specific instructions on the sequence of therapeutic interventions targeted at different components of the pathogenesis in such patients according to their age, clinical presentation, and with due consideration of all anatomical and functional components. Implementation of full and mandatory neurological examination of children with scoliosis is a topical issue. All patients with diagnosed spine pathology should be examined by medical specialists, including both orthopedists and neurologists, and subjected to follow-up if necessary. A differentiated approach to timing and methods for managing patients with different combinations of CM1, syringomyelia and scoliosis is required. The role of vascular pathology at the CVJ in development and progression of scoliotic spinal deformity still remains not fully investigated.

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With allowance for the numerical data on the prevalence of progressive spinal deformities in children, this problem is more than relevant. Scoliosis has historically been regarded as a merely orthopedic pathology and considered to be a “nosological form”.

The development of neuroimaging, and especially MRI, made it possible to distinguish the so-called “symptomatic scoliosis”, when the deformity is not a disease but a symptom of another (often neurosurgical) disease. The author is well-known for his long-term interest in researching the problems of craniovertebral junction pathologies, in particular Chiari I malformation. This literature review presents a comprehensive consideration of the scoliosis problem in neurosurgery and possible pathogenetic mechanisms of its development. This review is very useful not only for neurosurgeons, but also for primary care specialists (pediatric neurologists, surgeons and pediatric practitioners working at clinics) for well-timed diagnosis and proper planning of examination and treatment of children with newly diagnosed spinal deformities.

Yu. V. Kushel (Moscow, Russia)
Modern Molecular Approaches to Diagnosis and Treatment of High-Grade Brain Gliomas

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The current state of the problem of diagnosis and therapy of high-grade gliomas using the most promising present-day approaches is reviewed. The diagnostic and treatment perspectives of the molecular genetic analysis of glioblastoma markers located on the tumor cell surface are reviewed. Gene therapy and the use of dendritic cells and oncolytic viruses is discussed as the most interesting approaches to therapy of high-grade gliomas. This work was supported by the Russian Foundation for Basic Research (grant 13-04-40202 KOMFI (13-04-40200-N, 13-04-40203-N, 13-04-40201-N, 13-04-40202-N)) and the “Molecular and Cell Biology” program.

Keywords: glioblastoma, molecular analysis, targeted therapy, genetic markers.

Primary tumors of the central nervous system (CNS) amount to about 2% of all tumors and rank fourth in terms of cancer mortality rate [1]. About 60% of detected brain tumors are gliomas, and up to 50–70% of them have morphological features that allow one to classify them as grade III—IV gliomas. Glioblastoma multiforme (GBM) is the most common CNS tumor [2].

Despite the recent advances in neurosurgery, development of intraoperative navigation, chemotherapy and radiation therapy, the effectiveness of treatment of primary malignant brain tumors is still insufficient. The postoperative life expectancy of the patients who had undergone chemo- and radiotherapy is 14 and 25 months for GBM and anaplastic astrocytoma, respectively. Five-year survival of GBM patients does not exceed 10% [3].

In terms of molecular biology, GBM is a constantly evolving, polyclonal, genetically and phenotypically heterogeneous cell population characterized by multiple gene and genome changes, disregulated intracellular signaling pathways plastically reorganized during therapy. Due to these features of GBM, the existing treatments for GBM are ineffective, including the most recent cytotoxic chemotherapy and antiangiogenic therapy with monoclonal antibodies and small-molecule inhibitors. Therefore, the search for new effective methods of anticancer therapy is still highly relevant.

The development of innovative biomolecular approaches to GBM treatment goes in several directions. Specifically, the possibility of designing targeted anticancer drugs based on nanocontainers with “guiding” monoclonal antibodies [4], having pH-sensitivity or any other property that increases tropism for tumor foci, is being investigated [5]. Within the same direction, new treatments based on the delivery and expression of therapeutic genes that can cause tumor cell death, inhibit angiogenesis in tumors, or activate an effective immune response against glioblastoma are being actively developed. Immunostimulatory therapy of GBM and designing both DNA and cell antitumor vaccines are another line of research. Great expectations in this regard are laid on the use of autologous dendritic cells. Sensitization of these cells by tumor tissue antigens can significantly enhance antitumor cellular immune response. [6]

Another innovative approach to the therapy of low-differentiated gliomas is based on the use of oncolytic viruses (OVs). Preclinical studies using tumor cell cultures and animals with experimental human tumors (including experimental gliomas) demonstrated a very high therapeutic potential of OVs, surpassing the performance of all existing clinical and experimental therapies. The probability of forming an internal resistance of tumor cells to OVs is low, and there are no significant side effects even upon high-dose systemic administration, which makes them particularly attractive for designing improved genetically engineered alternatives with high therapeutic activity [7, 8].

The objective of this review is to analyze the most promising innovative approaches that can also be implemented in neuro-oncological practice in the near future. The review provides an integrated analysis of the currently known human glioma membrane markers that can serve as a basis for the development of targeted therapy of this disease.

Diagnosis of gliomas

The total annual incidence rate of gliomas is 5–6 per 100,000 population [2, 3]. Anaplastic astrocytomas, anaplastic oligodendrogliomas and oligoastrocytomas (Grade III accord-
ing to WHO grading) and glioblastomas (Grade IV according to WHO grading) are malignant gliomas, whereas grade I and II gliomas are considered to be benign and are characterized by a favorable prognosis according to WHO grading [9]. Histological diagnosis is one of the factors determining the tactics of postoperative treatment [11]. Grade III gliomas, unlike grade I—II tumors, are characterized by mitotic activity and polymorphisms of tumor cell nuclei. Increased vascular proliferation and the presence of macrobleeds and necrosis foci are important criteria in determining grade IV tumors (glioblastomas) [9].

Immunohistochemical analysis using antibodies to GFAP (a marker of low-grade astrocytomas), vimentin, S-100b protein, MBP (oligodendrocyte markers), p53 suppressor protein, etc. is currently used to confirm the histological type of glioma. Immunohistochemical features of malignant gliomas include the low level of the aforementioned proteins and the high tumor cell content of such proteins as Ki-67 (nuclear protein, proliferation inducer), CD34 (endothelial activation marker), cytokeratins and some other proteins associated with increased proliferative activity and inhibition of apoptosis [11].

A large number of studies focus on molecular genetic diagnosis of gliomas and finding genetic markers associated with long-term survival of patients with malignant gliomas. Recent data show that it is possible to classify gliomas according to expression of marker gene cluster. Based on such classification, it is possible to adjust treatments, leading to increased patient survival. Researchers have shown that approximately 44 genes involved in proliferation, migration, angiopoiesis stimulation, etc. can be used in such classification. Therefore, classification of gliomas into four groups depending on the expression of genetic markers was suggested. It was found that patient survival correlated with expression of certain genes. The highest survival rate was observed in patients with gliomas expressing factors responsible for the differentiation potential [12].

Determining the methylation status of MGMT promoter is another example of genetic prediction of patient survival. MGMT (O6-methylguanin DNA methyltransferase) is a DNA repair system enzyme, which prevents genotoxic effects of alkylating agents, such as temozolomide. Methylation of MGMT promoter inhibits MGMT gene expression and is associated with the most favorable outcome for patients with glioblastoma treated with temozolomide [13].

Currently, at least three molecular markers are considered to be important in the diagnosis of malignant gliomas [14]: 1p/19q codeletion, methylation of MGMT promoter, and mutation of isocitrate dehydrogenase-1/2 (IDH-1/2). Combined loss of chromosome regions 1 and 19 is probably caused by unstable translocations and is clearly associated with oligodendroglial morphology of gliomas [15]. 1p/19q codeletion can be detected using in situ fluorescence hybridization or analysis based on minisatellite polymerase chain reaction (PCR) to detect allelic losses and is associated with more favorable prognosis. Methylation of MGMT promoter can be assessed based on PCR of the methylation-specific promoter region [16]. It is supposed to result in loss of MGMT, an enzyme, inhibiting DNA damage caused by alkylating agents. This molecular marker is not differentially distributed among different types of gliomas, but remains a potential marker for predicting successful chemotherapy [17]. IDH gene mutations, mostly IDH-1, can be identified by PCR and directed sequencing. They are very common in grade II and III gliomas, but rare in glioblastomas [18, 19]. This is indicative of the fact that many glioblastomas are biologically distant tumors that are not related to typical progenitors of earlier grades. The pathogenic role of IDH mutations in gliomagenesis remains controversial, but it can include the emergence of new, alternative functions of mutant IDH enzymes that produce oncometabolite alpha-hydroxylglutarate. IDH mutations are prognostically favorable and almost never occur in elderly patients with malignant gliomas, which partly explains the negative prognostic impact of age in these patients [19]. Immunohistochemical analysis using specific antibodies to the mutant IDH R132H can be diagnostically valuable, since these mutations are common in grade II and III gliomas, but absent, for example, in pilocytic astrocytomas or ependymomas [18].

MicroRNAs can be very promising molecular markers of gliomas. In particular, it was shown that expression of certain microRNAs, such as miR-650 [20], increases in gliomas, whereas expression of others, such as miR-203 [21], is reduced. These changes in expression correlate with poor prognosis of the disease. It is expected that analysis of the miRNA pattern

Histological characteristics of malignant gliomas.

a — anaplastic astrocytoma: moderately cellular astrocytic tumor with mitoses and pleomorphic nuclei; b — oligodendroglioma: densely spaced tumor cells with round nuclei and perinuclear halos typical for anaplastic oligodendrogliomas; c — glioblastoma: areas of necrosis, hemorrhage and perinecrotic “palisade” formations characteristic of glioblastoma [10].
can provide additional valuable information not only about the prognosis, but also about the malignancy grade, as well as resistance to chemotherapy and radiotherapy [22].

**The principles of modern treatment of brain gliomas**

Combination therapy of malignant gliomas is currently used, which includes microsurgical resection of the tumor, radiotherapy and chemotherapy [1]. Resection of tumor tissue (cytoreduction) with minimal damage to the brain and establishing histological diagnosis are the main objectives of the surgical treatment of intracerebral tumor. Maximum radicality of surgery with allowance for physiological permisibility results in single-step elimination of a large number of viable tumor cells, including those resistant to therapy, reduces the intracranial hypertension, and can improve impaired neurological functions [23]. Complete removal of malignant intracranial tumors is virtually impossible due to the infiltrative nature of growth and involvement of important functional areas of the brain, which can lead to pronounced neurologic deficits after surgery.

Unfortunately, the 5-year survival rate of patients with glioblastomas who underwent all types of treatment does not exceed 10% [3]. Prognosis is mostly dependent on the pathomorphological characteristics of the tumor and patient's age [24], and to a lesser degree on surgery radicality [25].

**Gene therapy**

Gene therapy approaches by now have partially proceeded from preclinical studies to phase I and II clinical trials [36, 41]. The overall objective of gene therapy is to achieve selective expression of a gene-therapy construction in tumor cells to eliminate them and provide stable protection against relapses. The antiangiogenic therapy method is one of the options of gene therapy. It was developed to prevent tumor vascularization, which is required for their growth and metastasising [26]. Immunostimulatory approaches tend to use the patient's own immune system for targeted oncolysis [27]. It is supposed that this approach can also activate immunologic memory to prevent disease recurrence. Oncolytic viruses promote tumor cell lysis and spreading of the virus after infection, specifically infecting tumor cells with genetic or metabolic changes [28, 29]. Strategies based on directed toxins use receptors that are specifically expressed on glioma cells for targeted destruction of these cells [30, 31].

**Tumor suppressors, oncogenes and other vectors with replication component**

All tumor cells are originally derived from normal progenitors [33]. However, tumor cells contain “bad” mutations in the key genes (oncogenes or tumor suppressors) that regulate proliferation and/or apoptosis. It is generally admitted that tumorigenesis is a multistep process, which requires mutations of various genes in the DNA of certain cells, such as genes regulating the cell cycle, independence of growth factors, angiogenesis, cell migration, changes in adhesive properties, reduced apoptosis levels and decreased sensitivity to chemotherapeutic agents [33].

Genetics of gliomogenesis has been described well as compared to various types of cancer and this information can also be used to develop the gene therapy aimed at correction of these genetic disorders. Mutations in four signaling pathways (P53/ARF/MDM2 pathway, P16/Rb/cyclinD/CDK4 pathway, RTK/Ras pathway and PI3K/PTEN/Akt pathway) are usually associated with the development of human gliomas [34]. Viral vectors expressing transgenes usually mutated in gliomas were developed to correct genetic mutations [28].

There are adenoviral vectors for delivering p53 to tumor cells. Expression of the p53 gene is critical for normal cell cycle and apoptosis [35]. Mutations of p53 or its inactivating proteins are the most common mutations in human glioma. Inactivation of p53 allows tumor cells to bypass the normal cell growth control. When attempting to inhibit tumor cell growth and initiate apoptosis, the p53 gene was delivered to glioma cells using a replication-incompetent adenoviral vector [36].

In the first phase of the trial, patients were implanted with microcatheters for injecting adenoviral vectors with p53 into tumor tissue. The tumor was resected several days after virus inoculation, and the degree of biological effect was assessed. In the postoperative period, adenoviruses with p53 were further injected into the cavity formed after resection to assess toxicity. Under these conditions p53 transduction was shown, although transduced cells were detected at a distance of 5—8 mm from the injection site. Signs of apoptosis were detected in a small proportion of tumor cells. While no active virus was found outside the CNS, anti-adenovirus antibody titers were increased. Some patients developed neurological side effects, which were stopped by corticosteroid treatment. Average time to relapse was 7 months [37].

**Oncolytic viruses in treatment of glioblastoma multiforme**

The history of tumor virotherapy accounts for more than 100 years: the first report on regression of neck tumor in a female patient after administration of a vaccine containing attenuated rabies virus dates back to 1912 [7]. Later on, there have been other observations showing that a viral infection slows down tumor progression. The modern era of oncolytic virotherapy began in the 1990s when engineering of the viral genome became possible due to the development of genetic engineering, and understanding of the underlying molecular and genetic mechanisms of carcinogenesis and viral invasion allowed determining the targets, providing virus tropism for tumor cells. The first laboratory virus for oncolytic therapy was designed based on the herpes simplex virus (HSV) in 1991 by R. Martuza et al. [38]. In 1996, data on the first genetically engineered oncolytic adenovirus were published [39]. Over 20 potential OVs from more than 10 various virus families are currently known, and the list of modified OV forms designed on this basis is incalculable. OVs designed on the basis of HSV, adenovirus, Newcastle disease virus, reovirus, parvovirus H1 [40—42], measles virus, and polio virus [7] are undergoing clinical trials.

Almost from the very beginning of the OV concept development, glioblastoma multiforme has been considered to be
a candidate for oncolytic therapy, and it is not only because of the inefficiency of existing treatments. First, this tumor does not form distant metastases and is almost always located within a single organ, which allows for local administration of OV. Second, except for reactive astrocytes that form peritumoral glial shaft, all the other cells around the tumor are highly differentiated and are not involved in mitosis, which further increases OV tropism with respect to glioma cells, because proliferating cells are required for efficient virus replication. Third, the high specialization of nervous tissue cells due to the features of genetic expression implies in particular the presence of tissue-specific promoters (e.g., GFAP promoter and other neuron-specific proteins). The use of such promoters can also increase the virus tropism with respect to neuroepithelial tumor cells.

These advantages of OV application together with the high relevance of developing new therapies for GBM resulted in a large number of studies in this direction. Since the first publication by R. Martuza in 1991, a total of 250 studies on oncolytic virotherapy for gliomas using 15 different OVs have been published; 7 of those are currently undergoing phase I and II clinical trials.

The concept of oncolytic virotherapy. The concept of designing OVs implies selection or genetically engineered modification of the viral genome, resulting in a certain tropism of replication-competent virus. When injected into the human body it selectively replicates in neoplastic cells, resulting in their lysis and enhancing sensitization of the immune-competent cells by tumor antigens.

All the designed OVs can be divided into three groups: 1) human pathogenic viruses; 2) viral vaccines, 3) viruses that are conditionally pathogenic to humans. The most common member of the first group is herpes simplex virus (HSV) [43] and adenoviruses [44, 45]. The main problem for this OV group is to reduce pathogenicity for normal human cells. The examples of OVs based on viral vaccines include genetically engineered drugs, designed on the basis of variola virus (Vaccinia) [46], polio virus [47], and measles virus [48–50]. In the case of these OVs, the pathogenicity problem pales into insignificance after making viruses selective towards the tumor cells. In the case of designing OVs on the basis of viral vaccines, the problem of coping with long-lived immunity to the listed viruses that most people have can also come to the fore. Finally, the third OV group usually requires no modifications associated with elimination of pathogenicity. These are OVs designed on the basis of such viruses as Newcastle disease virus, myxoma virus, H1 parvovirus, vesicular stomatitis virus, Sindbis virus, pseudotot estanus virus, and Seneca Valley virus.

With few exceptions, these viruses are not virulent for normal human cells. They are able to selectively infect tumor cells due to significant rearrangements of membrane receptors and intracellular proteins in the latters, sometimes even without any genetic modifications. H1 parvovirus is a demonstrative example of the unmodified OV non-pathogenic to humans [40, 41].

The membrane mechanism of OV selectivity. The selective virus binding to membrane receptor of the target cell is the first and sometimes the key mechanism providing viral tropism to tumor cells. Specifically, the measles virus selectively interacts with CD46 receptor, which is found in large amounts on the surfaces of many tumor cells, including glioma ones [48]. CD155 co-receptor, which is required for adhesion and subsequent internalization of the pox virus, is hyperproduced on the surface of glioma cells [51]. High-affinity laminin receptor 67 kDa proved to be a receptor for Sindbis virus, which is over-expressed, e.g., in ovarian cancer cells [52]. Virus affinity to tumor-associated receptors can be developed by genetic engineering, by exposing the variable domains of antibodies or specific ligands on the virus surface. The following receptors are being investigated as targets for OVs: epidermal growth factor receptor vIII (EGFRvIII), platelet-derived growth factor receptor (PDGFR), interleukin-13 receptor (IL-13R) and some other tumor-associated proteins [7, 49]. The exposure of the well-known cyclic RGD tripeptide, which selectively interacts with tumor integrin αvβ3, on the adenovirus surface allows for appropriate targeting of the virus [44, 53]. Active search for tumor-selective surface markers is in progress.

Cytoplasmic mechanisms of tumor-specificity. The cytoplasm of normal cells contains potential antiviral agents. For example, the appearance of double-stranded RNA, which is required for cycle of some RNA-containing viruses, triggers antiviral protection system, which, in turn, activates protein kinase R (PKR) and the interferon pathway. The activated PKR inhibits viral protein synthesis and triggers apoptosis, while interferons lead to activation of some antiviral mediators [7]. Tumor cells often have various defects of pro-apoptotic cascade and can also have defects in the antiviral protection system. Thus, defect in the interferon pathway in some tumor cells makes them susceptible to vesicular stomatitis viruses [54, 55] and myxoma [56]. PKR function is impaired in tumor cells with activated RAS signaling pathway. This property underlies oncotropism of reoviruses [57] and HSV with the removed F134.5 gene [58]. Activation of the AKT-pathway in tumor cells makes them susceptible to infection by myxoma virus, which is also used in designing OVs [59].

miRNA pattern has a strong potential for the development of tumor-selective OVs. It is known that expression of many tumor-suppressive miRNAs is virtually absent in tumor cells [22]. It has been recently shown that replication of the vesicular stomatitis virus and measles virus in normal cells is almost entirely reduced when the sequence complementary to miR7 antitumor miRNA is incorporated into the viral genome. In this case, such miR7-sensitive viruses replicated well and contributed to the lysis of infected cells in tumor cells where there was no expression of this microRNA [50, 60].

Nuclear mechanisms of OV tumor specificity. Replication cycle of some viruses, such as autonomous paroviruses, requires that the host cell necessarily passes through S phase of mitosis [42]. This feature makes parovirus nonpathogenic for all postmitotic cells, which is especially important for the nervous system. Mutant HSV with removed thymidine kinase and ribonucleotide reductase genes gets almost the same property [61].

By interacting with pRB (cellular retinoblastoma tumor suppressor protein), the product of the E1A adenoviral gene
triggers S phase of mitosis in the host cell. In this case E1B protein functions as a suppressor of apoptosis by binding to p53, which normally triggers apoptosis in response to antiviral defense mechanisms, and its inactivation. Consequently, adenoviruses that have defective E1A and E1B genes cannot replicate in normal cells and become selective with respect to the tumor cells with defective pRB and p53 [62].

Another highly promising genetic engineering method to obtain tumor-specific OVs is to design viruses whose genes are controlled by tumor- or tissue-specific promoters such as Nestin-1, GFAP, Ki-67, etc. [45].

The 20-year-long research experience shows that OVs designed on the basis of the herpes simplex virus, adenovirus, Newcastle disease virus, measles, parvovirus, etc. are safe for the organism and characterized by selective replication in tumor cells. In addition, OVs promote presentation of tumor-associated antigens to the immunocompetent cells and thus can stimulate the antitumor immune response. Summarizing the data of preclinical studies and clinical trials of OVs, it is safe to conclude that this approach will undoubtedly be effectively used in the treatment of GBM in the near future.

Glioma biomarkers

Understanding of glioma biomarkers is required in all areas of gene therapy. Many new methods of glioma treatment are somehow based on the delivery of therapeutic agents to target cells. Typically, these agents are cytostatic drugs or killers genes; therefore, the more selective drug delivery to tumor cells is, the less pronounced side effects associated with damage to normal cells are. Such targeting can be ensured by directing a drug to surface receptors that are hyperproduced in glioma cells. On the other hand, the enormous heterogeneity of tumors from patient to patient, and even within a subpopulation of tumor cells in one patient, necessitates personalized approach to targeted therapy. Obviously, targeting a single tumor cell surface marker will not result in effective elimination of all tumor cells. Thus, the problem is to ensure the most complete analysis of glioblastoma cell surface markers and to develop a molecular target pattern, which can provide, on the one hand, selective delivery to the tumor, and, on the other hand, its versatility for heterogeneous populations of tumor cells. The data on the best-studied GBM markers are summarized in this section.

IL-13Rα

IL-13Rα is a marker receptor of glioblastoma cells, which is structurally different from the normal cell receptor [63]. IL-13Rα2 can only bind to IL-13, but not IL-4, and is represented in abundance on the surface of grade III and IV glioma cells [63]. IL-13Rα2 has properties of cancer testis antigen. It is located on X chromosome, and the tests are the only normal tissue where the gene of this protein is significantly expressed. It is assumed that IL-13Rα2 is a decoy receptor for IL-13 with no intracellular signaling cascade [65]. However, there is another view point, suggesting a signal role of this receptor [64]. IL-13Rα2 is the first receptor whose hyperproduction was detected in tumor cells in most patients with glioblastoma, while it was not observed in normal cells of the nervous tissue. Autoradiographic and immunohistochemical analysis revealed overexpression of IL-13Rα2 in patients with glioblastoma in 75% of cases [66]. Molecular drugs targeting IL-13Rα2 were designed, and the first of them is currently undergoing phase 3 clinical trials for treatment of recurrent glioblastoma [67].

IL-13Rα1 is a fragment of IL13Rα protein. This fragment itself has a low affinity for IL-13. When bound to IL4Rα chain, it forms IL-13R with high affinity to IL-13, and thus IL-13Rα1 sequence is important for IL-4/IL-13 binding. In the experiments, IL-13Rα1 was found on the membranes in all glioma cell lines [68].

EphA2

EphA2 is a member of the Eph receptor family with tyrosine kinase activity. They are unique in that their endogenous ligands, ephrins, are superficially anchored in membranes of adjacent cells. Eph receptors are divided into classes A and B based on the type of attachment to the plasma membrane [69]. A-ephrins are bound by glycosylphosphatidylinositol bond, whereas B-ephrins contain a transmembrane sequence with the intracellular domain, which is involved in binding to the cell membrane. All ephrins interact with specific ephrin receptors, and some of them can bind to more than one receptor [70].

Eph receptors and ephrins demonstrate specific expression pattern during development [71]. It was found that Eph receptors and their ligands play an important role in the development of the nervous system in directing axonal growth processes, involving contact-dependent processes between cells [72]. EphA2 is presented in the nervous system during embryonic development, but, unlike most other Eph receptors, it is also expressed on the surface of proliferating mature epithelial cells [73]. EphA2 plays an important role in angiogenesis and tumor neovascularization due to binding to its endogenous ligand ephrinA1 [74].

EphA2 is hyperproduced in glioblastoma [75] on the membrane of tumor cells, as well as in tumor-associated blood vessels, which makes EphA2 an attractive target. In addition, this receptor is overexpressed in some solid tumors, including breast [76] and pancreatic cancer [77]. Thus, we can conclude that EphA2 is an oncogene that plays an important functional role in the formation of malignant phenotype.

uPAR

uPA protein (urokinase plasminogen activator) and its receptor uPAR play an important role in localization of plasmin on the surface of uPAR-producing cells. Various physiological and pathological processes, e.g. organogenesis during embryonic development, invasive and metastatic expansion of malignant tumors, and inflammatory reactions require migration of certain types of cells from their standard location to various other areas of the body. The mechanisms providing focal degradation of extracellular matrix components should be available to allow for such cell migration. Based on several studies, it was suggested that extracellular proteolysis catalyzed by plasminogen activator can play an important role in the
events required for cell migration in tissues. It is currently well-known that different types of cells synthesize and secrete uPA. These are monocytes/macrophages, polymorphonuclear leukocytes and cells from malignant tumors. Plasmin formation on the cell surface destroys the extracellular matrix via activating matrix metalloproteinases. This event is probably important for tumor invasion, metastasizing and cell migration [78]. uPAR is strongly glycosylated, forms many disulfide bridges, and has a high affinity for uPA. uPAR consists of approximately 284 amino acid residues, including 3 repeats of 90 residues [79]. The first of them interacts with the ligand, while the latter anchors uPAR in plasma membrane by glycosylphosphatidylinositol chain [80]. The detected sites for AP-1 and Sp-1 at the pre-promoter region of uPAR play an important role in regulating this gene in colon cancer cells and other types of cancer cells [81].

It has been found that the elevated level of uPA and uPAR proteins correlates with increased malignancy [82]. Moreover, uPA and uPAR production on the surface of cell membranes of malignant brain tumors, but not of the normal tissues, suggests that these proteins may be involved in tumor invasion. The action of antibodies to uPAR [83] or antisense nucleotides [84] reduces the invasiveness of human glioblastoma cells. Invasive cell behavior in stable transfected clones of glioblastoma cell line is significantly reduced both in vitro and in vivo when using an antisense transcript (blocker) that is complementary to 300 bp (base pairs) at the 5’end of mRNA of uPAR, as compared to behavior of the parental cell line cells [84].

**FPR**

FPR is a G protein-coupled receptor originally found in phagocytic leukocytes involved in cell chemotaxis and activated in response to bacterial formylated chemotactic proteins. When bound to FPR, agonist promotes signaling cascade, involving phosphorylidylinositol 3-kinase, protein kinase C, mitogen-activated protein kinases and NF-kB transcription factor [88]. It is assumed that due to its expression in the immune system cells and interaction with bacterial chemotactic proteins FPR is involved in the body defense against microbial infections [85]. Several chemotactic agonists of FPR have been found: formylpeptides that are probably synthesized by mitochondria of damaged cells [86], annexin I produced by activated epithelium [89], and cathepsin, a neutrophil granule enzyme [90]. Additionally, functional FPR was found in non-hematopoietic cells, such as lung epithelial cells [91] and hepatocytes [92]. Consequently, the range of pathophysiological processes, which involve FPR, is expanding.

It was found that tumor cells of most human malignant gliomas, including anaplastic astrocytoma and glioblastoma, also express FPR [93, 94]. FPR expressed in tumor cells of human glioblastoma in response to related agonist protein fMLF and agonists of dying tumor cells causes directed migration, survival and production of vasoformative factors by tumor cells [93, 95]. Removal of FPR by short interfering RNAs significantly reduces tumorigenicity of glioblastoma cells in the brain of immunodeficient mice [93]. Thus, it was demonstrated both in vitro and in vivo that FPR can potentially exacerbate progression of malignant human gliomas.

**AMPAR**

AMPAR is the ionotropic transmembrane glutamate receptor involved in fast synaptic signal transmission to the CNS. It can be activated by a synthetic glutamate analog, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid. AMPAR consists of four types of subunits: GluR1, GluR2, GluR3 and GluR4, which together form a tetramer [96].

Glioma cells can regulate calcium conductance by altering the expression of AMPAR subunits. GluR2 subunit transcripts undergo Q/R editing, leading to receptor impermeability. When restoring GluR2 subunit in glioblastoma cells with a viral vector, glioblastoma cells were unable to form tumors in the brain of an immunodeficient mouse, indicating that suppression of GluR2 is required for glioblastoma cell survival [97]. It was shown that expression of AMPAR protein and mRNA is reduced in glioblastoma tissue samples and cell lines as compared to normal brain cells [98]. Moreover, GluR2 subunit mRNA undergoes partial post-transcriptional editing in primary tumor cells [98]. Inhibition of receptor expression probably allows glioblastoma cells to avoid cell death.

On the contrary, GluR1 subunit is overexpressed by glioblastoma cells, which leads to increased formation of focal contact complexes, colocalization of actin and paxillin, and cell polarization [99]. Cells overexpressing GluR1 contain increased amounts of FA kinase, and stimulation with glutamate leads to increased activity of Rac1 GTPase. Immunoprecipitation showed that GluR1 can bind to integrin receptors. The expression level of AMPAR correlates with invasiveness of glioma cells in vitro and in vivo [99].

**NgR**

Nogo-66 is a neuronal glycosylphosphatidylinositol-anchored protein that forms a signal transduction complex with transmembrane proteins p75NTR and LINNO-1 [101]. It serves as a receptor for myelin-bound molecule inhibiting neuronal growth, Nogo-A [100]. Nogo-66 is a C-terminal extramembrane domain of Nogo-A that binds to NgR [102].

Nogo-A is involved in maturation of oligodendrocytes and myelin formation [103]. Nogo-A is highly expressed in oligodendrocytes in the CNS and in demyelinating lesions [104]. Apart from demyelination, Nogo-A is also involved in tumorigenesis. Substrate binding and cell migration of U87MG glioma cell line is considerably weakened by extramembrane domains of Nogo-A (Nogo-66) and myelin-associated glycoprotein (MAG) [105]. Cells that were exposed to anti-NgR showed an increased ability to bind and move on substrates coated with Nogo-66 and MAG. Therefore, Nogo-66 and MAG can slow down the growth and movement of glioma, acting through NgR [105].

In samples of human glioma, NgR expression decreases with increasing glioma grade [106]. This probably reduces the inhibitory effect of Nogo-A.
CTR and CRLR

CTR belongs to the family of B, G protein-coupled receptors (GPCR). It was found to be highly expressed in fetal, normal and tumor tissues [107]. Some ligands and proteins, altering receptor activity (RAMPs), interact with CTR and, along with formation of various GPCR dimers, underlie a wide variety of responses to endogenous ligands.

CTR is expressed in most glioblastomas. CTR-immunopositive cells are mainly glial ones. CTR-immunopositive cells are also positive for glial fibrillary acidic protein, nestin, and CD133 [108]. Secondary messenger systems were significantly modified by calcitonin in A172 cell line [108], which indicates that CTR can be used as a target for therapy.

CRLR is also presented on the surface of human glioma cells. Receptor expression in endothelial cells and tumor astrocytes correlates with the fact that its endogenous ligand adrenomedullin can influence glioma growth both directly, by activating proliferation, and indirectly, providing a vasoactive effect. CRLR can be a valuable target in glioma therapy [109].

Chemokine receptors

Chemokines are a group of small (8—15 kDa) chemotactic chemokines. Their receptors are required for leukocyte migration in the immune system. However, they also play an important role in initiation, progression, and metastasizing of tumors [110]. CXCL12 chemokine is presumably of particular importance in the biology of cancer and especially metastases. Interaction between CXCL12 and CXCR4 receptor, which is expressed on some tumor cells, directs them to peripheral tissues such as the lungs, liver, lymph nodes or bone marrow, where the ligand is permanently expressed [111]. Moreover, CXCL12 and CXCR4 contribute to paracrine tumor growth, invasiveness of cancer cells and angiopoiesis [112]. Another receptor for CXCL12 has recently been found, it was called CXCR7 [113]. Apart from CXCL12, it binds CXCL11 with tenfold lower affinity. CXCL11 also serves as a ligand for CXCR3, which also binds to CXCL9 and CXCL10.

CXCR4, CXCR7 and CXCL12 were detected in human glioma cells. They are nearly absent in normal brain cells [112]. CXCR4 gene expression is limited to a small subset of glioma cells, having features of stem cells, and decreases after differentiation [114, 115]. On the contrary, another receptor CXCR7 widely occurs in glioblastoma and astrocytoma cells, its amount can increase depending on the degree of differentiation. Moreover, CXCR7 is functionally active in glioma cell lines and inhibits apoptosis induced by camptothecin and temozolomide derivatives [116].

Another protein CXCR3 belonging to CXC subfamily of chemokine receptors can also be found on the cell surface of grade III and IV glioma. In addition, CXCR3 is also expressed in activated T cells, natural killer cells, and microglia [117].

CXCR3 receptor and its ligand chemokine CXCL10 are expressed in several human glioma cell lines (U373MG, SW1033, SW1783, NP750/96, IPMS, IPTP/96) [118], which suggests that this chemokine plays a crucial role in biology of brain cancer. CXCL10 expression in grade III and IV gliomas is increased as compared to normal astrocytes. In addition, the CXCR3 level is also increased in grade III and IV gliomas, and its activation can enhance *in vitro* synthesis of DNA in these cells. The effect of enhanced DNA synthesis induced by CXCL10 in glioma cells can be eliminated by action of CXCL10-binding antibodies [118]. CXCR3 receptor was also detected in primary tumor spheres obtained from glioblastoma cells. CXCL10 and CXCL9 enhance proliferation of U87-GS and U188-GS cell lines, this effect is neutralized by an antagonist of the CXCR3 receptor NBI-74330, suggesting that CXCR3 can be possibly used as a therapeutic target [119].

ERBB receptors (EGFR, HER2, erbB3, erbB4)

ErbB is a family of tyrosine kinase receptors, which consists of four elements: erbB1/EGFR/HER1, erbB2/HER2, erbB3/HER3, and erbB4/HER4. ErbB receptors are activated by peptidic growth factors that belong to the EGF family. ErbB receptors are required for development and functioning of the nervous system. They regulate key processes, such as proliferation, self-renewal and migration of stem cells and progenitor cells, and also regulate their conversion into different types of neurons [120, 121]. Heterogeneity of CNS cells is most noticeable in glioblastomas, where tumor cells can express astrocytic and oligodendroglial markers (GFAP and Olig-proteins, respectively) [122] along with the neuronal markers (neurofilament proteins, MAP-2, and NeuN) [123, 124]. Moreover, a small population of stem-like cells was revealed that express CD133 marker and exhibit the properties of neural stem cells [125]. Based on this fact, it can be expected that the phenotypic heterogeneity may arise due to improper differentiation of cancer stem cells [126].

EGFR is one of the most frequently modified genes in glioblastoma. Elevated level of EGFR was observed in approximately 40% of cases and is often associated with rearrangements, leading to synthesis of constantly active mutant receptors. This dysregulation leads to excessive activation of EGFR signaling pathway, which activates proliferation, increases mobility, survival and resistance of glioma cells to apoptosis [127]. EGFRvIII mutant receptor is expressed in most glioblastomas [128]. EGFRvIII is formed as a result of deletions of exons 2—7, which encode the ligand binding domain. The receptor is permanently active due to the lack of the latter [129]. EGFRvIII enhances tumorigenicity of gliomas [130] and is responsible for the resistance of cancer cells to radiotherapy [131] and chemotherapy [132]. EGFR level is much higher in low-differentiated gliomas (III, IV grade, WHO) as compared to grade I—II gliomas [133]. EGFR may also be a molecular target for targeted treatment of gliomas.

HER2 receptor is not expressed in mature CNS cells [134], but its expression increases along with astrocytoma maturation [135]. HER2 overexpression was found in glioblastomas at different ratios [136] and it was a poor prognosis marker [137]. Moreover, primary glioblastomas demonstrated high intensity of HER2 expression, while secondary glioblastomas demonstrated low expression. Low expression of HER2 is associated with more favorable prognosis and long-term survival rate. HER2 expression profiles are similar in III grade gliomas and...
secondary glioblastomas [138]. Anti-HER antibodies induce in vitro apoptosis and cell toxicosis in glioblastoma cell lines (U251, U373, and T98G) [139]. The effect increases with increased HER2 density on the membrane [140]. Furthermore, implantation of cells of U251MG human glioblastoma cell line in a bab/lc immunodeficient mouse increased receptor density [141]. Thus, HER2 is an attractive target in treatment of glioma.

As for other EGF receptors, it can be noted that the ErbB2-3 level does not correlate with glioma malignancy, while the ErbB4 gene, on the contrary, is overexpressed in gliomas with a favorable prognosis and low tumor grade [16]. At the same time, a great quantity of ErbB3 can be found in CD133-positive cells. This fact suggests that this receptor can also be associated with tumorigenicity [142].

CD133

The CD133 gene is located on 4p15.33 human chromosome and encodes a 120 kDa protein [143]. Structurally, CD133 contains five transmembrane domains: an extracellular N-terminal domain, C-terminal cytoplasmic domain, two long extracellular and two short cytoplasmic loops [144]. Although CD133 function is unknown, the location of AC133 antigen expression (CD133 glycosylated epitope) on the epithelial cell microvilli suggests its possible role in maintaining the functional asymmetry of the plasma membrane, in particular, the apical-basal cell polarity. Binding of CD133 to membrane cholesterol can indicate that CD133 is involved in regulation of cell membrane lipid composition [145]. It was found that CD133+ cells from the human embryonic aorta activated Wnt-dependent angiopoiesis during wound healing in diabetic ischemic ulcer. In addition, AC133 expression in glioma tissues was shown to increase with tumor grade and be associated with poor prognosis, indicating that AC133-positive cells play a key role in tumor growth [146].

CD133 mRNA and the protein itself are found in all currently obtained glioblastoma cell lines. In normal cells, CD133 is accumulated in the endoplasmic reticulum (ER) and Golgi apparatus. Membrane-associated expression of CD133 mRNA can be observed in cancer cells, bearing extracellular epitope AC133. It is only in these cells that differentiation and oxygen level clearly affect the expression of AC133 and, to some extent, affect the expression of mRNA and CD133 protein content. It is noteworthy that modulation of the AC133 level can occur independently of changes in CD133 mRNA transcription, protein translation, storage or loss of protein [147].

MELK

MELK is an atypical member of the snf1/AMPK serine-threonine kinase family [148]. This family is associated with cell survival under adverse environmental conditions, such as nutrient deficiency [149]. MELK regulates self-renewal of neural stem cells by controlling the cell cycle [150]. It was also found that MELK affects the cell cycle regulation in carcinoma cells, such as colon, lung, and ovarian cancer [151].

MELK is widely expressed in high-grade gliomas. Functional tests showed that MELK is an important regulator of proliferation and survival of glioblastoma cells and regulates the proliferation of CD133-positive stem cells of glioblastoma in the culture. MELK is also essential for survival and proliferation of medulloblastoma cells in vitro. Summarizing these data, one can conclude that MELK is a high-priority target in brain tumor therapy targeted at stem-like tumor cells [152].

Notch receptors

The Notch signaling pathway is involved in a wide variety of cellular processes, including the maintenance of self-renewal, proliferation, cell fate specification or differentiation, and apoptosis in stem cells [153, 154].

The Notch genes encode receptor family involved in short-range signaling events. In mammals, there are four types of Notch receptors: Notch1, Notch2, Notch3, Notch4, and 5 ligands: Delta-like 1, 3, 4 and Jagged 1 and 2. Notch receptor is a single transmembrane protein comprising various structural domains. The extracellular portion contains a lot of EGF repeats and three cysteine-rich Notch/Lin 12 repeats. N-terminal EGF-like repeats bind to ligands. Intracellular part comprises RAM domain, 6 ankyrin repeats, 2 nuclear localization signals, transcriptional transactivation domain and proline-glutamine-serine-threonine-rich domain. The structures of the 4 types of Notch receptors are highly homologous. There are differences in the number of EGF repeats in the extracellular domain and the presence/absence of TAD in the cytoplasmic domain [155]. The Notch signaling pathway is activated when Jagged and Delta family ligands of adjacent cells bind to receptors and induce proteolytic cleavage of Notch receptor.

Activation of the Notch signaling pathway has different effects, varying from proliferation control to apoptosis, differentiation, maintenance of stem cell status, and cell fate choice [156]. Dysregulations of the Notch signaling pathway are involved in some genetic diseases and tumorigenesis. Investigations show that the Notch pathway can be activated during oncogenesis of many tumors. Its role in oncogenesis was demonstrated for such diseases as acute lymphoblastic leukemia [157], breast cancer [158], and colorectal cancer [159]. However, it was shown that Notch can also act as a tumor suppressor, in particular in skin cancer [160]. Thus, the role of the Notch signaling pathway in various cancer types can be either oncogenic or suppressive, depending on the specific cellular context.

It is only recently that the potential role of Notch signaling pathway in the development of brain tumors has been noticed. Overexpression of Notch1, 3 and 4 in astrocytomas was detected, while Notch2 is not expressed in astrocytomas [161]. The percentage of immunopositive tumor cells and the Notch 1 expression level increase with glioma grade. Moreover, in vitro and in vivo astrocytoma cell growth slows down under the influence of Notch1 siRNA [162]. However, Notch2 gene is overexpressed in medulloblastoma, whereas expression of Notch1, 3, 4 and 4 is low or not detected. Inhibition of the Notch2 signaling pathway suppresses medulloblastoma cell growth. Based on this fact, it can be assumed that Notch1, 2, 3 and 4 can have different impacts on tumor growth within the same tumor type [161]. It is important that Notch receptors...
are virtually absent in normal cells of the nervous tissue [161]. Thus, Notch receptors are an attractive target in treatment of glioma.

VEGFR

There are two main VEGF receptors: VEGFR1 (fms-like tyrosine kinase Flt-1) and VEGFR2 (KDR or, as a murine homologue, embryonic liver kinase-1, Flk-1). VEGF receptors have a similar structure with a molecular weight of 170—180 kDa and belong to receptor tyrosine kinases.

VEGF-A vasoformative factor serves as a VEGFR ligand. It was originally described as a protein derived from cancer cell lines (TA3-St, HSV-NIL8, MOPC 21, BALB/c 3T3, B77 Rat 1, RR 1022) that increases the permeability of tumor blood vessels [164]. VEGF-A is a glycoprotein with a molecular weight of about 45 kDa consisting of two identical protein chains linked by disulfide bridges [165]. Due to alternative splicing of a single precursor mRNA, there are 6 VEGF-A isoforms in humans. The length of each chain in isoforms varies from 121 to 206 amino acid residues. Isoforms also differ in tissue-specific expression patterns and in their biochemical and biological characteristics. All six isoforms bind to VEGF receptors. Ligand binding causes receptor dimerization, self-phosphorylation of tyrosine residues, and further phosphorylation of intracellular proteins, e.g. mitogen-activated protein kinases or phosphoinositide 3-kinases 3-kinases. VEGF-A is a potential mitogen for endothelial cells, causing their migration and expression of several genes involved in degradation of extracellular matrix. Both VEGFRs are primarily expressed on endothelial cells, but they are also expressed by some other cell types [166], including GBM cells [167].

Gliomas are characterized by high vascularization [169]. Both mRNA and VEGF-A proteins are actively produced by glioma cells [170], and the amount of VEGF correlates with glioma grade [171]. These and other data suggest that VEGF is a key factor in angiogenesis and increased vascular permeability of gliomas [172]. Along with endothelialcytes, VEGF-A targets also include microglial cells, constituting up to 30% of all glioma cells, in which it activates migration and proliferation. Moreover, VEGFR2 expression was also detected in glioma cells [167]. Therefore, the autocrine mechanism of VEGFR2 activation and transmission of mitogenic signals through their own VEGF is suggested in glioblastoma cells [168].

VEGFR3 is a receptor tyrosine kinase that is structurally similar to VEGFR1 and VEGFR2 [173]. VEGFR3 is actively produced in blood vessels during embryogenesis, suggesting that VEGFR3 plays an important role in embryonic angiogenesis. There is no expression of this receptor gene in definitive endotheliocytes [174], but it is abundantly observed in the endothelium of lymphatic vessels. VEGF-C and -D are VEGFR3 ligands, and, since these proteins play a pivotal role in formation of lymphatic vessels, their role in tumor expansion and metastasizing has been demonstrated [175]. In glioblastomas, VEGFR3 is highly expressed in the tumor endothelium. VEGF-C and -D are present in cells in the areas with high density of blood vessels. Significantly increased expression of VEGFR3 was observed in glioblastoma at the mRNA level as compared to low-differentiated gliomas and normal brain. Expression of VEGFR3 is moderate in anaplastic astrocytoma. The same conclusion can be drawn regarding the expression of VEDF-C and -D at the mRNA and protein levels. Therefore, VEGFR3 expression correlates with glioma grade. VEGFR3 is primarily localized on endothelial cells, as evidenced by expression of multiple endothelial markers by cells isolated from glioblastoma [172]. VEGFR3 can also serve as a target for anti-angiogenic therapy of gliomas.

PDGFR

PGFRA is one of the most frequently mutated tyrosine kinase receptors in glioblastomas [176]. PGFRA is a transmembrane receptor with 5 immunoglobulin-like repeats in the extracellular domain and tyrosine kinase in the intracellular domain. It belongs to the family of platelet growth factor receptors. Ligand binding to the receptor activates the main underlying signaling pathways that induce tumorigenesis, including MAP kinase, P13K/AKT, JAK/STAT, and the PLC-PKC [177].

It is known that PDGFRA plays an important role in normal development of the CNS by regulating normal proliferation of glial cell and differentiation of oligodendrocytes [178]. Additionally, PDGFRA is involved in oncogenesis and tumor progression of some solid tumors, including neuroepithelial one [179]. Indeed, some abnormalities of expression and processing of PDGFRA were found in gliomas (amplification, overexpression, in-frame deletions, point mutations and rearrangements) [176, 180]. Point mutations of PDGFRA were observed only in glioblastomas. Abnormalities of PDGFRA are now potential targets for innovative molecular therapies of glioma in personalized medicine.

PDGFRB is another member of the platelet growth factor receptor family. The expression pattern of this receptor in gliomas is still poorly understood. It is known that the level of mRNA encoding PDGFRB is increased twofold in glioblastoma as compared to normal tissues [181].

ERR

ERRα and ERRγ together with ERRβ form the orphan nuclear receptor subfamily having significant sequence homology with ERα and ERβ estrogen receptors [182]. Like other nuclear receptors, ERR are arranged as modular domains with less characteristic N-terminal domain, highly conserved DNA binding domain, and potential ligand binding domain. ERRs are highly homologous in terms of DNA-binding domain and constantly active without binding to natural estrogens [183]. Similarly to ER, ERRs bind to the classical ERE motif (AGGTCAANNTGACCT), suggesting the possible involvement of ERR in the respective ER-mediated signaling pathways through association with co-regulatory proteins and regulation of target genes expression. ERRs also bind to ERE-bound regulating elements with extended basic semi-site (TNAAGTCA; ERR/ER-1RE), indicating that ERR can possibly have its own independent regulatory pathways or functions that are far from ER functions. Therefore, it is quite possible that ERRs can regulate a wide variety of genes in the target cell. The studies revealed that ERRα and ERRγ were
expressed by ER-negative glioma cell lines (A172, U87, U118, U373) in a context-dependent manner, and U87 glioblastoma cell line expressed both receptors [184]. However, the character of ERR expression in glioma is still poorly understood. Further research in this area may lead to development of new treatments for gliomas.

Conclusion

Currently, there are numerous studies on human gliomas with detected changes in expression of various genes. The studies are being conducted in glioma cell lines, inoculated cultures, primary cell cultures, as well as tissue material obtained after tumor removal. The results obtained using different samples (tissues, cultures, lines) are often contradictory to each other, which is indicative of the excessive variety of causes of glioma tumor formation. In this regard, it is necessary to organize the available knowledge in the field of molecular genetic studies, which will allow classifying gliomas according to genetic disorders. It is clear that individual development is regulated by a hierarchically organized system of gene ensembles. A crucial role in regulation of cell differentiation is played by “master” genes that determine the specificity of development of a particular tissue or organ. Such genes trigger cascades of structural gene expression that are necessary for the synthesis of tissue-specific proteins. Therefore, changes in expression of the key genes can change not only the cell differentiation, but also differentiation of the entire tissue, thus causing the processes leading to tumorigenesis. Search and study of evolutionary conservative systems that control neurogenesis will allow one to understand the processes occurring in gliomas.

In this review we tried to cover the maximum amount of data on promising approaches to treating human gliomas. The probable molecular genetic markers of human gliomas were described and the database of these markers was composed. Finding a stable range of genetic and protein changes associated with human brain tumors will facilitate the development of individual treatment of glioma and provide an opportunity to improve the early diagnosis of malignant brain tumor formation, which in turn will allow for less traumatic surgeries. In addition, better understanding of glioma markers will enable targeted therapy that preserves healthy brain cells. Consolidated efforts of neurosurgeons, histologists, immunohistochemists, molecular biologists, and chemists will allow summarizing the knowledge in various areas of medicine and science and finding new ways to treat and diagnose human gliomas.

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Penetrating Skull and Brain Injuries Caused by Non-metallic Foreign Bodies (Literature Review over the Past 50 Years)

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Penetrating brain injuries (PBI) are common in neurosurgical practice. Most of them are civil or wartime gunshot and mine blast injuries. This type of trauma is widely presented in neurosurgical publications, textbooks and clinical evidence-based guidelines. Meanwhile, PBIs caused by non-metallic foreign bodies are very rare. All the data are limited to sporadic case reports and small series of cases; no recommendations are available. This review summarizes the features of diagnosis, treatment, and possible complications in patients with PBI caused by non-metallic foreign bodies.

Keywords: penetrating brain injury (PBI), penetrating craniofacial trauma, non-metallic foreign bodies, transorbital injuries, brain abscess.

Introduction

Gunshot and mine blast injuries of the skull and brain that occur both in peacetime and wartime are adequately represented in Russian- and English-language literature, including monographs, clinical guidelines, as well as predictive algorithms and recommendations designed based on the evidence-based medicine principles [1—7]. However, penetrating injuries caused by non-metallic foreign bodies occur sporadically, and relevant publications are mainly represented by single cases or small series. Moreover, there are no recommendations concerning the diagnosis and treatment tactics, possible complications and outcomes in this type of injury.

The purpose of this publication is to summarize the literature data and formulate recommendations on optimizing the diagnosis and treatment of penetrating skull and brain injuries caused by foreign non-metallic bodies based on the analysis of the available publications.

Material and Methods

For this review, we selected publications over the past 50 years, from January 1963 to January 2013, that were retrieved using the Medline search engine upon the requests “penetrating brain injury or head injury” and “non-metal” or “wooden” or “glass foreign bodies”, as well as reference articles. In addition, we analyzed publications in Russian presented in periodicals and monographs. A total of 49 publications were selected in this way.

When discussing injuries caused by non-metallic bodies, it is necessary to mention how they differ from gunshot and mine blast injuries of the skull and brain. Gunshot wounds are characterized by high kinetic energy of a missile and, in addition to the direct action of a foreign body, the effect of additional damaging factors, i.e. fragments of barriers (in the case of rebounding injuries) and scull bones [1, 2, 6—8]. Furthermore, a molecular vibration zone occurs along the wound canal due to the high speed of the bullet. Penetrating injuries caused by non-metallic bodies most frequently occur when sharp wooden objects (sticks, pencils, toothpicks), or, more rarely, stones and glass penetrate into the cranial cavity or result from injuries caused by sports weapons [9—13]. In English-language literature it was suggested to classify such injuries to a separate “non-missile injuries” group [7, 9, 14]. In these injuries speed of a wounding object is less than 100 m/s, there are no additional damaging factors, and only mechanical damage to tissues occurs along the path of a foreign body, followed by swelling and inflammation.

Because of the low kinetic energy of a wounding object (as opposed to the bullet and shrapnel wounds) and the relative strength of the skull bones, its “vulnerable spots” near to the natural openings, such as the superior orbital fissure [15—18], optic canal [19], the thin bony walls of the orbit [14, 19—28], and ethmoid plate [10, 30] the main ways for a foreign body to penetrate into the cranial cavity [15—18]. Due to this localization of entry wound, this pathology is within the professional scope of neurosurgeons, ophthalmologists, craniofacial surgeons, otolaryngologists, etc. Extremely rare cases of injuries to the calvarial bones have also been reported [9, 11, 26].

With allowance for the age-related features (bone thickness, suture density), children are more likely to suffer from penetrating injuries caused by non-metallic bodies [16, 17, 20, 30—32] than adults. The literature currently presents studies based on small series or single clinical case reports. C. Miller et al. [33] published their own observation of a patient with a penetrating skull and brain injury caused by a wooden body and conducted the first meta-analysis of 42 publications of various authors on this subject since 1834. The total disability rate in all the case reports was 75% and the mortality rate was 45%. The clinical cases were additionally divided into two groups, before and after sulfonamides and penicillin started to be used in

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1944. An analysis of the mortality rate in both groups revealed that this number decreased from 85% (12 of 14 patients) in the first group to 25% (7 of 28 patients) in the second group. It should also be noted that surgical approach became more aggressive in the second period, and postoperative mortality significantly decreased. Thus, while in the 1st group surgery was performed in 3 of 14 patients and only one of those survived, 20 of 28 patients in the 2nd group were operated on and the postoperative lethal outcome was observed in only 2 cases. The percentage of fatal cases when using the conservative treatment strategy was 62%, while being only 10% for surgical treatment. It is possible that the results of conservative treatment were actually even worse than it was shown as not all the patients were followed-up, and complications could occur during a longer period after the injury [8, 10, 34].

In 2004, Y. Nishio et al. presented an analysis of 23 published case reports of penetrating injuries of the skull and brain caused by non-metallic foreign bodies. It was noted that during the acute phase of injury the clinical presentation is limited to solely local symptoms without neurological deficit in 43% of cases, thus leading to diagnostic pitfalls. Moreover, neurological symptoms can develop after a long period after injury. It was more than 6 months (up to 13 years) in 17% of cases.

**Diagnosis of penetrating injuries caused by non-metallic foreign bodies**

**Clinical presentation**

In some cases, injured persons are conscious before complications develop and make no reckoning of the injury [22, 34, 35]. Therefore, patients with cranioorbital injury and suspected intracranial foreign body need special care, as severe complications in the future can occur at the back of apparent lack of evident symptoms in the acute period.

The primary symptoms in the clinical presentation of transorbital injuries can include ophthalmic syndromes: the superior orbital fissure syndrome [15, 36] and optic nerve injury of the [19], some oculomotor nerves or orbital structures. When a foreign body damages calvarial bones and large brain areas, the neurological status is dominated by depression of consciousness and focal symptoms [9, 11, 26, 30]. Penetrating skull and brain injuries can also be accompanied by damage to the great vessels, basal structure, etc. D. Mitilian et al. [36] reported a penetrating transorbital injury of the cavernous sinus, the pons, and the cerebellar vermis caused by a wooden stick in a 4-year-old child. In such cases, the clinical presentation can be very diverse, and the deficit corresponds to the damaged structures along the path of a foreign body. Such damages necessarily require comprehensive diagnosis and evaluation of intracranial lesions using neuroimaging.

**Neuroimaging methods**

The conventional X-ray diagnostic methods, such as craniography and computed tomography (CT), are the “gold standard” for the diagnosis of any penetrating skull and brain injuries [3, 7]. According to the recommendations on the diagnosis and treatment of penetrating traumatic brain injury (TBI), it is reasonable to perform axial soft tissue and bone CT imaging. In the case of skull base injury, more information can be obtained using coronal and sagittal scans. 3D reconstructions using spiral computed tomography (SCT) of the head with a minimum scan step are highly informative and can be successfully used in craniobasal injuries [11, 12, 27, 28, 37, 38]. In the case of injuries caused by wooden and other non-opaque objects, it is not always possible to clearly differentiate them from the surrounding tissue using CT [19, 31, 36, 39—42]. In doubtful cases, when CT shows no clear intracranial pathology, magnetic resonance imaging (MRI) is indicated [19, 21, 24, 33, 43]. T1-weighted MRI, where wood can be easily differentiated from adipose tissue or air, is especially informative [19, 41, 42].

It should be kept in mind that neuroimaging presentation of a wooden foreign body can change over time due to soft-tissue swelling, formation of inflammatory infiltrate and even swelling of wood [40, 44]. J. Hansen et al. [40] reported a clinical observation of penetrating brain injury caused by a wooden foreign body and provided experiment-based description of radiological properties of different types of wood, as well as changes observed for different water contents in its structure.

Both direct and SCT angiography techniques are highly informative before the inspection of an injury, especially in the cases of suspected damage to major blood vessels at the basal surface of the brain. S. Kasamo et al. [24] reported 7 cases of penetrating skull injuries caused by various foreign bodies followed by operations carried out in the acute phase of the injury. The article detailed the diagnostic algorithm: CT and MRI used to verify a foreign body and direct angiography used to assess the damage to intracranial vessels. Intracerebral hematoma, pneumocephalus, intraventricular hemorrhage, brain stem injury and carotid-cavernous fistula were detected. A single case of traumatic aneurysms of the carotid artery as a result of injury caused by a wooden stick was reported in the literature [37].

Thus, the modern arsenal of diagnostic methods allows us to attack the problem of injured area inspection being “fully armed”, and to plan the correct and safest surgery [12, 22, 28, 45].

**Therapeutic tactics**

Available series of observations are unfortunately not sufficient to provide statistically reliable recommendations on the management of this group of patients. Conservative measures are standard: prophylactic administration of antitetanic serum is required regardless of the forthcoming operation [23]. Antibiotic prophylaxis using broad-spectrum drugs is required in the acute period [3, 7, 9, 14, 19, 21, 23, 24, 43, 44, 46, 47], although the question about the duration and optimal regimen of antibiotic prophylaxis is still open [3, 7]. Non-metallic foreign bodies, in particular wooden ones, are a fertile ground for the growth of microorganisms because of their microstructure. In this context, non-metallic foreign bodies
can be compared to bone fragments in gunshot and mine blast wounds [1—8].

Symptomatic epilepsy occurs in 30—50% of patients with penetrating skull and brain injuries [3, 7]. The recommendations on penetrating head injury [7] state that administration of anticonvulsants is indicated during the first week after TBI, while prophylactic administration of anticonvulsants during the later period is not justified.

Surgical tactics with respect to intracranial non-metallic foreign bodies should be aggressive due to the risk of infectious complications. The approach can be transorbital or transcranial depending on location of the entry wound, location of a foreign body, its size, shape, presence of abscesses and other complications. The access should be sufficient for inspection and total removal of the foreign body. In the case of sufficient preoperative examination (CT, MRI, angiography) and the absence of signs of damage to major blood vessels, the “pull and see” approach is sometimes acceptable, i.e. removal of the foreign body and inspection of the wound canal as necessary with minimal tissue traction [23, 24, 26, 40].

When a foreign body is located in the area of the anterior cranial fossa, the supraorbital approach is convenient to use as it provides good visualization of the anterior cranial fossa structures without excessive traction of the brain substance and allows for plastic reconstruction of the dura mater [28]. A.A. Potapov et al. [12] used the extended pterional approach to remove a foreign body in the middle cranial fossa. In this observation, the foreign body has destroyed a part of the great cerebral vein and allowed to assess its damage [22, 34]. The

<table>
<thead>
<tr>
<th>Author, year of publication</th>
<th>Number of patients</th>
<th>Wounding foreign body</th>
<th>Time after the injury</th>
<th>Symptoms</th>
<th>Type of purulent complication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>D. Bursick, R. Selker, 1981 [20]</td>
<td>1</td>
<td>Pencil</td>
<td>26 months — 7 years</td>
<td>Epilepsy, later on — meningitis</td>
<td>Abscess, meningitis</td>
<td>Recovery</td>
</tr>
<tr>
<td>P. Foy, M. Sharr, 1980 [31]</td>
<td>3</td>
<td>Same</td>
<td>5 weeks</td>
<td>Epilepsy, septic condition</td>
<td>Abscess</td>
<td>Epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 weeks</td>
<td>Depression of consciousness, severe focal symptoms (hemiparesis)</td>
<td>Meningitis, abscess</td>
<td>Recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 weeks</td>
<td>Meningal and severe focal symptoms (hemiparesis)</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>S. Gordon et al., 1992 [10]</td>
<td>1</td>
<td>Glass</td>
<td>10 years</td>
<td>Meningal and focal symptoms (hemiparesis)</td>
<td>Abscess</td>
<td>Same</td>
</tr>
<tr>
<td>A. Gupta et al. 2011 [49]</td>
<td>1</td>
<td>Wood</td>
<td>4 days</td>
<td>Septic condition, depression of consciousness</td>
<td>Meningitis, abscess</td>
<td>Same</td>
</tr>
<tr>
<td>R. Kahler et al., 1998 [23]</td>
<td>1</td>
<td>Fern</td>
<td>2 days</td>
<td>Depression of consciousness, meningal symptoms</td>
<td>Meningitis</td>
<td>Improvement</td>
</tr>
<tr>
<td>J. Maruya et al., 2002 [44]</td>
<td>1</td>
<td>Bamboo</td>
<td>14 days</td>
<td>Inflammatory changes in blood</td>
<td>Abscess</td>
<td>Recovery</td>
</tr>
<tr>
<td>E. Mutluakan et al., 1991 [45]</td>
<td>1</td>
<td>Wood</td>
<td>5 days</td>
<td>Depression of consciousness, meningal symptoms</td>
<td>Same</td>
<td>Limited outward eye movement</td>
</tr>
<tr>
<td>Y. Nishio et al., 2004 [34]</td>
<td>1</td>
<td>Same</td>
<td>7 years</td>
<td>Headache, fever, vomiting</td>
<td>Same</td>
<td>Epilepsy, amaurosis</td>
</tr>
<tr>
<td>A. Potapov et al., 1996 [28]</td>
<td>1</td>
<td>Same</td>
<td>2 months</td>
<td>Right-sided ptosis, ophthalmoplegia, amaurosis</td>
<td>Same</td>
<td>Right-sided ptosis, ophthalmoplegia, amaurosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 week</td>
<td>Headache</td>
<td>Same</td>
<td>Death (myocardial infarction)</td>
<td></td>
</tr>
<tr>
<td>A. Sanli et al., 2012 [17]</td>
<td>1</td>
<td>Wood</td>
<td>2 months</td>
<td>Purulent discharge from the wound</td>
<td>Abscess</td>
<td>Recovery</td>
</tr>
<tr>
<td>A. Shein-Filipowicz et al., 2010 [38]</td>
<td>1</td>
<td>Same</td>
<td>4 days</td>
<td>Septic condition, ophthalmoplegia, painful left eyeball</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>C. Smely, M. Orszagh, 1999 [42]</td>
<td>2</td>
<td>Same</td>
<td>4 days</td>
<td>Meningal symptoms</td>
<td>Abscess</td>
<td>Right-sided paresis of nerve III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 days</td>
<td>Depression of consciousness, meningal symptoms</td>
<td>Meningitis</td>
<td>Death (pulmonary embolism)</td>
<td></td>
</tr>
<tr>
<td>C. Specht et al. 1992 [41]</td>
<td>1</td>
<td>Same</td>
<td>2 days</td>
<td>Septic condition, meningal symptoms, right-sided amaurosis</td>
<td>Same</td>
<td>Right-sided amaurosis</td>
</tr>
</tbody>
</table>
use of the frontal and bifrontal approaches allows one to visualize a foreign body in the anterior cranial fossa and, if necessary, to carry out orbitotomy with inspection of the foreign body fragments in the superior orbital fissure and orbital cavity [35, 36]. A. Shein-Filipowicz et al. [38] used the more complex orbitofrontozygomatic approach in their observation, which allowed for detailed inspection of damaged structures in the anterior cranial fossa, orbit and optic canal.

It the case of small damage to the orbit, a foreign body can be removed transorbitally [40]. Thus, J. Hansen [40] successfully removed a foreign body from the orbit, superior orbital fissure, and left cavernous sinus using the transorbital transconjunctival approach. A combination of the transorbital and transcranial approaches can be used, if necessary [38].

In the case of depressed fractures of the calvarial bones, it is possible to remove bone fragments, perform resection craniotomy around the foreign body followed by its removal under the direct visual control [7, 9, 11].

Endoscopic transnasal removal can be the method of choice in the case of transnasal injuries. Endoscopic inspection of the injury site and the entry wound allows one to perform detailed visualization of the entry wound and remove the foreign body. [29]

Complications

Infectious complications are the most dangerous ones. Despite the lack of evidence, the literature data suggest that a non-magnetic foreign body left in the cranial cavity will sooner or later lead to some suppurative complications (Table). Terms of their development range from 2 days to 7 years according to different authors [8, 14, 28, 29, 35, 40, 48]. Microbial landscape of purulent complications is represented by the following flora: *Staphylococcus aureus*, *Streptococcus mitis*, *Bacteroides spp.* and *Enterobacteriaceae* [6, 11, 17, 23, 36, 49].

Brain abscesses are the most common form of purulent complications in the late period of penetrating trauma [8, 10, 11, 29, 31–33, 35, 44, 49]. According to N.K. Serova et al. (2005), the analysis of 6 cases of transorbital wounds caused by wooden foreign bodies revealed purulent-inflammatory complications in 4 patients, intracerebral abscesses in 3 patients, and orbital abscess in one patient. Clinical presentation included ophthalmologic symptoms (ophthalmoplegia, amaurosis, and signs of optic nerve atrophy on the affected side), local symptoms in the entry wound (fistula with purulent exudate, hydropsyemia and swelling in the area of the orbit) and neurological symptoms. In one case, a female patient developed amenorrhea as a result of an abscess in the chiasmosellar area.

In the case of inadequate intervention recurrent abscesses are possible [20]. D. Bursick and R. Selker (1981) reported a penetrating cranio-orbital injury, in which case only primary surgical debridement of palpebral wound was carried out, while no intracranial foreign body was detected. Eighteen months after the injury a purulent fistula developed on the eyelid scar and was treated conservatively. After another 8 months, the first epileptic seizure developed, brain abscess was found during examination and drained. After 3 years the patient was readmitted to the hospital with clinical signs of meningitis and otitis media, where he successfully underwent conservative treatment. After another 2 years (7 years since the injury), against a background of apparent well-being, the patient developed an attack of severe headache, persistent vomiting and depression of consciousness. CT visualized the recurrent abscess. Direct approach was performed and open inspection of the abscess in its cavity revealed fragments of pencil lead and pieces of wood. No further recurrences were observed after foreign bodies had been removed.

**Conclusions and recommendations**

The rarity of this pathology and the lack of statistical data required for meta-analysis currently allow formulating recommendations at the optional level only.

1. Axial bone and soft-tissue CT is recommended to all patients with penetrating skull and brain injuries. Coronary or sagittal CT is advisable in patients with damage to the basal structures or the upper part of the calvarium.

2. 3D CT reconstruction is advisable in order to plan the surgical approach in the case of craniobasal injuries. Usual craniography may be useful in assessing bone injuries, presence of air and radiopaque foreign bodies.

3. It is advisable to use MRI for injuries caused by wooden or other non-magnetic foreign bodies.

4. CT angiography and/or conventional angiography are indicated when injuries of arterial vessels or venous sinuses accompanied by formation of traumatic arterial aneurysm or fistula are suspected.

5. It is advisable to perform surgical treatment of the entry wound and wound canal including the removal of intracranial hematomas and foreign bodies with minimum damage to intact brain tissues, careful sealing of the dura mater and soft tissues of the head and sanitation of damaged paranasal air-filled sinuses.

6. Wooden and other non-metallic foreign bodies should be removed, as they are a risk factor for intracranial pyoinflammatory complications, including delayed abscesses.

7. Drainage of abscesses containing foreign bodies may be followed by recurrent abscesses, which indicates that abscess drainage with the removal of foreign bodies is required.

8. Prophylactic administration of broad-spectrum antibiotics is required in the case of penetrating skull and brain injuries. If inflammatory complications develop, antibiotic therapy depends on the nature and sensitivity of inoculated microorganisms.

9. Administration of anticonvulsants is recommended during the first week after penetrating injury to prevent early post-traumatic epileptic seizures. Prophylactic administration of anticonvulsants at later period is not recommended because their preventive anticonvulsant effect has not been proven.
REFERENCES

Management of patients with penetrating craniocerebral injuries is a topical issue of modern neurotraumatology. Penetrating skull and brain injuries caused by non-metallic foreign bodies of complex configuration are rare. In the literature, there are no recommendations regarding diagnosis and tactics of surgical and conservative treatment of this complex group of patients. In this study, a team of staff of the Burdenko Neurosurgical Institute analyzed Russian- and English-language literature dealing with this interesting problem for the past 50 years.

In contrast to gunshot craniocerebral wounds, injuring non-metallic foreign bodies do not have a high kinetic energy. They penetrate into the cranial cavity through its so-called “weak spots” and mainly cause craniofacial and craniobasal injuries. These patients are generally admitted to general hospitals, where the treatment strategy is determined by neurosurgeons in collaboration with maxillofacial surgeons, ophthalmologists and otorhinolaryngologists.

The authors pay great attention to the diagnosis of injuries. Apart from the clinical and neurological examination, neuroimaging methods are also important. In modern neurotraumatology, it is impossible to imagine the management of a TBI patient without using computed tomography examination. Spiral bone and soft-tissue CT of the brain in its different variations (frontal and axial slices, 3D reconstruction) provides a complete picture of the extent of damage to the brain, bone structures of the skull base, and allows determining the shape and size of the most complex intracranial foreign bodies.

Diagnosis of wooden foreign bodies is complex and varies over time. The authors quite adequately note that craniography and brain MRI complement CT findings. T1-weighted MRI is informative in the case of X-ray opaque foreign bodies.

Of course, determining the surgical tactics and methods of conservative, especially antibiotic, therapy is of great importance. In our opinion, these patients should be operated on in collaboration with other specialists (ENT specialist, ophthalmosurgeon, maxillofacial surgeon). The patient should be operated on by a neurosurgeon who has mastered complicated approaches to craniofacial and craniobasal foreign bodies. Furthermore, the surgery should not exacerbate the degree of brain injury. Sealing the dura mater and the soft tissues of the head to prevent liquorrhea (both basal and traumatic) is an important factor in the surgery.

When analyzing the literature, the authors note that intracranial pyoinflammatory complications, mainly brain abscess around a non-metallic foreign body, which was not removed during the acute phase, are the main complications in the late period of traumatic disease of the brain. Even emptying and drainage of an abscess without removing a foreign body does not guarantee the positive outcome. Unfortunately, the contemporary literature does not offer an antibiotic therapy algorithm.

In conclusion, the summary of the literature data is provided, including recommendations for diagnosis and treatment of penetrating injuries of the skull and brain caused by non-metallic foreign bodies. They are substantiated and reasonable and, in the absence of sufficient material for the meta-analysis, are undoubtedly of great practical importance for neurosurgeons working in emergency hospitals.

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Topics to be covered in our next issue:

- Stereotactic radiation therapy for spinal meningiomas and neuromas
- Fluorescent angiography in cerebral aneurysm surgery
- Ependymomas of the cauda equina in adults