PROBLEMS OF NEUROSURGERY
named after A.N. Burdenko

Vol. 80 6’2016

FUNDAMENTAL AND PRACTICAL JOURNAL

EDITORIAL BOARD

Editor-in-Chief A.N. Konovalov
Deputy Editor-in-Chief O.N. Dreväl’
Executive Editor A.V. Kozlov
Science Editors B.A. Kadashiev, O.B. Belousova

A.V. Golanov  A.A. Potapov
S.K. Gorelyshev  I.N. Pronin
A.O. Gushcha  A.S. Saribekyan
G.L. Kob yakov  S.V. Tanyushin
N.A. Konovalov  T.P. Tissen
V.N. Kornienko  A.A. Tomsky
A.G. Korshunov  D.Yu. Usachev
V.V. Krylov  Yu.M. Filatov
Yu.V. Kushel  V.A. Cherekaev
L.B. Likhterman  V.A. Shabalov
A.Yu. Lubnin  A.R. Shakhnovich
A.G. Melikyan  I.N. Shevelev
A.G. Nazarenko  V.M. Shimansky
V.V. Nazarov  L.V. Shishkina
A.L. Parfenov  Sh.Sh. Eliava

EDITORIAL COUNCIL

V.P. Bersnev (St. Petersburg)
A.A. Lutsik (Novokusnetsk)
O.A. Gadzhieva (Moscow)
D.E. Matsko (St. Petersburg)
B.V. Gaydar (St. Petersburg)
V.E. Olyushin (St. Petersburg)
V.N. Dobzhansky (Moscow)
E.G. Pedachenko (Kyiv)
G.F. Dobrovol’sky (Moscow)
D.A. Rzaev (Novosibirsk)
T.A. Dobrokhотовa (Moscow)
N.K. Serova (Moscow)
S.G. Zograbyan (Yerevan)
Sh.M. Safin (Ufa)
Yu.A. Zozulya (Kyiv)
A.F. Smeyanovich (Minsk)
D.N. Kapitanov (Moscow)
A.P. Fraerman (Nizhny Novgorod)
V.B. Karakhan (Moscow)
V.A. Khachatryan (St. Petersburg)
A.N. Kondratyev (St. Petersburg)
V.A. Khil’ko (St. Petersburg)
E.N. Kondakov (St. Petersburg)
V.I. Tsymbalyuk (Kyiv)
V.A. Lazarev (Moscow)
S.B. Yakovlev (Moscow)

The Editorial Board is not responsible for the content of advertising materials. Editorial opinion does not always coincide with the opinion of the authors. Only the articles prepared in compliance with Authors’ guidelines are accepted for publication. When submitting an article to the Editorial Board, the authors accept the terms and conditions of the public offer agreement. Authors’ guidelines and the public offer agreement can be found on website www.mediasphera.ru. Complete or partial reproduction is allowed by written permission of the Publisher (MEDIA SPHERA Publishing Group).
### ORIGINAL ARTICLES

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khabarova E.A., Denisova N.P., Rogov D.V., Dmitriev A.B.</td>
<td>The Preliminary Results of Subthalamic Nucleus Stimulation after Destructive Surgery in Parkinson’s Disease</td>
</tr>
<tr>
<td>Kondrakov S.V., Zakharova N.E., Fadeeva L.M., Tanyashin S.V.</td>
<td>Phase Contrast MRI-based Evaluation of Cerebrospinal Fluid Circulation Parameters in Patients with Foramen Magnum Meningiomas</td>
</tr>
</tbody>
</table>

### CASE REPORTS

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasin R.A., Krasnikov M.A., Vasin S.V.</td>
<td>Infant Form of Alexander Disease (Clinical Case and Literature Review)</td>
</tr>
</tbody>
</table>

### GUIDELINES FOR THE PRACTITIONER

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shimanskiy V.N., Karnaukhov V.V., Tanyashin S.V., Poshataev V.K., Shevchenko K.V., Odamanov D.A., Kondrakov S.V.</td>
<td>Use of Surgical Approaches to the Posterior Cranial Fossa in Patients in a Lying Position</td>
</tr>
</tbody>
</table>

### REVIEWS

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zay'yanov D.M., Pereteshkiv A.V.</td>
<td>Prevention and Treatment of Postoperative Epidural Scar Adhesions</td>
</tr>
</tbody>
</table>
In accordance with the resolution of the Higher Attestation Commission of the Ministry of Education and Science of the Russian Federation, the Problems of Neurosurgery named after N.N. Burdenko was included in the List of Leading PeerReviewed Journals and Periodicals issued in the Russian Federation where the main results of Candidate and Doctor Theses are recommended to be published.

Topics to be covered in our next issue:

- The current status of neurosurgical services in the Russian Federation
- Anatomy of the neural pathways of the brain
- Clinical recommendations for management of acoustic neuromas
Objective. The objective of this study is to describe the procedure and outcomes of comprehensive first-line treatment in glioblastoma patients.

Material and methods. We analyzed 107 glioblastoma patients who were operated on in 2010—2011. Seventy five patients underwent combined chemoradiotherapy (CRT) with simultaneous administration of 75 mg/m² temozolomide (TMZ) followed by chemotherapy with 200 mg/m² TMZ for 5 days, every 28 days. Separately, we examined 32 patients with large tumors, who received alternative treatments.

Results. The median time to progression was 11.7 months in the study group and 7.2 and 8.1 months in the groups of alternative therapy. The one-year progression-free survival rate was 37%. Overall survival was 29.2 months.

Conclusion. The chemoradiotherapy regimen involving TMZ followed by one-year TMZ monotherapy is an appropriate treatment for patients who underwent glioblastoma resection. With this approach, no tumor progression occurs in one third of patients during the first year. Thorough study of clinical and radiological findings in the course of treatment makes it possible to achieve maximum efficacy, avoid unnecessarily early switch to second-line therapy, and timely detect tumor recurrence signs. The Response Assessment in Neuro-Oncology (RANO) criteria should be used to assess MRI-detected changes in the tumor size. The rates of overall and recurrence-free survival were significantly lower in patients with inoperable or partially resected tumors. The applied approaches provide only a slight advantage in tumor growth control, which necessitates the search for more effective treatment options for these patients. Inclusion of bevacizumab to the first-line therapy regimen may be a possible approach.

Keywords: glioblastoma, chemotherapy, evaluation criteria, tumor pseudoprogession.
structures. These patients underwent CT in TC mode; in the case of regression of intracranial hypertension signs and decrease in tumor signs, RT was performed in combination with CT. Postoperative treatment was carried out at the Burdenko Neurosurgical Institute and Oncology Centers in Moscow and other regions of Russian Federation.

General information about the patient is shown in Table 1.

Tumor size dynamics was assessed based on the archival data of contrast-enhanced MRI of the brain performed before CRT, 1 month after completion of the CRT, and then after every 3 CT courses. Upon completion of treatment, MRI was performed every 3—5 months and in the case of clinical signs of tumor progression and evaluated according to RANO (Response Assessment in Neuro-Oncology International Group) criteria.

Results

At the time of data analysis, progression of the disease was observed in 91 (85%) of 107 patients. Progression-free survival for more than 1 year was observed in 37% (40 patients). Progression-free survival for 12—18 months was observed in 17 (15.8%) patients, PFS for 18—24 months was observed in another 12 (11.2%) patients, more than 24 months — 11 patients (10 — up to 3 years and 1 — more than 3 years). Regardless of treatments, MTTP was 10.3 months, OS — 29.2 months. In treatment groups, MTTP was as follows: combined CRT with TMZ followed by therapy with TMZ — 11.7 months; combined CRT with TMZ followed by TC treatment — 7.2 months; patients who started CT possibly followed by RT — 8.1 months \((p=0.008)\) (Fig. 1). Overall survival was 33.3, 26.3, and 18 months, respectively \((p=0.007)\).

Discussion

Objective of the study was to assess treatment outcomes of patients with glioblastoma, using high-level surgical techniques, modern RT techniques, and sufficient number of modern CT courses.

The number of followed patients

We describe treatment outcomes of only 107 patients, which accounts for 31.4% of all patients, who were for the first time operated on for GB at the Burdenko Neurosurgical Institute in 2010—2011. Relatively small number of patients included in the analysis was due to both loss of medical history and failure to comply with GB treatment standards [4]. Our findings are consistent with data of A.V. Smolin et al., who conducted the Russian multi-centered study on the epidemiology of malignant gliomas from 01.01.2012 to 31.12.2013. This study included 325 patients from 29 medical centers in Russia. It has been shown that only every fourth patient received combined CRT and 1/3 of patients received no first-line CT. Among the patients who received first-line CT, some patients received medications other than TMZ [5].

Thus, higher numbers of MTTP obtained in this study were due to the use of modern glioblastoma treatment regimens. Furthermore, patients who did not receive treatment, did not request re-consultation, those who were unavailable for history taking and possibly died in the early postoperative period, were not included in our study.

Combined chemoradiation therapy with temozolomide followed by adjuvant therapy with temozolomide

In the study group, MTTP was 11.7 months. In patients, who were treated at the Burdenko Neurosurgical Institute using an identical regimen in 2006—2007, MTTP was 9.7 months [6].

In world practice, the standard CRT mode with TMZ followed by treatment with TMZ includes only 6 CT courses.

However, some clinicians are inclined to the opinion that larger number of courses are advisable, especially in patients with contrasted tumor remnants. There were no comparative randomized trials assessing the effectiveness of this approach. When comparing suitable groups from various studies, the following results were obtained. In the study by M. Stupp et al. [2], MTTP was 6.9 months in the group of patients, who received CRT + 6 courses of TMZ; in the study by Chint O. et al. [7], MTTP was 6.2 months in the group of CRT + 6 courses of TMZ; in the study by M. Gilbert et al. [4], MTTP was 8.8 months in

Table 1. General information about 107 patients with glioblastoma

<table>
<thead>
<tr>
<th>Combination therapy</th>
<th>CRT + TMZ, abs. (%)</th>
<th>CRT + TC, abs. (%)</th>
<th>TC +/- RT, abs. (%)</th>
<th>Total, abs. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>75 (70)</td>
<td>20 (18,7)</td>
<td>12 (11,3)</td>
<td>107</td>
</tr>
<tr>
<td>Males</td>
<td>37 (49,4)</td>
<td>8 (40)</td>
<td>7 (58,4)</td>
<td>52 (49)</td>
</tr>
<tr>
<td>Females</td>
<td>38 (50,6)</td>
<td>12 (60)</td>
<td>5 (41,6)</td>
<td>55 (51)</td>
</tr>
<tr>
<td>Average age, years</td>
<td>49</td>
<td>47</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Local lesion</td>
<td>74 (98)</td>
<td>19 (95)</td>
<td>8 (66,6)</td>
<td>101 (94)</td>
</tr>
<tr>
<td>Multiple lesions</td>
<td>1 (2)</td>
<td>1 (5)</td>
<td>4 (33,4)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Tumor resection</td>
<td>75 (100)</td>
<td>19 (95)</td>
<td>9 (75)</td>
<td>103 (96,2)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>0</td>
<td>1 (5)</td>
<td>3 (25)</td>
<td>4 (3,8)</td>
</tr>
</tbody>
</table>
the group of patients who received CRT + 12 courses of TMZ. It should be noted that in the study of R. Stupp et al., 16—17% of patients underwent only tumor biopsy, in the study of Chinot O. et al., the proportion of biopsies was 9.5—13.1%, M. Gilbert — 3%. Thus, it is still unclear what exactly has determined increase in MTTP, either longer CT or radical tumor resection.

In our series, 3.8% of patients underwent only tumor biopsy. When prescribing more than 6 CT courses, we were primarily guided by tolerability of therapy and the presence of residual tumor. If therapy was tolerated satisfactorily (blood parameters), we continued treatment up to 10 courses. Retrospective analysis has shown that 51 patients had no progression after CRT and 6 CT courses. In the cases, where CT was stopped or continued, MTTP was 17.7 and 17.3 months, respectively, the differences are not significant \( p = 0.512 \) (Fig. 2). When extending CT for more than 10 courses, we were guided by the presence of contrasted tumor remnants, absence of progression signs during continued treatment, as well as increased metabolic activity in a tumor as shown by positron emission tomography (PET) of the brain with C11 methionine. In 20 patients without progression after 10 CT courses, MTTP was 26.4 months in the cases when CT was termination, and 19.2 months when it was continued over 10 courses \( p = 0.015 \) (Fig. 3). The differences were not significant. This results lead to conclusion that these patients require continued antitumor therapy, by probably in other regimens.

**Bevacizumab in the first-line therapy for GB**

The study of Cloughesy was one of the first researches that provided the basis for the use of bevacizumab (Bev) in patients with GB progression. The study described 167 patients with GB relapse, who were treated with Bev or Bev in combination with irinotecan. Partial response (tumor reduction by 50% or more) was achieved in 28.3% of patients who received Bev and 37.8% of patients who received Bev + irinotecan; in several patients, complete response was achieved. We obtained similar results in 36 patients with GB relapse, who received combinations of various cytostatics with Bev (in Russian Federation, Bev was approved for the treatment of GB since November 2009). Partial response was achieved in 13 patients, complete response – 3 patients [9].

According to the results of Avaglio and RTOG 0825 studies, application of Bev in the first-line treatment in addition to R. Stupp’s regimen increases the MTTP, but does not affect the OS. For example, MTTP was 6.2 months in patients, who were included in Avaglio and used CRT regimen with TMZ. When this regimen was supplemented with Bev at a dose of 10 mg/kg every 2 weeks starting from the first day of the CRT and further until progression, MTTP was 10.8 months. OS was 16.7 and 16.8 months, respectively [7]. Such a difference in the effect of Bev on the MTTP and OS was due to the fact that patients, who did not receive Bev in the first line treatment, received it in the second-line treatment and for this reason OS was similar in both groups of patients.
Currently, Bev is not recommended as the first-line therapy for GB.

Criteria to assess the efficacy of treatment of central nervous system tumors

When speaking of tumor progression, the criteria for determining progression signs should be mentioned. Since 1990, criteria suggested by D. Macdonald et al. [10] were used in neuro-oncology for tumor evaluation. They take into account tumor size, the presence of new lesions, the dynamics of neurological symptoms, and the use of steroid therapy. However, these criteria can not be used to assess non-contrasted tumors, which is a drawback. Another serious problem lies in the fact that Macdonald’s criteria are used for the tumors subjected to therapy with anti-angiogenic drugs (e.g., Bev), which change the permeability of the capillaries and thereby inhibit tumor contrast. In this situation, the true spread of the tumor can only be determined in the T2/FLAIR-mode. For this reason, RANO [11] criteria are used since 2010. RANO criteria assess tumor size over time using T1 contrast-enhanced MRI and hyperintensive signal area using T2 and FLAIR modes and also take into account neurological status and the use of dexamethazone (Table 2).

Case report

Here we provide a case report to illustrate our treatment strategy.

Patient C., 40 years old. Since May 2012, the patient experienced progressive headaches, there was an episode of generalized seizure. MRI of the brain with intravenous contrast performed on 26 May 2012 detected a mass lesion of the right temporal lobe, actively accumulating contrast and accompanied by a pronounced perifocal edema (Fig. 4a). Tumor was resected on 02.07.12. Histological examination identified GB. In July — August 2012, the patient underwent CRT: RT single dose of 2—3 Gy, total dose of 48 Gy (unfortunately, in some institutions in the Russian Federation, non-standard single-dose radiation therapy is used in the treatment of patients with brain tumors) with simultaneous oral intake of TMZ at a dose of 140 mg daily. MRI in September 2012 detected no contrasted tumor remnants (see Fig. 4b). During the period from September 2012 to July 2013, the patient underwent 11 courses of chemotherapy with oral intake of TMZ at a dose of 400 mg for 5 days every 28 days. MRI in July 2013 detected no contrasted tumor remnants (see Fig. 4c). In July 2013, PET of the brain with C11 methionine detected the area with enhanced accumulation of radiopharmaceutical, accumulation index (AI) 1.62, tumor remnants with moderate metabolic activity. Due to this fact, CT with TMZ was continued and a total of 17 courses were conducted by February 2014. Patient’s condition was satisfactory, steroid therapy was not carried out, seizures did not recur, and the patient returned to work. During the period from February 2014 to September 2015 (20 months), chemotherapy was not carried out. Scheduled MRI in September 2015 (38 months after surgery) detected increased area of hyperintensive signal in FLAIR mode at the surgical area and in the right pole of the temporal lobe. There was no worsening of neurological symptoms. On 28.09.15, PET detected hypermetabolic area with AI of 2.05 at the pole of the temporal lobe in accordance with the changes detected by MRI, continued tumor growth (see Fig. 4c). During the period from...
19.10.15 to 21.10.15, the patient underwent stereotactic radiotherapy using hypofractionation regimen at the area of tumor recurrence in the right temporal lobe, including 3 mm margin around this area (GTV/CTV 2.969/5.612 cm³), a total of 3 fractions, 8 Gy per fraction until average total dose of ≈24.82/24.1 Gy using multiple beams method (Σ=145), until total dose of 21.5 Gy prescribed at the isodose of 81%. TMZ chemotherapy was resumed from October 2015 to March 2016, a total of 6 courses were carried out. In February 2016 (44 months after surgery), MRI showed decrease in the hyperintensive signal area in FLAIR mode at the pole of the right temporal lobe and stable pattern at the surgical area. PET of the brain with C11 methionine: decreased accumulation of the radiopharmaceutical, AI 1.23 (see Fig. 5d). There was no worsening of neurological status. Headache and seizures did not recur since the surgery. At the time of writing of this article, 48 months have elapsed, there is no signs of disease progression.

Pseudoprogression

“Pseudoprogression” term was first suggested in 2007. Pseudoprogression (PsP) is a name for subacute changes, developing within 12 weeks after RT and characterized by X-ray picture of increase in contrasted area by more than 25%. It is believed that combined CRT with TMZ increases the incidence of PsP phenomenon. Despite the MR-signs of disease progression, spontaneous regression of both clinical symptoms and contrasted area (MRI) is subsequently observed in some of these patients. The incidence of PsP averages 20—30%. It was shown that development of PsP correlates with methylated MGMT gene in the tumor and may be a predictor of high efficacy of the therapy [12]. Therefore, the use of the aforementioned evaluation criteria is relevant no earlier than 12 weeks after completion of RT. Before that time, appearance of new lesions outside the irradiated area is the main symptom of tumor progression.

For clinicians, pseudoprogression phenomenon causes doubts in the choice of further treatment strategy. On the one hand, when ignoring the PsP phenomenon and changing treatment schedule, we deprive a patient of the possibility to continue effective and convenient therapy with TMZ. On the other hand, true progression is much more common, and in this case, continuation of previous therapy is inadvisable. A number of investigators [13] “modify” pseudoprogression criteria, considering as PsP only those cases, where increase in contrasted area is not associated with worsening of symptoms and the time acceptable for PsP diagnosis does not exceed 1 month after chemoradiotherapy.

It is highly important to distinguish between true progression and pseudoprogression, when planning a second-line therapy of GB. False-high effectiveness values can be obtained when including PsP patients in the study.

In our series, we observed increase in contrasted area by more than 25% within the period of 160 days after diagnosis, i.e. about 12 week after completion of CRT, in 17 patients (10 of these patients continued treatment). Seven (41%) of 17 patients survived for more than 1 year after detection of progression. At the time of writing of this article, 6 patients died and 1 patient is alive; overall survival in this group is 22 to 66 months (average survival is 33 months). Most likely, these 7 patients had pseudoprogression phenomenon.

Metabolic, perfusion, diffusion, and X-ray studies can be used to distinguish between progression and pseudoprogression. Further studies are required to investigate reliability and procedure of their use [12].
Table 2. Criteria to assess the dynamics of central nervous system tumors

<table>
<thead>
<tr>
<th>Complete response</th>
<th>Partial response</th>
<th>Stabilization</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>*M</td>
<td>**R</td>
<td>M</td>
<td>R</td>
</tr>
<tr>
<td>Contrasted foci in T1 mode</td>
<td>No</td>
<td>No</td>
<td>Decrease by 50% and more compared to the baseline</td>
</tr>
<tr>
<td>T2/FLAIR</td>
<td>Not considered</td>
<td>Stable or decrease</td>
<td>Not considered</td>
</tr>
<tr>
<td>New foci</td>
<td>No</td>
<td>No</td>
<td>Stable or decrease</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>No</td>
<td>No</td>
<td>Stable or decrease</td>
</tr>
<tr>
<td>Clinical status</td>
<td>Stable or improved</td>
<td>Stable or improved</td>
<td>Stable or improved</td>
</tr>
<tr>
<td>Considered in evaluation</td>
<td>All</td>
<td>All</td>
<td>All</td>
</tr>
</tbody>
</table>

Note: *Macdonald's criteria; **RANO criteria.

Patients with large and inoperable GBs

In 2009, the study “Chemotherapy in the treatment of patients with inoperable malignant supratentorial astrocytic gliomas” was completed at the Burdenko Neurosurgical Institute. In this study, 37 patients with inoperable large GBs, who underwent only STB followed by CT, were treated using three regimens: PCV was used in 15 (40.5%) patients, TMZ — 5 (13.5%), TMZ + cisplatin — 17 (45%) patients. MTTP was 5, 4, and 8 months, median OS — 8.5, 6.0, and 10.5 months, respectively. In the cases, where only CT was applied, the highest direct effectiveness was obtained when using the TMZ + cisplatin regimen: complete response was observed in 2 patients, partial response — 10, stabilization — 7, and progression — 7. When using monotherapy with TMZ, stabilization was the maximum effect [14].

The study of combination of TMZ + cisplatin was preceded by a series of studies performed in patients with recurrent GB. The study by A. Brandes et al. [15] was the first and the largest series of cases that showed the efficacy of the combination of TMZ + cisplatin in patients with recurrent GB, who were not previously treated with CT. The investigation was based on in vitro study, showing that cisplatin is capable of not only reducing activity of MGMT, but also enhancing the efficacy of TMZ in this direction. Additionally, the efficacy of combination TMZ + cisplatin as the first-line treatment was shown in patients, who already received TMZ and thereafter had PROI [16]. S. Balana et al. [17] have shown the effectiveness of the use of TMZ + cisplatin as the first-line treatment in patients with verified inoperable GB.

We used carboplatin instead of cisplatin in combination with TMZ in this group of GB patients. Carboplatin is less nephrotoxic and significantly less emetogenic.

In 792 patients with advanced ovarian cancer, combination carboplatin + paclitaxel was no less effective than combination cisplatin + paclitaxel, had fewer side effects and more convenient administration regimen [18]. When comparing the effectiveness of combinations bleomycin + etoposide + carboplatin or cisplatin (BEC/BEP), it was shown that BEP is essentially superior to BEC in terms of relapse-free and overall survival [19]. Previous treatment of 618 patients with disseminated non-small cell lung cancer using carboplatin + paclitaxel or cisplatin + paclitaxel modes showed that, while the number of responses to treatment was similar, OS of patients was higher in the case of the combination cisplatin + paclitaxel, and carboplatin + paclitaxel combination is a reasonable alternative, with the same response rate, good safety profile, acceptable toxicity, and ease of application [20]. No comparative evaluation of the efficacy of the combinations cisplatin + paclitaxel and TMZ + carboplatin was carried out in patients with inoperable gliomas.

In our series, 12 patients received only CT as a first-line therapy. Multifocal GBs were detected in 4 patients, STB was performed in one of them and the rest underwent resection of one tumor node. Disseminated diffuse GB was observed in 8 patients. STB was done in 2 cases, partial tumor resection — 6. In all cases, the size of the original tumor or tumor remnants after resection excluded the possibility of RT. These 12 patients received CT in the TC mode. Six patients underwent RT after tumor size reduction. MTTP was 8.1 months in the entire group.

Based on the available data on the effectiveness of TMZ in combination with platinum preparations in patients with large GBs, we administered TC after completion of CRT in patients with partially resected GBs, a total of 20 patients. Of these, tumor progression before completion of 6 CT courses was observed in 16 patients. Four patients continued treatment for more than 6 courses, including 3 patients who had progression after 8, 9 and 12 courses, respectively. The treatment was
stopped after 10 courses in 1 patient. The median time to progression in this group was 7.2 months.

Historical data show that patients with inoperable GBs who receive only symptomatic therapy survive for about 3 months, while those who receive radiotherapy survive for 6—7 months [21]. Therefore, temozolomide + cisplatin and TMZ + carboplatin regimens can be recommended for the use in patients with disseminated diffuse glioblastoma. However, in spite of the improved OS, the results of treatment of patients with large GBs remain unsatisfactory.

Early tumor progression in these patients is indicative of relatively low efficacy of therapy and the need for more effective medications, for example, Bev.

As mentioned above, the results of randomized phase III studies show that Bev is not indicated in the first-line treatment of GB. However, data analysis by O. Chinot have shown that the use of Bev in the first-line treatment has different effects on survival of patients with various subtypes of GB. Thus, in patients with proneural GB and no mutations of IDH1 gene, who received Bev in the first-line treatment, OS was 17.1 months, while in the placebo group it was 12.8 months (p = 0.002) [22]. It was also shown that the use of Bev resulted in significantly longer time to worsening of overall health status, physical and social functioning, communication, and motor deficits. It was reported that Bev can effectively reduce the cerebral edema [23].

It should also be noted that the criteria for inclusion of patients to Avaglio and RTOG 0825 implied that they have Karnofsky score of 70 or higher, while the majority of patients in our series who received TC had a lower score. Thus, taking into account high direct efficacy of Bev, which was detected both clinically and in MRI studies, it is reasonable to examine its efficacy in the first-line treatment of patients with diffuse disseminated GB. The factors, predicting beneficial effect of Bev, such as GB subtype, serum level of matrix metalloproteinase, and methylation status of the MGMT gene, should be studied.

---

**Fig. 4. Example of treatment of a patient with glioblastoma of the right temporal lobe.**

Explanation in the text.

1, a — preoperative MRI; 1, b — MRI 2 months after surgery; 2 — MRI one year after surgery; 3 — PET and MRI 38 months after surgery, tumor progression; 4 — PET and MRI 44 months after surgery, positive dynamics.
Conclusion

Chemoradiation therapy with temozolomide followed by a year-long temozolomide monotherapy is an optimal treatment regimen for patients who underwent resection of GB. A third of patients treated using this approach have no signs of tumor progression during the first year. Thorough study of clinical and radiological findings in the course of treatment makes it possible to achieve maximum efficacy, avoid unreasonably early switch to second-line therapy, and timely detect tumor recurrence signs. The Response Assessment in Neuro-Oncology (RANO) criteria should be used to assess MRI-detected changes in the tumor size. The rates of overall and recurrence-free survival were significantly lower in patients with inoperable or partially resected tumors. The applied approaches provide only a slight advantage in control of tumor growth, which necessitates the search for more effective treatment options for these patients. Inclusion of bevacizumab to the first-line therapy regimen may be a possible approach.

Commentary

This work focuses on an obviously important issue, the treatment of patients with brain glioblastomas. Strength of this study lies in the analysis of authors’ own results of treatment of patients in their routine practice, careful follow-up history taking, thoughtful analysis of the results, and the use of both international and Russian studies in their discussion. The authors collected information about 107 patients treated at the Burdenko Neurosurgical Institute in 2010—2012. Treatment of glioblastomas is expensive, and for this reason in does not meet international standards in a significant number of cases in Russia. The situation, when a large number of patients were treated at the same institution in full compliance with its standards, is quite rare. However, as shown in this study, this approach enables not only reproducing, but also going beyond the results of treatment obtained in the world’s best clinics. The authors’ findings, demonstrating that there is no need to increase the number of temozolomide chemotherapy courses to more than six, is important from a practical viewpoint.

A.V. Smolin (Moscow, Russia)

There is no conflict of interest.

REFERENCES


19. Horwich A, Sleijfer DT, Fossa SD, Kaye SB, Oliver RT, Cullen MH, Mead GM, de Wit R, de Mulder PH, DeMabley DP, Cook PA, Sylvester RJ, Stemming SP. Randomized Trial of Bleomycin, Etoposide, and Cisplatin Compared With Bleomycin, Etoposide, and Carboplatin in Good-
The First Experience with a New Technique of Portal Endoscopic Discectomy for Herniated Cervical Discs

A.O. GUSHCHA, S.O. ARESTOV, A.V. VERSHININ

Research Center of Neurology, Moscow, Russia

Selection of the most appropriate tactics for surgical treatment of herniated cervical discs is a topical issue to be discussed. The idea of herniated disc removal using an endoscopic technique is not new. This is a routine surgery for the lumbar spine. However, application of endoscopic techniques in the cervical spine surgery was first reported only in 2014 (J. Yang, et al.).

Objective. This study was aimed at mastering the methodology of a new technique, portal endoscopic discectomy, determining the indications for this surgery for herniated cervical discs, and comparing outcomes of this surgery with outcomes of anterior microsurgical discectomy. A comparison group consisted of 25 patients, who underwent portal endoscopic cervical discectomy. The study included 25 patients, who underwent anterior microsurgical discectomy and placement of an interbody cage.

Results. Comparison of surgical outcomes showed no significant difference (p>0.05) in the severity of postoperative local and radicular pain syndrome. According to the Neck Disability Index (NDI), significant improvement occurred in patients with endoscopic surgery. According to the Odom criterion, significant advantage in the number of excellent and good outcomes was observed in study group patients. There were significant differences between the groups in the duration of postoperative hospital stay. The average duration was 3 days in the study group and 5 days in the control group.

Conclusion. Portal endoscopic discectomy is a highly effective treatment for herniated cervical discs, which provides clinical outcomes associated with much less surgical trauma. The study demonstrates not only the efficacy of the suggested technique, but also its safety compared to conventional anterior microsurgical techniques, which usually involve interbody fusion. This surgery is superior to other interventions in terms of the rate of rehabilitation and social adaptation of patients and reduces postoperative hospital stay.

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

The incidence of cervical discogenic compression syndromes is extremely high. According to J. Lawrence [1], despite the relatively small proportion of detectable lesions of the cervical intervertebral disc among the total number of degenerative spinal diseases, about 10% of the population experience periodic compression-related pain in the cervical spine or in the hand.

Assessment of cervical hernia is based on conventional staging classification of intervertebral disc herniation (protrusion, prolapse, and sequester) proposed by A. Decoulx [2], which is important in evaluation of the clinical course of the process and selection of treatment strategy, as well as classification of herniated intervertebral discs in terms of their axial arrangement and relationship with the bony structures of the spinal canal. The latter distinguish between median, paramedian (laterally shifted with respect to the sagittal plane), lateral, and foraminal hernia.

Based on the analysis of a large number of cases, J. Bland et al. [3] determined characteristic clinical symptoms associated with cervical radicular compression, having practical value to assess the severity of impairment and axial arrangement of hernia. Along with the characteristic radicular irradiation of pain, sensory disturbances, loss of tendon reflexes corresponding to innervated myosclerotome, and paresthesia, which are indicative of root compression in the intervertebral foramen, are often detected. In the case of questionable data, Spurling’s test is recommended (axial load on the neck along with side-to-side shaking), which leads to worsening of paresthesia [4].

J. Knightly [5] conveniently distinguish two pathoanatomical type of compression substrate formation at the level of intervertebral disc: soft disc (or fragments of prolapsing disc as the acute phase of the disease) and hard disc (uncovertebral osteophytes as the chronic phase of the disease). In our opinion, the structural state of the compressing factor, as well as its axial arrangement is the key factor in in the choice of surgical treatment. In patients with “soft disc”, clinical presentation is dominated by symptoms of brachialgia that often occur after physical activity, sudden movement of the head, or neck injury. Irradiation of acute radicular pain corresponds to dermatomes and often depends on the position of the head and limbs. “Helmet”-like or homolateral hemicrania-like irradiation of the pain is very typical for this group of patients. Hypesthesia, accompanying this kind of compression, always involve individual dermatomes and may be accompanied by an isolated reduction of tendon reflexes in adjacent muscles. Decrease in strength (paresis) of the proximal parts of the upper limbs, which is often unilateral and transient.

The symptoms associated with the development of “hard disc” are characterized by headache and armache, which are often symmetrical and accompanied by transient localized palpatory tenderness at the level of
hernia, which has a certain diagnostic value. This variant of the disease is characterized by multiple areas of desensitization up to conduction anesthesia, originating at the level of the lesion and accompanied by impaired muscle strength below the segment concerned, sometimes up to deep paresis. Clinical presentation of calcified compressing structures in the cervical spinal canal is characterized by normoreflexia or hyperreflexia, which is most likely due to chronic circulatory disturbances in the anterior spinal artery system.

In patients with “hard disc”, development of clinical symptoms takes much more time compared to those in with “soft” hernias.

Conventional CT and MPT-studies provide complementary information in the diagnosis of the disease. The former method is preferable to identify compression factors (hernia, osteophytes), and the latter is preferable to detect the results of compression (compression of the spinal cord and roots). Bischoff (2003) investigated sensitivity, specificity, and accuracy of CT, MRI, and myelography when establishing the “herniated disc” and “spinal stenosis” diagnoses. The accuracy and sensitivity of CT is slightly higher compared to MRI. CT remains the best method to assess central stenosis. MRI provides images of the whole cervical spine and enables detecting stenosis in frontal and sagittal projections (Fig. 1).

The studies of J. Wilmink [6] showed the following clinical and radiographic correlations of CT results.

1. Complete occlusion of the intervertebral foramen by laterally migrated masses of the degenerated intervertebral disc (“soft disc”) is always accompanied by radicular syndrome.

2. Narrowing of the intervertebral foramen due to osteophyte (“hard disc”) results in the root swelling and less pronounced radicular syndrome compared to the first variant.

3. Paramedian disc protrusion that does not result in complete occlusion of the intervertebral foramen and pronounced compression of the spinal cord often causes the development of radicular symptoms on the contralateral (with respect to hernia) side.

Treatment of compression syndromes caused by degenerative changes in the cervical spine has a 50-year-long history, and, despite this fact, there is currently no common viewpoint on the criteria for selection of certain surgical procedures. This can be explained, on the one hand, by continuous improvement of the techniques of cervical spine surgery and development of “spinal design” operations, and, on the other hand, deepening of understanding of the pathogenesis and biomechanics of these changes. Both anterior and posterior approaches in the cervical spine surgery have been developing in parallel over 50 years. Many surgeons developed the anterior approach through the interfascial space, using the transverse or oblique incision along the anterior margin of the sternocleidomastoid muscle [7, 8]. The history of
posterior approaches begins in 1955, when D. Northfield [9] proposed bilateral laminectomy, extended by one segment above and below the pathological level. In 1961, W. Scoville [10] performed the limited bilateral laminectomy supplemented with bilateral facet resection. The development of the posterior approach was aimed at decompression of neural structures by means of resection of the posterior supporting complex of the arch and spinous process. These approaches did not always enable removal of compressing masses located on the ventral surface of the spinal canal, although several cases of removal of disc hernia and vertebral body osteophytes have been reported [11]. Posterolateral approaches include posterior foraminotomy or facetectomy. This surgical technique was developed in 1944 by R. Spurling [4] and later on, in more detail, by Frykholm, W. Scoville [12] (“keyhole” technique). This posterior approach enabled foraminotomy and herniated disc resection through a small incision. However, most neurosurgeons still prefer to use a more safe anterior approach due to the probability of neurological deficit and the need for segment stabilization [13]. Existing endoscopic methods belong to intradisc interventions, but are technically similar to microsurgical interventions, but differ from the latter in the degree of soft tissue traumatization associated with these approaches and visualization quality, which in this case enables “peeking behind the root”.

The study was aimed at mastering the methodology of the new technique, portal endoscopic discectomy, determining the indications for this operation in patients with herniated cervical disc, and comparing the results of this operation with the results of the anterior microsurgical discectomy.

Material and Methods

We compared surgical outcomes in 25 patients with C5—C6 [9] and C6—C7 lateral disc herniation [16], who underwent endoscopic portal cervical discectomy. Retrospective evaluation of surgical outcomes in 25 patients, who were also operated on by the first author and underwent a microsurgical single-level anterior cervical discectomy with interbody fusion at C5—C6 or C6—C7, was used as a comparison group. The operation performed in the control group patients is described in detail in relevant guidelines [14, 15].

In both groups, early postoperative outcomes were assessed as follows: VAS (visual analogue scale) — timing and extent of radicular pain regression; decrease in pain based on NDI (Neck Disability Index) — social adaptation of patients; Odom criteria — overall postoperative recovery. NDI provides a measure of patient’s social adaptation based on summation of points characterizing the possibility of usual activities (walking, sleeping, reading, recreation, etc.). Odom characterizes the effect of the surgery in general, from good to unsatisfactory. Evaluation of NDI and Odom criteria was carried out immediately before the discharge. In addition, the time of postoperative hospital stay was evaluated.

Mann-Whitney test was used in statistical processing to assess the validity of the results.

The technique of portal endoscopic cervical discectomy

Patient’s positioning on the operating table

The patient is laid on the operating table in prone position with hands placed along the body. The head is placed on the soft headrest or fixed in Mayfield head clamp. The cervical spine is placed in neutral position.

Planning the incision

Electron-optical converter (EOC) is typically used for incision planning, images of the cervical spine are taken in the lateral projection. A sterile needle is placed in the plane of the target intervertebral disc. Incision is planned 1—2 cm lateral to the midline, depending on patient’s physique (Fig. 2).

Operative approach

Skin incision is followed by incision of fascia and EOC-controlled punctual placement of surgical cone at the projection of the desired interval (Fig. 3). The base of the lower articular process of the overlying vertebra is an optimal point to place a port. Surgical port installation is followed by preserving resection of adjacent vertebral arches and flaval ligament is released. When the port is properly installed, no significant resection of the intervertebral joint is required. It should be remembered that, according to various authors [16—18], resection of
25 to 50% of the intervertebral joint results in segmental instability. Soft tissue removal from the intralaminar space is followed by opening of the flaval ligament, preferably as medial as possible and by blunt dissection [19].

**The main stage of the surgery**

Opening of the flaval ligament usually results in visualization of dural sac, whose separation provides the approach to the gaine radiculaire. There is usually venous plexus along the latter (see Fig. 3a), which is coagulated and intersected. After that, the root becomes more mobile despite the compression. Root displacement enables visualization of disc hernia and its removal (see Fig. 3b).

**Surgical wound closure**

The wound is closed layer by layer. Particular attention is paid to restoration of the integrity of the muscle aponeuroses in the surgical area.

Rigid cervical collar should be used for 3 weeks in the early postoperative period to reduce axial loads on the operated spinal motion segment.

**Results**

There was no worsening of neurological deficit in both the study and control groups. In 2 (8%) patients in the group of endoscopic removal of disc hernia, transient numbness in the region of innervated dermatome was observed followed by full regression by the time of discharge. Preoperatively, median intensity of pain in the shoulder and forearm as assessed by VAS score was 6 (3; 8) in the endoscopic discectomy group and 6 (4; 8) in the microsurgical anterior discectomy group. After surgery, this value decreased to 1 (0; 6) in the posterior endoscopic discectomy group and 2 (1; 6) in the microsurgical anterior discectomy group. In both groups, there was significant decrease in pain ($p=0.016$ and $p=0.034$, respectively). Immediately before discharge from the
hospital, the level of pain in the shoulder and forearm did not differ significantly in these two groups \((p>0.05)\). When assessing pain in the neck, two groups were comparable in the preoperative period \((p>0.05)\) and significant decrease in the severity of pain was observed in the postoperative period \((p=0.024\) in the study group and \(p=0.034\) in the control group) (Table 1).

All study group patients noted complete or nearly complete regression of pain syndrome immediately after the operation.

Significant improvement of the score was observed in patients who underwent endoscopic surgery. In both groups, patients were subjectively satisfied with the outcome. As for Odom criteria, there were significantly more excellent and good outcomes in study group patients (Table 2).

Significant differences were found, when comparing the time of postoperative hospital stay: it was 3 (2; 5) days in the study group and 5 (4; 6) days in the control group. In the study group, 1 (4%) patient reported the recurrence of radicular pain one week after surgery. Preoperative and postoperative MPT of this patient are shown in Fig. 4 and 5. Control MRI showed that disc hernia was completely removed and the pain was not associated with its recurrence. Antineuritic therapy for 2 weeks resulted in complete regression of pain syndrome.

Thus, these studies demonstrate safety and efficacy of the posterior portal endoscopic discectomy. When the anatomy of the compressing factor is quite clearly understood, this type of intervention is superior to other operations in terms of the rate of rehabilitation and social adaptation of patients and shortens postoperative hospital stay.

Our results provided the basis for formulation of indications and contraindications for the portal cervical endoscopic discectomy.

**Surgery is indicated in the following cases:**
- clinical presentation of radiculopathy corresponds to the side and level of the lesion detected by MRI/CT;
- CT/MRI studies confirm the correspondence between the “soft” compression of the root, which is located in the lateral third of the width of the spinal canal, and the clinical presentation of the disease;
- there is no effect of conservative treatment during 3 weeks.

**The operation is contraindicated in the following cases:**
- There are signs of segmental instability;
- There is kyphotic deformity of the spine at the level of disc herniation.

**Discussion**

The choice of surgical approaches in the treatment of compression syndromes presenting with neurological and vascular disorders is associated with a number of controversial issues [20, 21], although these interventions have been existing for rather long period [15]. The main problem is, which decompression option should be selected, either anterior or posterior one. Both methods enable quite adequate solution of this problem. Selection of decompression direction is determined by localization.

<table>
<thead>
<tr>
<th>Table 1. The intensity of pain in the neck, shoulder, and forearm on the visual analogue scale (VAS) before and after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criterion</strong></td>
</tr>
<tr>
<td>Pain in the shoulder and forearm (median and range)</td>
</tr>
<tr>
<td>Preoperative score</td>
</tr>
<tr>
<td>Score before discharge</td>
</tr>
<tr>
<td>Whitney-Mann test, (p)</td>
</tr>
<tr>
<td>Pain in the neck (median and range)</td>
</tr>
<tr>
<td>Preoperative score</td>
</tr>
<tr>
<td>Score before discharge</td>
</tr>
<tr>
<td>Whitney-Mann test, (p)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Surgical outcomes according to NDI index and Odom criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criterion (criterion)</strong></td>
</tr>
<tr>
<td>NDI (median and range)</td>
</tr>
<tr>
<td>Preoperative score</td>
</tr>
<tr>
<td>Score before discharge</td>
</tr>
<tr>
<td>Whitney-Mann test, (p)</td>
</tr>
<tr>
<td>Very good/good</td>
</tr>
<tr>
<td>Satisfactory/unsatisfactory</td>
</tr>
</tbody>
</table>
**Fig. 4. Preoperative MRI.**
a — sagittal projection; b — axial projection (explanation in the text).

**Fig. 5. Postoperative MRI.**
a — sagittal projection; b — axial projection (explanation in the text).

**Fig. 6. The algorithm of selection of surgical approach in patients with cervical spondylogenic compression.**
of compressing factor as proved for single-level procedures.

According to opinion of H. Jho expressed in a private conversation, posterior cervical foraminotomy has limitations in the case of frontal compression with osteophyte, posterior compression with uncovertebral joint, and pronounced cicatricial process. The cardinal clinical syndrome of cervical radiculopathy requires more thorough examination of the patient, since it is often not accompanied by unequivocal x-ray data about the cause of the compression, and almost never has pathognomonic changes in neurovascular structures. The highest accuracy of detection of muscular atrophy in corresponding muscles was proved to be the main criterion of the level of radiculopathy. Modern neurovisualization methods enable identification of the compressing factor: “soft” (herniated disc) or “hard” (osteophyte or bone spike), which is a decisive factor in the choice of surgical approach. In the case of lateral “soft” disc, posterior portal endoscopic resection is indicated, whereas more radical removal of osteophyte in this area can be achieved through the ventral approach. The nature of the compressing factor in patients with the cervical radiculopathy syndrome should also be considered in the context of neurological symptoms. In the case of osteophyte, the severity of radicular symptoms (especially pain) is substantially lower than in the case of “soft” hernia.

To our knowledge, inefficiency of surgical treatment of patients with radiculopathy is primarily due to underestimation of neurological symptoms and interpretation of neurovisualization data. In particular, the paramedian location of disc hernia is often accompanied by radicular symptoms in the contralateral hand. The ignorance of this fact may cause inadequate choice of the side of surgical approach and therefore the lack of clinical effect of the surgery.

Confirmed spine deformity and detected segmental instability are significant factors in choosing the direction of surgical approach. Cervical spine kyphosis associated with degenerative processes in the vertebrae always suggests the use of ventral approach accompanied by appropriate stabilizing measures.

Based on these data and surgical outcomes, we developed the algorithm for selection of surgical approach in patients with cervical spondylogenic compression (Fig. 6).

The use of endoscopic microdiscectomy in the treatment of herniated cervical intervertebral discs is highly effective and provides clinical results with considerably less surgical trauma. We discovered technical features and proposed recommended applications, which will contribute to widespread use of this promising minimally invasive technique in neurosurgical practice.

There is no conflict of interest.

REFERENCES

The article provides a detailed description and comparative analysis of the use of innovative technique of portal endoscopic discectomy in treatment of herniated cervical discs. The study included 25 patients, who were operated on in 2014—2016. The control group included 25 patients, who were operated on using anterior cervical discectomy with installation of a single-level interbody implant. The authors suggested indications for the use of portal endoscopic discectomy: paramedian or lateral herniation of the cervical disc with monoradicular symptoms and no calcification of disc herniation as evidenced by CT. The signs of segmental instability and spinal deformity, which is usually indicative of segment stabilization, are considered as contraindication. The technique of surgical intervention from patient positioning on the operating table to surgical wound suturing is described in detail.

Treatment outcomes were assessed on VAS scale (visual analog scale), preoperative and postoperative values were compared. Preoperative comparison of the groups showed no statistically significant difference between the groups of patients. Social adaptation and quality of life have been assessed using NDI (Neck Disability Index). Additionally, overall recovery of patients was compared using Odom criterion and time of patients’ hospital stay was evaluated. High level statistical processing of the results was performed using modern statistical processing tools, which proves the validity of the results of the study.

In my opinion, this article is a valuable and relevant scientific work. The provided information can be used to develop methods of portal cervical endoscopic discectomy. The presented data demonstrate the efficacy and safety of the method.

Commentary

The bulk of the article focuses on describing the techniques and nuances of the operation. In our clinic, we use portal endoscopic discectomy to treat lumbosacral intervertebral disc herniation, but the use of this technique in the cervical spine is associated with a number of difficulties. The correct positioning of the endoscopic port is the most challenging problem. The authors carefully describe this issue and note the nuances, so that it is, in fact, guidelines to master this method.

Selection of patients for this operation is a disputable question. Indeed, the posterior approach is only suitable for resection of lateral and paramedian disc hernia, since even a small traction of the compressed spinal cord can cause severe postoperative neurological disorders. This fact was the main argument to switch from the posterior microsurgical approach to anterior approaches in the late 1900s. The authors supplemented the standard preoperative examination complex with CT of the cervical spine to measure preoperative density of disc hernia. This is due to the fact that significant traction of nerve structures and the use of bulky microsurgical instruments is required for removal of ossified herniation of intervertebral discs, which in turn eliminates the advantages of endoscopic approach. In our view, this additional preoperative examination is reasonable and improves safety of the technique.

Therefore, this material is relevant and highly informative. The detailed description of the procedures and techniques of the portal endoscopic discectomy makes this work a valuable guideline for the operation. This technique is a new promising trend in neurosurgery. The authors fully proved the effectiveness and safety of the method.

N.L. Konovalov (Moscow)
Clinical and Morphological Characteristics, Diagnostic Criteria, and Outcomes of Surgical Treatment of TSH-secreting Pituitary Adenomas

L.I. ASTAF’EVA1, B.A. KADASHEV1, L.V. SHISHKINA1, P.L. KALININ1, D.V. FOMICHEV1, M.A. KUTIN1, I.A. AREF’EVA1, L.K. DZERANOVA2, YU.G. SIDNEVA1, I.S. KLOCHKOVA1, D.L. ROTIN3

1Burdenko Neurosurgical Institute, Moscow, Russia; 2Endocrinology Research Center, Moscow, Russia; 3Moscow Scientific Clinical Center, Moscow, Russia

Thyrotropinomas (TSH-secreting tumors) are a rare type of pituitary adenomas, which account for about 0.5—2.0% of all pituitary tumors. The criterion of thyrotropinoma includes visualization of the tumor along with normal or elevated blood level of the thyroid-stimulating hormone (TSH) and high level of free T4 (fT4) and free T3 (fT3).

Objective. The study was aimed at investigating clinical, diagnostic, and morphological characteristics and treatment outcomes of TSH-secreting pituitary tumors.

Material and methods. The study included 21 patients aged 15 to 67 years with pituitary adenoma and normal or elevated blood level of TSH in combination with elevated levels of fT4 and fT3, who were operated on at the Burdenko Neurosurgical Institute in the period between 2002 and 2015. The patients were tested for the levels of TSH, fT4, fT3, prolactin, cortisol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol/testosterone, and insulin-like growth factor (IGF-1) before surgery, in the early postoperative period, and 6 months after surgery. The thyroid status was evaluated using the following reference values: TSH, 0.4—4.0 mIU/L; fT4, 11.5—22.7 pmol/L; fT3, 3.5—6.5 pmol/L. An immunohistochemical study of material was performed with antibodies to TSH, PRL, GH, ACTH, LH, FSH, and Ki-67 (MiB-1 clone); in 13 cases, we used tests with antibodies to type 2 and 5 somatostatin receptors and D2 subtype dopamine receptors.

Results. Thyrotropinomas were detected in patients aged 15 to 67 years (median, 39 years) with an equal rate in males (48%) and females (52%). Before admission to the Neurosurgical Institute, 11 (52%) patients were misdiagnosed with primary hyperthyroidism; based on the diagnosis, 7 of these patients underwent thyroid surgery and/or received thyrostatics (4 cases). Hyperthyroidism symptoms were observed in 16 (76%) patients. The blood level of TSH was 2.47—38.4 mIU/L (median, 6.56); fT4, 22.8—54.8 nmol/L (median, 36); fT3, 4.24—12.9 pmol/L (median, 9.66). Tumors were endosellar in 4 (19%) cases and the endo-extrasellar in 17 (91%) cases. Total tumor resection was performed in 7 (33%) patients. All these tumors were either endosellar or endo-suprasellar. No total resection was performed in patients with infiltrative growth of adenoma (invading the skull base structures). An immunohistochemical study of resected tumor specimens detected only TSH expression in 3 (14%) cases; 18 (86%) tumors were plurihormonal and secreted TSH and GH and/or PRL. Of 13 tumors, expression of the type 2 dopamine receptor was detected in 9 (69%) cases; expression of type 5 and type 2 somatostatin receptors was found in 6 (46%) and 2 (15%) cases, respectively.

Conclusion. Postoperative decrease in the TSH level to 0.1 mIU/L or less was the criterion of total tumor resection. Total resection was performed in 33% of patients, having only endosellar and endo-suprasellar tumors. In most cases, tumors were plurihormonal and secreted TSH and GH and/or PRL.

Keywords: thyrotropinoma, TSH-secreting pituitary adenoma, central hyperthyroidism, acromegaly, somatostatin analogues.

Abbreviations:
ACTH — adrenocorticotrophic hormone
AB — antibodies
IMH — immunohistochemical study
IGF-1 — insulin-like growth factor-1
LH — luteinizing hormone
OGTT — oral glucose tolerance test
PRL — prolactin
fT3 — free T3
fT4 — free T4
STH — somatotropic hormone
TRH — thyrotropin-releasing hormone
TSH — thyroid stimulating hormone, thyrotropic hormone
TSH-PA — TSH-secreting pituitary adenoma
FSH — follicle stimulating hormone
CAIT — chronic autoimmune thyroiditis
D2DR — D2 subtype dopamine receptors
L-T4 — levothyroxine
SSt2 — type 2 somatostatin receptors
SSt5 — type 5 somatostatin receptors
Thyrotropinomas (TSH-secreting tumors) are a rare type of pituitary adenomas, which account for about 0.5—2.0% of all pituitary tumors. The mechanism of thyrotropinoma includes visualization of the tumor along with normal or elevated blood level of the thyroid-stimulating hormone (TSH) and high level of free T4 (fT4) and free T3 (fT3). Overproduction of TSH by these tumors leads to hyperstimulation of the thyroid gland and clinical presentation of so-called central hyperthyroidism. This TSH production is autonomous due to impaired down-regulation of thyroid hormones, which affects the hypothalamic-pituitary-thyroidal system. Low incidence of these tumors as well as sometimes insufficient doctors’ awareness of clinical features and diagnosis of central hyperthyroidism can lead to hyperdiagnosis of Basedow’s disease or other thyroid diseases involving hyperthyroidism, which can result in unreasonable thyroid surgery and/or therapy with radioactive iodine.

**Material and methods**

The study included patients with pituitary adenoma and normal or elevated blood level of TSH in combination with elevated levels of fT3 and fT4, who were operated on at the Burdenko Neurosurgical Institute during the period from 2002 to 2015. The group included 21 patients aged 15 to 67 years (median 39 years), 11 females (52%) aged 15 to 63 years (median 30 years) and 10 males (48%) aged 15 to 67 years (median 49 years).

All patients underwent MRI of the brain. All identified tumors were macroadenomas sized 16 to 64 mm in diameter (median 26 mm). We classify them according to their growth pattern and location (see Table). Thus, endo-sellar and endo-suprasellar adenomas not invading skull base structures (10 cases) were considered as non-infiltrative. Endo-extrasellar tumors invading the skull base structures, including cavernous sinus, were considered as infiltrative (11 cases).

The patients were tested for the levels of TSH, fT4, fT3, prolactin, cortisol, LH, FSH, estradiol/testosterone, and, in 13 cases, IGF-1 before surgery and in the early postoperative period. In the case of high level of IGF-1, growth hormone level was additionally studied during oral glucose tolerance test. Thyroid status was evaluated using the following reference values: TSH, 0.4—4.0 mIU/L; fT4, 11.5—22.7 pmol/L; fT3, 3.5—6.5 pmol/L. At admission to the Burdenko Neurosurgical Institute, thyroid status of patients who had a history of thyroidectomy and patients treated with somatostatin analogues or thyrostatics was assessed prior to the first operation is unknown.

Follow-up study was carried out in 12 patients. Follow-up time was 1 month to 7 years (median, 6 months).

**Results**

Clinical presentation of the disease included mainly symptoms of hyperthyroidism in 16 (76%) of patients, whose history was 1 to 13 years (median 4 years). Furthermore, we detected symptoms of mass effect of the tumor: visual impairment in 8 (38%) patients and cephalic syndrome in 7 (33%). Two patients were admitted in grave condition with large tumors accompanied by occlusive symptoms due to compression of the third ventricle (case 2, 8).

Four of eight reproductive-age females had amenorrhea (in two of them it was primary); 4 female patients had normal menstrual function. Lactorrhea was observed in 3 females. Androgen deficiency was diagnosed in 3 males.

Psychopathology usually fit into the presentation of anxiety and phobic disorders in the form of neurotic syndrome (12 patients) and panic attacks (11). Emotional disturbances in the form of depression were observed only in 3 patients. Eight patients complained of fatigue and weakness, 8 — palpitations, 5 — anxiety, 11 — mood lability, 3 — sleep disorder, 3 — sweating, 3 — tremor, 2 — subfebrile temperature, 2 — weight loss. The patients often had a combination of the aforementioned complaints. Psychiatric symptoms were most often moderate (13 patients).

Seven patients (see Table) had a history of thyroid surgery (6 — hemithyroidectomy, one of these patients had been operated on twice; 1 — thyroidectomy).
Four patients received thyrostatic therapy; at the time of admission, 2 of them (cases 9 and 10) still received thyrostatics. In these patients, fT4 levels before treatment with thyrostatics were 27.4 and 54.8 nmol/L and TSH levels were 5.59 and 6.52 mIU/L, respectively. At the time of admission to the Burdenko Neurosurgical Institute, normalization of fT4 level to 17.5 and 22.0 nmol/L was accompanied by increase in TSH levels to 9.72 and 10.2 mIU/L, respectively.

Thyroid ultrasound was performed in 13 patients: diffuse goiter was detected in 4 patients, nodular goiter — 3, diffuse nodular goiter — 1, and thyroid hypoplasia was observed in 1 patient with secondary TSH-PA.

At admission, three patients received levothyroxine: one of them previously underwent thyroidectomy (case 8), two patients with chronic autoimmune thyroiditis (CAIT) had primary hypothyroidism. Despite the high dose of levothyroxine (200 and 175 μg) and high level of free fractions of the thyroid hormones, TSH level was high (cases 16 and 19). We regarded these tumors as secondary thyrotropinomas. One of them had previously been operated on at the other hospital and was admitted to the Burdenko Neurosurgical Institute with recurrent pituitary adenoma.

Three patients had symptoms of acromegaly (change in appearance, growth of extremities, etc), confirmed by the results of hormonal blood test (high levels of IGF-1 and absence of STH suppression below 1.0 ng/ml during the oral glucose tolerance test, OGTT).

In patients with TSH-PA, blood level of TSH was 2.47—38.4 mIU/L (median, 6.56), fT4 level — 22.8—54.8 nmol/L (median, 36), fT4 level — 4.24—12.9 pmol/L (median, 9.66).

We found no correlation between the levels of TSH and fT4 (Fig. 1), between the level of TSH and fT3, as well as fT4 and fT3.

IGF-1 was tested in 10 patients with no clinical symptoms of acromegaly, 2 of them had elevated levels of IGF-1. They were tested for STH during OGTT, suppression of STH below 1.0 ng/ml was found. Five (24%) patients had hyperprolactinemia from 528 to 2678 mIU/L (median, 758).

Two patients (one with TSH-PA and the other with mixed TSH-STH-secreting adenoma) were preoperatively treated with prolonged somatostatin analogues, which resulted in normalization of TSH, STH, and IGF-1 levels (cases 12 and 14).

All 21 patients had macroadenomas: 4 cases — endosellar, 6 cases — endo-suprasellar, not invading the skull base structures (non-infiltrative). In 11 patients, tumors invaded the skull base structures, including the cavernous sinus (infiltrative). When comparing the growth pattern of tumors in 7 patients having a history of thyroid surgery, we found that, in this group, infiltrative growth occurred in 5 (71%) cases, whereas in 14 patients, who had no previous thyroid surgery, infiltrative growth occurred in 6 (43%) cases. However, there were no statistical differences, when comparing tumor growth pattern in the groups of patients with and without history of thyroid surgery, as well as in various age and gender groups.

Postoperative TSH level was elevated in only 1 out of 21 patients. It decreased in 20 patients; in 10 cases, it was even lower than normal (0.01 ± 0.19 mIU/L), and in 10 patients it reached the normal range (0.68—2.9 mIU/L). Maximal reduction occurred on day 1 after operation. The rate of decrease in fT4 levels were significantly lower. Thus, fT4 level tested on day 1—3 after surgery remained high in all patients. However, subsequent measurements on day 5—7 days after surgery showed its normalization or reduction in most of the cases.

The tumor was totally resected only in patients with endosellar (3 cases) and endo-suprasellar (4) tumors. In the case of infiltrative tumor, there were no cases of total resection. We studies protocols of operations and concluded that thyrotropinomas were in most cases similar to other typical adenomas, they were rarely dense and well perfused. Intense venous bleeding occurred only in 2 cases during tumor resection from the cavernous sinus. Close adherence of the tumor with vessels and nerves was observed in 2 cases during transcranial operations. One patient had a large hemorrhagic cyst within the tumor.

We compared postoperative TSH levels in patients with radical and non-radical tumor resection. In the first case, TSH level measured in the early postoperative period was not detectable or no more than 0.1 mIU/L. Normalization of TSH or its reduction to 0.1 mIU/L, as well as transient postoperative hypothyroidism, are not the criteria of completeness of tumor resection. Thus, normalization or reduction of serum level of TSH, fT4, and fT3 was observed in all patients even in the case of subtotal resection. However, further follow up of 5 patients with postoperative euthyroidism and tumors remnants showed that 4 patients had elevated levels of TSH and/or fT4 6—12 months after surgery; one patient with mixed STH-TSH-secreting tumor maintained euthyroidism, but the levels of STH and IGF-1 remained high. These patients underwent stereotactic radiotherapy of residual tumor tissue.

Fig. 2 shows the dynamics of TSH and fT4 in patient A, 21 years old, with non-radical tumor resection. Fig. 3 shows changes in the level of TSH and fT4 in patient B, 38 years old, with radical tumor resection.

As can be seen from Fig. 2, subtotal tumor resection in patient A led to decrease in TSH level to 0.52 mIU/L on day 1 after the operation and development of transient hypothyroidism. However, euthyroid state was diagnosed in 1 month, and recurrence of hyperthyroidism occurred in 1 year. The patient underwent a course of stereotactic radiation therapy followed by remission of the disease. TSH level below 0.1 mIU/L was considered as the criterion of radical tumor resection.
Summary table of the main data of 21 patients with thyrotropinoma

<table>
<thead>
<tr>
<th>S/N</th>
<th>Sex</th>
<th>Age, years</th>
<th>History of treatment</th>
<th>Thyroid status</th>
<th>TSH, mIU/L</th>
<th>fT4, pmol/L</th>
<th>PRL, mIU/L</th>
<th>Tumor growth pattern</th>
<th>TSH, mIU/L</th>
<th>fT4, pmol/L</th>
<th>MRI signs of tumor remnants</th>
<th>Thyroid status</th>
<th>Treatment</th>
<th>TSH</th>
<th>PRL</th>
<th>STH</th>
<th>DR-D2</th>
<th>Sst2</th>
<th>Sst5</th>
<th>Ki-67, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>25</td>
<td>-</td>
<td>HyperT</td>
<td>2.71</td>
<td>43.17</td>
<td>266</td>
<td>Inf</td>
<td>0.19</td>
<td>20.60</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>0—1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>15</td>
<td>-</td>
<td>HyperT</td>
<td>3.15</td>
<td>37.00</td>
<td>147</td>
<td>Inf</td>
<td>2.35</td>
<td>30.40</td>
<td>Yes</td>
<td>HyperT</td>
<td>RT</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0—1</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>26</td>
<td>-</td>
<td>HyperT</td>
<td>4.05</td>
<td>31.70</td>
<td>850</td>
<td>Non-inf</td>
<td>&lt;0.01</td>
<td>11.70</td>
<td>No</td>
<td>HyperT</td>
<td>L-T4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>38</td>
<td>-</td>
<td>HyperT</td>
<td>4.28</td>
<td>23.60</td>
<td>420</td>
<td>Non-inf</td>
<td>0.06</td>
<td>28.30</td>
<td>No</td>
<td>HyperT</td>
<td>L-T4</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>67</td>
<td>-</td>
<td>HyperT</td>
<td>4.75</td>
<td>39.50</td>
<td>133</td>
<td>Non-inf</td>
<td>0.09</td>
<td>17.30</td>
<td>No</td>
<td>HyperT</td>
<td>L-T4</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>45</td>
<td>HME</td>
<td>HyperT</td>
<td>5.01</td>
<td>39.20</td>
<td>134</td>
<td>Non-inf</td>
<td>0.92</td>
<td>22.30</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>30</td>
<td>-</td>
<td>HyperT</td>
<td>5.21</td>
<td>40.50</td>
<td>273</td>
<td>Non-inf</td>
<td>&lt;0.01</td>
<td>10.40</td>
<td>No</td>
<td>HyperT</td>
<td>L-T4</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>39</td>
<td>-</td>
<td>HyperT</td>
<td>5.59</td>
<td>20.56</td>
<td>420</td>
<td>Inf</td>
<td>2.90</td>
<td>21.50</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0—1</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>56</td>
<td>HME, TS</td>
<td>HyperT</td>
<td>5.59</td>
<td>27.40</td>
<td>2678</td>
<td>Inf</td>
<td>2.40</td>
<td>21.30</td>
<td>Yes</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0—1</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>21</td>
<td>TS</td>
<td>HyperT</td>
<td>6.52</td>
<td>54.80</td>
<td>237</td>
<td>Inf</td>
<td>0.52</td>
<td>33.11</td>
<td>Yes</td>
<td>HyperT</td>
<td>RT</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0—1</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>34</td>
<td>-</td>
<td>HyperT</td>
<td>6.56</td>
<td>36.40</td>
<td>528</td>
<td>Inf</td>
<td>2.13</td>
<td>21.50</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0—1</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>65</td>
<td>HME, SA</td>
<td>HyperT</td>
<td>7.50</td>
<td>26.90</td>
<td>280</td>
<td>Inf</td>
<td>1.12</td>
<td>11.80</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>0—1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>59</td>
<td>HME</td>
<td>HyperT</td>
<td>7.70</td>
<td>36.10</td>
<td>148</td>
<td>Inf</td>
<td>0.14</td>
<td>10.50</td>
<td>Yes</td>
<td>EuT+</td>
<td>SA, RT</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>5</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>53</td>
<td>SA</td>
<td>HyperT</td>
<td>7.96</td>
<td>26.86</td>
<td>151</td>
<td>Non-inf</td>
<td>0.10</td>
<td>15.10</td>
<td>No</td>
<td>EuT</td>
<td>No</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>33</td>
<td>-</td>
<td>HyperT</td>
<td>10.87</td>
<td>39.73</td>
<td>1909</td>
<td>Inf</td>
<td>0.16</td>
<td>16.90</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>0—1</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>39</td>
<td>-</td>
<td>HyperT</td>
<td>13.50</td>
<td>22.80</td>
<td>705</td>
<td>Non-inf</td>
<td>0.10</td>
<td>13.00</td>
<td>No</td>
<td>HyperT</td>
<td>L-T4</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>3</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>15</td>
<td>-</td>
<td>HyperT</td>
<td>13.96</td>
<td>23.70</td>
<td>540</td>
<td>Non-inf</td>
<td>0.01</td>
<td>10.90</td>
<td>No</td>
<td>HyperT</td>
<td>L-T4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>63</td>
<td>TE</td>
<td>HyperT</td>
<td>22.93</td>
<td>28.30</td>
<td>758</td>
<td>Non-inf</td>
<td>1.44</td>
<td>9.80</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>0—1</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>21</td>
<td>-</td>
<td>HyperT</td>
<td>27.90</td>
<td>24.50</td>
<td>288</td>
<td>Non-inf</td>
<td>2.47</td>
<td>27.20</td>
<td>No</td>
<td>EuT</td>
<td>L-T4</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>F</td>
<td>56</td>
<td>HME, TS</td>
<td>HyperT</td>
<td>28.10</td>
<td>36.20</td>
<td>483</td>
<td>Inf</td>
<td>4.20</td>
<td>24.90</td>
<td>Yes</td>
<td>HyperT</td>
<td>RT</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>0—1</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>60</td>
<td>HME, TS</td>
<td>HyperT</td>
<td>38.40</td>
<td>52.80</td>
<td>499</td>
<td>Inf</td>
<td>1.60</td>
<td>24.50</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>0—1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: HME — hemithyroidectomy; TE — thyroidectomy; TS — thyrostatics; HyperT — hyperthyroidism; HypoT — hypothyroidism; EuT euthyreotic; ACRO — acromegaly, the active phase; Inf — infiltrative tumor; Non-inf — non-infiltrative tumor; ND — no data; L-T4 — levothyroxine; SA — somatostatin analogues; RT — radiotherapy. * no cases of expression of LH, FSH, ACTH were detected.
As can be seen from Fig. 3, radical tumor resection in patient B. was accompanied by decrease in TSH level to 0.06 mIU/L on day 1 after surgery and persistent hypothyrosis. Disease remission was observed throughout the whole follow-up period (2 years). The patient was administered with levothyroxine 1 month after surgery.

Four patients with radical tumor resection developed panhypopituitarism, which persisted 6—18 months after surgery (secondary hypothyroidism, hypocorticism, hypogonadism, STH-deficiency); in 3 of them, it occurred in combination with diabetes insipidus.

IMH-study of resected tumor samples showed that all tumor were stained with AB to TSH; expression of only TSH was detected in 3 (14%) cases (“pure” TSH-secreting tumors), in 18 (86%) cases, tumors were plurihormonal: 2 cases demonstrated expression of TSH and PRL, 4 cases — TSH and STH, 12 cases — TSH, STH, and PRL (Fig. 4).

In 4 (29%) out of 14 cases with expression of PRL, there was increased blood level of PRL before surgery (758 mIU/L, 850 mIU/L, 1909 mIU/L, 2678 mIU/L); the remaining 10 (71%) tumors were accompanied by normoprolactinemia (133—288 mIU/L). Tree (19%) out of 16 patients with STH expression in tumor tissue were diagnosed with acromegaly (see Table).

Expression of type 2 dopamine receptors (D2DR) was detected in 9 (69%) of the 13 tumors, type 5 somatostatin receptor (SSt5) — 6 (46%), type 2 somatostatin receptor (SSt2) — 2 (15%) (see Table).

In 5 of 9 cases, D2DR expression occurred in combination with expression of PRL. In 4 of 6 cases, SSt5 expression was accompanied by STH expression. Two tumors with SSt2 expression were also associated with expression of STH, however, there were no cases of adenoma with concomitant expression of SSt5 and SSt2. The patients, who preoperatively received somatostatin analogues with a positive effect in the form of normalization of TSH and fT4 levels, demonstrated expression of TSH and STH (case 12) and SSt5 (case 14) in tumors.

There was no relationship between expression of PRL and dopamine receptors, as well as STH and somatostatin receptors in tumor cells.

The group average Ki-67 MI was 0—5% (median 1%), it was less than 3% in 13 cases, 3% or more in 8 cases. No statistical difference was found when analyzing the proliferative activity of the pituitary tumor (Ki-67 MI) in patients who previously underwent thyroid surgery and not operated patients (see Table).

### Discussion

TSH-PA accounts for 0.5—2% of all pituitary tumors [1]. The first case of hyperthyroidism and increase in sella dimensions was described in 1960. [2]. In 1970, S. Hamilton et al. [3] described TSH-PA with proved TSH measurement using radioimmunoassay. Previously, these tumors were considered casuistic and were detected at the stage of large invasive pituitary macroadenomas. However, the discovery of supersensitive hormonal methods and high-resolution neuroimaging techniques facilitated detection of TSH-PA at the stage of small tumors. Recently published data show that the incidence of TSH-PA in European countries may be 0.28 cases per 1 million population [4]. The incidence of TSH-PA is equal in males and females, in contrast to the predominance of females among the patients with thyroid diseases [5]. Familial cases of TSH-PA were described within MEN-1 [6] and in FIPA-families (familial isolated pituitary adenoma associated with AIP gene mutation) [7].

![Fig. 1. Preoperative blood level of TSH and fT4 in patients with thyrotropinoma.](image)

Dotted lines show the upper limits of reference values for both parameters. No correlation between blood levels of TSH and fT4 were found.
TSH-PA occurs in various age groups of patients from 8 to 84 years [8—10]. However, most of the cases described in the literature occurred in patients aged 50—60 years [1]. In our study, the average age of males was 49 years, females were younger, their average age was 30 years.

The criteria of TSH-secreting pituitary tumors include its visualization and normal or elevated blood levels of TSH along with elevated levels of fT4 and fT3. The symptoms of hyperthyroidism in combination with these hormonal values exclude Graves disease [11]. In difficult diagnostic cases, when there is no obvious clinical hyperthyroidism and TSH-PA cannot be reliably diagnosed based on the analysis of basal levels of hormones, functional tests are used (test with thyrotropin-releasing hormone, TSH), triiodothyronine suppression assay, assessment of the molar ratio of α-subunit/TSH). Differential diagnosis with the syndrome of thyroid hormone resistance, which is also characterized by high levels of fT4 and fT3 in combination with high or normal level of TSH is the most challenging problem. This syndrome is characterized by reduced sensitivity of peripheral tissues to thyroid hormones; it is an autosomal dominant hereditary disease caused by mutation in the gene encoding β-type receptor to thyroid hormones [1, 12]. Pituitary adenoma detected by MPT-study in most cases confirms TSH-PA. However, there are reported cases of combination of the syndrome of thyroid hormone resistance with TSH-secreting pituitary microadenomas and pituitary incidentaloma [13].

According to the literature [14], normal level of TSH is detected in approximately 30% of cases of TSH-PA. Despite the TSH-dependent genesis of hyperthyroidism, we found no direct correlation between the level of fT4 and TSH in our study. Similar data are reported in the review by R. Beck-Peccoz [1].

Normal level TSH along with high levels of fT3 and fT4 can be explained by increase in biological activity of TSH molecule [15]. TSH molecules secreted by pituitary tumors are heterogeneous and may have normal, reduced, or increased ratio between their biological and immunological activity, which can be associated with post-translation changes in the tumor cell [16, 17]. Normal blood level of TSH in some TSH-PA patients justifies the need for testing both TSH and free fractions of thyroid hormones in all patients with pituitary adenoma.

**Fig. 2. Patient A., 21 years old, with non-radical tumor resection (case 10).**

- a — dynamics of TSH level; b — dynamics of fT4 level (yellow dotted line show upper and lower limits of reference values of blood level of TSH and fT4, respectively; red dotted line shows the threshold, below which TSH values correspond to completeness of surgery).
Cases of TSH-secreting tumors associated with chronic autoimmune thyroiditis have been reposted in the literature [18—20]. Normal or elevated level of TSH along with high level of fT4 and fT3 [18] is also considered a diagnosis criterion of TSH-PA in patients with primary hypothyroidism resulting from CAIT or thyroidectomy, who receive replacement therapy with levothyroxine. We reported 2 cases of TSH-PA in CAIT patients. Despite the high dosed of levothyroxine and elevated level of fT4, TSH level remained high. MRI study detected decrease in tumor size in one case, and relapse after previous pituitary adenomectomy in the other. Histological examination confirmed the presence of mixed pituitary adenoma with expression of TSH, PRL, and STH in both cases. The role of long-lasting increase in TSH level and pituitary hyperplasia in CAIT patients in the pathogenesis of TSH-PA was discussed in the literature [19, 20].

Clinical presentation of TSH-PA consists of symptoms of hyperthyroidism and mass-tumor effect. Symptoms of hyperthyroidism were detected in most (76%) patients and were similar to manifestation of primary hyperthyroidism, but they were characterized by milder course and absence of other autoimmune syndromes, which are common in diffuse toxic goiter (endocrine ophthalmopathy, pretibial myxedema, and acropathy). Prevalence of circulating antibodies to thyreoglobulin and thyroid peroxidase in TSH-PA patients is similar to that in the general population. However, the literature [21, 22] described the patients who developed Graves’ disease after resection of pituitary adenoma; bilateral exophthalmos in combination with autoimmune thyroiditis. In most patients, hyperstimulation of thyroid with TSH results in diffuse increase in thyroid size, in 72% of cases — to formation of single or multiple nodules [1]. Goiter is usually detected even in patients who previously underwent partial thyroidectomy due to growth of residual thyroid tissue. Differentiated thyroid cancer was reported in several patients with TSH-PA [23—26]. In patients with thyroid nodules, monitoring of thyroid nodules and thin-needle aspiration biopsy are required.

In most cases of TSH-PA reported in the literature, where patients were first misdiagnosed with primary...
hyperthyroidism (Graves' disease), they often had a history of thyroid surgery and/or radioactive iodine therapy. In these cases, tumors often become more aggressive and demonstrate infiltrative growth pattern. Decrease in blood levels of circulating thyroid hormones resulting from this treatment leads to activation of tumor growth by a mechanism similar to development Nelson syndrome after bilateral adrenalectomy during treatment of Cushing's disease [1]. Likewise, more than half (52%) of patients in our study were misdiagnosed with primary hyperthyroidism. For this reason, most of them underwent thyroid surgery and/or received thyreostatic therapy. In our study, we found no clear statistical differences in the infiltrative growth pattern depending on the previous thyroid surgery. Nevertheless, 7 patients were operated on at our institution over the last 2 years (2014—2015), and only 3 (43%) of them had endosellar adenomas and hyperthyroidism without symptoms of tumor mass effect, whereas during the period from 2002 to 2013, most patients, 13 (93%) of 14, had large tumors and were diagnosed at the stage of tumor mass effect with pronounced visual or other neurological disorders. It is likely that in the future, given the use of ultra-sensitive hormonal methods, as well as better doctors’ awareness of these rare tumors, the rate of early detection of TSH-PA at the stage of small-size tumor will increase.

Most of TSH-PA secret not only TSH, but also other pituitary hormones, mainly STH and PRL. This may be due to the fact that somatotropic, lactotropic, and thyrotropic cells have a common progenitor cell. A rare type of mixed TSH/gonadotropin secreting adenoma is described in the literature without hypersecretion of ACTH in the blood; the mechanism of occurrence of these tumors has not been studied, because thyrotropic and gonadotropic cells have different progenitor cells [1]. Clinically silent thyrotropinomas with TSH expression but without increase in blood level of TSH and clinical presentation of hyperthyroidism have been reported [27].

In our study, most tumors, 18 (86%), were plurihormonal with preferential secretion of TSH, STH, and/or PRL. None of the tumors secreted gonadotropin and ACTH. “Pure” TSH-secreting tumors were found only in 3 (14%) cases. Tumors with concomitant expression of PRL or STH were associated with increased blood level of RLP and clinical presentation of acromegaly only in 4 (29%) and 3 (19%) cases, respectively. The absence of clinical presentation of hyperprolactinemia and/or acromegaly in other patients with expression of PRL and/or STH was probably due to secretion of biologically inactive forms of PRL and/or STH.

According to the literature [1], most TSH-PAs demonstrate expression of various receptors, including receptors to TRH, dopamine, and somatostatin. Expression of somatostatin receptors is often detected in TSH-PA, especially in mixed STH-TSH-secreting tumors. This explains the effective ability of somatostatin analogs to lower TSH levels in patients with these tumors [28, 29]. In our study, SST5 expression was detected in 46% of cases and in most cases, it was accompanied by STH expression in the tumor, while SST5 expression was rarely detected.

Surgery followed by radiotherapy is the basic method of treatment for TSH-PA in the case of non-radical resection [30, 31]. The literature provides no strict criteria for remission after surgical treatment of thyrotropinomas. However, clinical remission of hyperthyroidism, normalization of thyroid hormone levels, and regression of neurological symptoms are considered as remission criteria. At the same time, these biochemical and clinical criteria can be transitory and are not considered as indicators of complete resection [1]. Normalization of blood level of TSH also cannot be an indicator of completeness, especially in patients with normal preoperative level of TSH. Normalization of α-subunit and/or the molar ratio of α-subunit and TSH may be used to assess the effectiveness of therapy [32, 33]. Nevertheless, these two parameters are of low sensitivity and are not applicable in patients with normal preoperative levels. Triiodothyronine suppression test and TRH stimulation test, which have optimal sensitivity and specificity, were suggested as the most valid tests for completeness of tumor resection [32, 33]. Undetectable blood level of TSH may be a good indicator of radical resection. It is important to clarify
that virtually undetectable TSH level should be understood as its level below the functional sensitivity threshold of detection method (<0.01 mIU/L). Indeed, in our series of observations, postoperative decrease in TSH levels below 0.01 mIU/L was characteristic of completely resected tumors. However, all these cases were accompanied by the development of panhypopituitarism, including hypothyroidism, which required administration of levothyroxine. Patients with postoperative TSH levels of 0.01–0.1 mIU/L remained euthyroid during the follow-up period (6–18 months). Therefore, we arbitrarily defined TSH level of 0.1 mIU/L and below as a marker of radical tumor removal. However, these patients should be followed in the future since delayed relapse of hyperthyroidism can occur.

Although adenomectomy is currently the treatment of choice, treatment with somatostatin analogues is believed to be effective in reducing TSH level, normalization of fT4 and fT3 levels, and restoring euthyrosis in 90% of cases [30, 34, 35]. In our study, preoperative therapy with somatostatin analogues in 2 patients successfully normalized euthyrosis and the levels of TSH and fT4.

The literature provides no data on the incidence of TSH-PA recurrence. We observed 2 cases of continued tumor growth in previously operated patients, which required reoperation. In our series of observations, none of the patients operated on at the Burdenko Neurosurgical Institute had continued tumor growth during the aforementioned follow-up period. Given the possibility of delayed recurrence of hyperthyroidism in patients with non–radical tumor resection, the possibility of stereotactic irradiation of residual tumor tissue should be considered even in the cases of euthyroid state. In the case of complete resection of the tumor and the development of hypothyroidism, tumor recurrence is unlikely at least during the first years after the surgery.

**Conclusion**

In summary, TSH-secreting tumors are rare representatives of pituitary adenomas. Early diagnosis of these tumors and differential diagnosis, which rule out other conditions accompanied by hyperthyroidism, are of key importance. Surgical treatment is currently the main method of treatment, however radical removal of infiltrative tumors is impossible. Postoperative TSH level of no more than 0.1 mIU/L can be considered as the criterion of radical removal. It should be noted that transient euthyrosis often occurs in patients with non-radical tumor resection. However, the likelihood of recurrence of hyperthyroidism necessitates considering the question of stereotactic irradiation of residual tumor tissue. Therapy with somatostatin analogs can be effective to achieve euthyrosis.

**There is no conflict of interest.**

**REFERENCES**


The article analyzes clinical cases of TSH-secreting tumor, which is an extremely rare endocrine disease. Measurement of TSH level is among the most commonly prescribed hormonal tests. Increased TSH requires an accurate differential diagnosis, because it can be caused by various endocrine disorders and therefore it can require fundamentally different approaches to the choice of treatment. In typical cases, thyrotropinoma is accompanied by development of thyrotoxicosis with normal or elevated TSH levels. Long-lasting untreated thyrotoxicosis (including cases of misinterpretation of hormonal disorders) leads to severe changes in many body systems (cardiovascular, nervous, digestive, reproductive, etc.).

The authors provide very important guidelines for practicing endocrinologists and neurosurgeons, characterizing clinical cases of thyrotropinomas. They pay attention to the very high percentage of misdiagnosis at the stage of outpatient examination before admission to the Burdenko Neurosurgical Institute; in some cases, patients with thyrotropinomas even underwent thyroid resection.

All reported tumors were macroadenomas, in 91% of cases they were endo-extrasellar. Most patients (76%) had clinical signs of hyperthyroidism. Along with clinical signs of hyperthyroidism, these patients also had various neurological symptoms, including visual disturbances and cephhalgic syndrome. According to US study of the thyroid gland, 13 patients had various structural changes (diffuse goiter, nodular goiter, diffusely nodular goiter). When combined with thyrotoxicosis, this could contribute to inadequate differential diagnosis of primary, rather than central thyrotoxicosis. When comparing tumor growth patterns in 7 (71%) patients with a history of thyroid surgery, most of them were diagnosed with infiltrative growth. However, no statistical differences were found, when comparing tumor growth patterns in the groups of patients with and without history of thyroid surgery. In any
case, erroneous management of these patients may have irreversible consequences.

Concomitant primary hypothyroidism, either postoperative or resulting from chronic autoimmune thyroiditis, with thyrotropinoma is one of the most disputable and challenging problems. The authors regard these tumors as secondary thyrotropinomas.

Complex hormonal examination of some patients also detected other hormonal disorders. Tumors polymorphism was further confirmed by immunohistochemical studies, where isolated TSH expression was detected in only 14% of cases, while the majority of tumors showed expression of TSH and STH and/or PRL.

The paper points out that radical resection was possible in 33% of patients, having only endosellar and endo-suprasellar tumor. There were no cases of complete resection of infiltrative tumors. It would be proper to specify the tactics of management of these patient, when radical adenomectomy is impossible.

It was found that normal postoperative level of TSH or its decrease to 0.1 mIU/L, as well as transient postoperative hypothyroidism are not the criteria of the effectiveness of tumor removal. This proves once again that the verification of the diagnosis and radical treatment pose significant problems. The literature provides evidence of high efficacy of the use of somatostatin analogues for thyrotropinomas, as also shown in this work.

In this regard, the study of expression of dopamine and somatostatin receptors in the resected tissue of pituitary adenoma becomes highly important. The paper demonstrated high incidence of expression of type 2 dopamine receptors and type 5 somatostatin receptors.

In conclusion, the authors once again emphasize diagnostic criteria of TSH-secreting pituitary tumor and differential diagnosis of various types of thyrotoxicosis.

The article is extremely important, since it covers very challenging issues of diagnostic criteria and management of pituitary adenomas.

F.M. Abdulhabirova (Moscow, Russia)
The Preliminary Results of Subthalamic Nucleus Stimulation after Destructive Surgery in Parkinson’s Disease

E.A. KHABAROVA, N.P. DENISOVA, D.YU. ROGOV, A.B. DMITRIEV

Federal Center of Neurosurgery, Novosibirsk, Russia

Objective. The study was aimed at evaluating the efficacy of bilateral electrical stimulation (ES) of the subthalamic nucleus (STN) in patients with Parkinson’s disease (PD) after prior pallidotomy or ventrolateral (VL) thalamotomy.

Material and methods. The study included 9 patients with bilateral STN ES, who previously underwent unilateral destructive surgery on the subcortical structures: pallidotomy (5 patients) and VL thalamotomy (4). Control group consisted of 9 patients with STN ES and without prior destructive surgery.

Clinical and neurological examination included quantitative assessment of motor disturbances using the Hoehn—Yahr scale and Unified Parkinson’s Disease Rating Scale (UPDRS). UPDRS was used to evaluate the motor activity (part III of the scale) and severity of drug-induced dyskinesia and motor fluctuations (part IV of the scale).

Results. In the group of STN ES with preceding destruction of the subcortical structures, an improvement in motor functions in the early period (6 months) was 45%, and severity of drug-induced complications decreased by 75%. In a group of STN DBS without destruction, motor disturbances were improved by 61%, and drug-induced complications were decreased by 77%. Improvement in motor functions amounted to 51.9% in patients with preceding pallidotomy (GPI destruction) and 37.5% in a group with preceding VL thalamotomy.

The equivalent dose of levodopa was reduced by 51.39%, from 1,008±346 to 490±194, in the study group and by 55.04%, from 963±96 to 433±160, in the control group.

Conclusion. Bilateral STN neurostimulation is effective after unilateral stereotaxic destruction of the subcortical structures in PD patients.

Keywords: Parkinson’s disease, bilateral subthalamic nucleus neurostimulation, pallidotomy, VL thalamotomy.
segment of the globus pallidus has been acknowledged as the effective treatment of PD patients [12, 13].

At the same time, it is poorly understood how effective is bilateral STN ES after destructive interventions. Additionally, there is no reliable information, whether the result of this procedure in patients after destructive operations is comparable to that in patients, who did not undergo destructive surgery on the subcortical structures, and whether destructive operation provides the patient with any long-term advantages.

The objective of this research was to demonstrate our own experience with bilateral neurostimulation of the subthalamic nucleus in PD patients after previous pallidotomy and VL thalamotomy and evaluate the effectiveness of this method in the early follow-up period.

**Material and methods**

The study included PD patients with bilateral STN ES after prior destructive surgery. The patients were operated on at the department of functional neurosurgery of the Federal Neurosurgical Center in Novosibirsk from 2013 to 2014.

The study included 9 patients (5 males, 4 females) with STN ES, who previously underwent unilateral destructive operations on the subcortical structures (study group). Of these, pallidotomy was performed in 5 patients, VL thalamotomy was performed in 4 patients. At the time of destructive surgery, average age of patients was 54.9 years (47—64 years), at the time of STN ES — 55.9 years (47—65 years). Disease duration ranged from 5 to 20 years (mean duration, 12 years). The average period between operations was 14 months (5 — 26 months).

Bilateral neurostimulation was carried out in the case of progression of motor disorders. The control group consisted of 9 patients (5 males, 4 females) with STN ES, which did not undergo destructive surgery. The average age in the group was 54.9 years (48—61 years). The disease duration was 7—16 years (mean duration, 12 years).

Indications for surgery and selection criteria for STN ES were identical in both groups. In patients with bilateral neurostimulation, minimum follow-up time was 12 months, maximum — 30 months (average, 21 months).

Motor disorders were quantified in the clinical neurological study before and after operations on the following scale:

Hoehn–Yahr Scale (M. Hoehn, M. Yahr, 1967) modified by Lindvall, Tetrud, and Langston (O. Lindvall et al, 1987; J. Tetrud, J. Langston, 1987), which includes both the conventional 3-point classification of severity of parkinsonism and 1.5 and 2.5-point severity gradations.

The third edition of the unified PD evaluation scale (Unified Parkinson’s Disease Rating Scale, UPDRS), (S. Fahn, R. Elton, 1987) contains 42 criteria. It estimates motor activity (part III) and severity of drug-induced dyskinesias and motor fluctuations (part IV). Each criterion may score 0 to 4 points. The decrease in the total score resulting from treatment was considered as a positive dynamics.

There were no significant differences between study and control group patients in age and duration of history.

In both groups, patients underwent a bilateral STN ES. Neurostimulator programming was carried out 1 month after surgery. Neurostimulation parameters were selected based on better clinical response of motor manifestations and absence of side effects (dysarthria, levodopa-dependent dyskinesia). No surgical complications were observed in patients in the early postoperative period.

Daily dose of dopaminergic preparations was assessed based on determining the equivalent doses of levodopa, which were calculated according to the formula: 100 mg of levodopa = 130 mg of levodopa with controlled drug release = 70 mg of levodopa + catechol-O-methyltransferase inhibitor = 1 mg of pramipexole = 5 mg of ropinirole = 50 mg of piribedil [14]. Calculation was made in the study and control groups before and 12 months after STN neurostimulation.

**Results**

In the study group, improvement of motor functions after 12 months averaged 45% (22 to 50 UPDRS points) (Table 1). Notably, 66.6% of patients in this group had a dextral destruction (Table 2).

The number of UPDRS points (part III) 6 months after the destructive intervention in this group decreased by an average of 17% (33—65 points) (see Table 2). This time interval for estimation was determined by the fact that some of patients underwent STN ES in 6 months.

In the control group, improvement of motor disorders in 12 months averaged 61%.

In 12 months, the severity of treatment complications (medicinal dyskinesias and motor fluctuations) decreased by an average of 75% in the main group and by 77% in the control group (see Table 1).

Study group patients with bilateral STN ES had various degrees of improvement depending on the location of destruction. In patients with unilateral pallidotomy, improvement of motor disorders was 51.9%, in the group with preceding VL thalamotomy — 37.5% (Table 3).

According to UPDRS (part III), clinical presentation before ES was more severe in the control group patients compared to that in the study group. This is due to preserved clinical effect of unilateral stereotaxic destruction in the study group, which occurred in the form of milder rigidity, tremor, and dyskinesias on the contralateral side.

The results of tests were similar in both groups 12 months after connection of neurostimulator (see...
Table 1). Prior to STN ES, study group scored 51 UPDRS points (35—65), control group — 74 points (63—82). During STN ES, study and control groups scored 28 (22—50) and 29 points (20—42), respectively (see Table 1). After bilateral neurostimulation, equivalent dose of levodopa decreased by 51.39%, from 1008±346 to 490±194, in the study group, and by 55.04%, from 963±96 to 433±160, in the control group.

Discussion

Stereotactic thermal destruction of the deep structures of the brain is a technique that enabled safe and effective suppression of PD symptoms at certain stage of the disease [6].

Unilateral pallidotomy (destruction of the internal segment of the globus pallidus, GPI) effectively treats medicamentous dyskinesia in the contralateral limbs, and, to a lesser extent, in the ipsilateral limbs, and also reduces fluctuations of daily motor activity [9].

For many years, ventrolateral thalamotomy was used to treat pharmacoresistant tremor in PD patients [9, 15, 16]. In this case, the incidence and severity of perioperative complications significantly increase after the second operation on the contralateral side [7].

Despite the excellent initial clinical effect in the case of optimal positioning of destruction point, 10—15% of patients resume preoperative symptoms within 1—2 years after the operation, often in the ipsilateral extremities and axial muscles, which is associated with progression of the disease [15]. Therefore, further surgery is required in the future. Bilateral destructive interventions are associated with high risk of complications. According to J. Siegfried and B. Lippitz [17], chronic ES of subcortical structures is the method of choice in PD patients, who previously underwent stereotactic destruction. This method uses autonomous implantable systems, which enable chronic neurostimulation [18].

The main advantages of ES include minimal injury to the brain tissue, which occurs during implantation of the electrode, and reversibility of neurostimulation effects. Modern neurostimulators enable noninvasive correction of many parameters of stimulation program (the use of monopolar or bipolar stimulation, various intensity of electrical stimulation) [19]. Minimal invasiveness of this techniques prevent from persistent neurological complications characteristic of destructive methods [12, 20].

Minimal invasiveness of this technique enables single-stage bilateral surgery even in elderly patients [4, 20, 21]. The results of postmortem studies of operated patients, who died of intercurrent diseases, have shown that prolonged exposure to electrical stimulation does not cause damage to the structures around the active electrode [22]. The possibility of noninvasive correction of neurostimulation parameters enables selecting an individual effective and comfortable treatment program, and eliminates side effects of neurostimulation [4].

The literature provides scarce information on the effectiveness of STN ES in patients with previous destructive interventions. The study of G. Kleiner-Fisman et al. [23] showed that prior unilateral pallidotomy does not impair the effectiveness of the subsequent bilateral STN ES. In this study, electrophysiological parameters also did not change significantly in the study and control groups.

Our study showed that decrease in the severity of motor disorders as assesses on the UPDRS scale was lower in the group of patients with bilateral STN EN preceded by unilateral pallidotomy and VL thalamotomy as compared to the control group. This is due to preserved clinical effect of previous unilateral stereotactic destruction, which occurs in the form of milder rigidity, tremor and/or drug-induced dyskinesias on the side contralateral to destruction area. Similar results were obtained in the work of W. Ondo et al. [14]. In our study, improvement in motor disturbances resulting from STN ES were less pronounced in the group with prior VL thalamotomy compared to the group with prior destruction of GPI.

Assessment of the dynamics of drug-induced complications showed that improvement was similar in the study and control groups, which is consistent with the aforementioned studies [14, 23]. Decrease in the equivalent dose of levodopa in the study and control
groups before STN EN and after 12 months of ES also did not differ significantly.

W. Ondo et al. [14] believe that unilateral VL thalamotomy may cause insufficiently accurate positioning of STN EN electrode on the side of prior destruction. A. Zaidel et al. [24] reported change and decrease in neuronal activity of the subthalamic nucleus after previous pallidotomy. In this regard, in patients with preserved good clinical effect of destructive operations or extensive destruction area, an option of unilateral STN ES on the side contralateral to the destruction area may be considered in the case of further progression of the disease and emergence of indications to STN ES.

Conflicting results of analyzed studies may be due to a small number of patients with prior destruction of subcortical structures in all these studies.

Methods of functional neurosurgery are currently an integral part of the treatment of PD patients [25, 26]. Modern trends are towards earlier surgical treatment of patients [3, 4]. In some patients, motor disorders can be significantly reduced by unilateral stereotactic interventions [14, 23]. However, disease progression is accompanied by depletion of reserves of pharmacotherapy, and some patients, who previously underwent destructive operations, may require repeated surgery [27, 28].

**Conclusion**

The literature data and the results of our study show that bilateral STN electrostimulation is effective and can be used in patients with Parkinson's disease, who previously underwent unilateral stereotactic destructive operations on subcortical structures.

There is no conflict of interest.
REFERENCES


Commentary

The article focuses on electrical stimulation (ES) of the subthalamic nucleus (STN) in patients with Parkinson’s disease, who previously underwent destructive operation on the deep structures of the brain. Modern literature provides numerous publications dealing with ES of STN and the internal segment of the globus pallidus. The effectiveness of this method of treatment during short follow-up period was proved by a number of randomized trials; there are also publications reporting long-term results. A large number of studies cover the issues of the effect of neurostimulation on various manifestations of Parkinson’s disease: motor symptoms, cognitive impairment, balance and gait disorders, impulsive-compulsive disorders.

In recent years, destructive operations were abandoned in favor of neurostimulation all over the world, which is very promising due to the adjustability of its effect. However, destructive operations still can be used in some cases with predominance of unilateral manifestations of Parkinson’s disease. At the same time, patients who underwent destructive operations can be sent for neurostimulation in the case of disease progression.

In recent studies dealing with neurostimulation, previous destructive operation was considered as an exclusion criterion. However, there are several studies containing information on the use of STN ES in small groups of patients, who previously underwent destruction, and its effectiveness.

In general, this study is highly relevant and the results are interesting and important for functional neurosurgery of Parkinson’s disease. Further studies will provide valuable data to develop the optimal strategy of neurosurgical treatment of Parkinson’s disease.

A.A. Tomsky (Moscow, Russia)
Phase Contrast MRI-based Evaluation of Cerebrospinal Fluid Circulation Parameters in Patients with Foramen Magnum Meningiomas

S.V. KONDRAKHOV, N.E. ZAKHAROVA, L.M. FADEEVA, S.V. TANYASHIN

Burdenko Neurosurgical Institute, Moscow, Russia

Background. Meningiomas of the foramen magnum (FM) region account for 1.8 to 3.2% of all meningiomas. The international literature provides insufficient data describing the state of cerebrospinal fluid (CSF) circulation in these patients.

Material and methods. We studied 38 patients with FM meningiomas aged 35 to 79 years (mean age, 56.7 years). Meningioma size averaged 30 mm (10—60 mm). Anterolateral meningiomas were observed in 29 patients, ventral — in 5 patients, and dorsal — in 4 patients. Twenty nine patients underwent surgery. All operated patients were examined before and after surgery. CSF circulation was studied using phase contrast MRI (PC-MRI).

Results. The size and localization of FM meningiomas do not significantly affect CSF circulation parameters. Pyramidal symptoms, sensory disorders, and XIth cranial nerve dysfunction correlate with CSF circulation parameters. According to preoperative PC-MRI data, CSF circulation parameters were significantly higher in all patients with FM meningioma compared to normal values. Surgery was followed by decrease in the peak positive velocity, peak negative velocity, and range of maximum linear velocity amplitude. Positive and negative volumes and stroke volume did not change. Recovery dynamics of CSF circulation parameters was similar, regardless of surgery completeness. According to PC-MRI data, CSF circulation parameters did not reach normal values in all groups of operated patients.

Conclusion. The results of investigation of CSF circulation in patients with FM meningiomas support the use of palliative surgery (partial resection, dural plasty, craniovertebral junction decompression) in the case of inoperable meningiomas.

Keywords: foramen magnum meningioma, surgery, cerebrospinal fluid circulation, phase contrast magnetic resonance imaging.

According to available preliminary data, the effectiveness of tumor resection characterized by various extent can be assessed based on both clinical signs and reliable quantitative values of CSF circulation.

Phase-contrast MR is the main non-invasive imaging method for CSF spaces. As opposed to MR and CT cisternography, this technique can be used to assess not only anatomical characteristics of the CSF system and geometry of CSF spaces with slow CSF motion, but also to visualize fast CSF motion [12—16]. Thus, phase contrast MRI provides the most adequate assessment of CSF dynamics without limitation to the craniovertebral junction [17—22]. The literature [23] provides data on the evaluation of CSF circulation using phase contrast MRI in patients with syringomyelic and arachnoid cysts. Elucidation of the mechanisms of CSF circulation disorders in patients with FM meningiomas will clarify the pathogenesis of clinical manifestations of the disease caused by direct tumor action on the neural structures and impaired CSF circulation.

The research was aimed at studying the characteristics of the CSF circulation in patients with meningiomas of the craniovertebral junction and changes in the CSF circulation parameters depending on the extent of the surgery.

The study was aimed at:

— Evaluating CSF circulation disturbances depending on the size of FM meningiomas;
— Assessing CSF circulation disturbances depending on the location of meningiomas (anterior, anterolateral, posterior);

e-mail: skondrahov@nsi.ru
— Assessing the impact of CSF circulation disorders on the severity and dynamics of clinical symptoms in patients with FMR meningiomas;
— Assessing the severity of CSF circulation disorders before and after surgery and the nature of changes in CSF circulation parameters, depending on the extent of surgical intervention.

Materials and methods

The study was based on the results of examination of 38 patients with FM meningiomas aged 35 to 79 years (mean age, 56.7 years). In our series, most patients were 45—50 and 60—65 years old (Fig. 1).

Maximum tumor size was calculated based on contrast enhanced T1-weighed MRI anatomical slices in three projections. Maximum size of meningiomas ranged 10 to 60 mm, median 30 mm. Distribution of the maximum size of meningiomas is shown in Fig. 2.

Most patients in our series had anterolateral FM meningiomas, a total of 29 cases. Ventral meningiomas were detected in 5 patients, dorsal — 4 (Fig. 3).

Surgery was conducted in 28 patients. The extent of the surgery varied from total resection to biopsy accompanied by dural plasty with aponeurosis. One patient underwent ventriculoperitoneal shunting due to occlusive hydrocephalus. Nine patients had not been operated on. Five of them underwent radiotherapy. In 1 patient, operation was canceled due to the burdened somatic status. In 3 cases, surgery was not proposed due to small tumor size and minimal symptoms. These patients were followed. We used the classification proposed by K. Amautovic [24, 25] to assess the completeness of tumor resection:
— total resection (gross-total resection) — complete tumor resection, including the involved DM fragments. It corresponds to grade I tumor resection according to Simpson’s classification (Simpson I);
— almost total resection (near-total resection) — in the case of preservation and coagulation of the tumor at the DM matrix. It corresponds to grade II tumor resection according to Simpson’s classification (Simpson II);
— subtotal resection — resection of more than 60% of tumor volume It corresponds to grade III tumor resection according to Simpson’s classification (Simpson III);
— partial resection — resection of less than 60% of the tumor, including biopsies and simple decompression. It corresponds to grade IV—V tumor resection according to Simpson’s classification (Simpson IV—V).

The examples of total and subtotal resection of meningiomas are shown in Fig. 4 and 5.

Distribution of patients according to the extent of tumor resection is shown in Fig. 6.

All operated patients underwent preoperative and postoperative (in 3—6 months) examination. Nine
The studies were carried on Signa HDxt MR tomograph (General Electric Medical Systems) using the magnetic field strength of 1.5 T.

All patients underwent MRI in the following modes:
- standard T1 and T2-weighted MRI in the axial and sagittal planes; they were obtained using spin echo pulse sequence, SE (600/20) and FastSE (4500/84);
- 3D T2-weighed MRI modes (3D-CUBE mode, which provides a clear view of the outline of the subarachnoid spaces, and FIESTA mode, showing pulsatile CSF movement);
- phase contrast MRI (PC-MRI) with reference to the cardiac cycle based on the PC-MRI pulse sequence with parameters TR 26/TE 11/FA 20 gy, 256/160 image matrix, in two replicates. The slice (4 mm thick) was selected at C2—C3 level, perpendicular to the vertebral canal, with FOV = 200 mm. The average scan time was 3—4 min.

Heart contraction curve was recorded using peripheral plethysmograph. A total of 16 images per cardiac cycle were recorded, corresponding to the different phases of the cardiac cycle. Spin velocity encoding (VENC-Velocity encoding) averaged 15 cm/s. In the case of artifacts, VENC could be changed in the range from 0 to 20 cm/s. Data were processed in offline mode based of the Report Card software package. Region of interest in the intradural space was selected based on PC-MRI (Fig. 7), stroke volume, linear and volumetric velocity of CSF circulation were calculated as a function of the cardiac cycle phase (Fig. 8).

Data processing using Report Card software provided the following characteristics of the CSF circulation: positive peak velocity, negative peak velocity, positive volume, negative volume, amplitude range of the maximum linear velocity, and stroke volume. The physical meaning of CSF circulation parameters obtained by PC-MRI is as follows:
- positive peak velocity — maximum linear velocity of CSF in the craniocaudal direction;
- negative peak velocity — maximum linear velocity of the CSF in the caudocranial direction;
- amplitude range of the peak velocity — the range of maximum linear velocity variation in one cardiac cycle.

These three parameters represent velocity characteristics of CSF circulation, wherein the latter one is derived from the positive and negative velocities.

Positive volume — the amount of CSF passing through the axial slice at C2—C3 during systole.

Negative volume — the amount of CSF passing through the axial slice at C2—C3 during diastole.

Stroke volume — the amount of CSF passing through the axial slice at C2—C3 during one cardiac cycle.
Positive and negative volume and stroke volume are volumetric characteristics of CSF circulation. As in the case of linear velocity, stroke volume is derived from the positive and negative volume.

Normal values of the main indices at C2–C3 were obtained based the study including healthy volunteers, which was previously performed at the Burdenko Neurosurgical Institute (Table 1) [26].

Statistical processing of the material used Descriptive Statistics methods (scattering diagram, distribution of variables, mean and standard deviation) and nonparametric statistics methods describing the ordinal values (linear relationship between the Spearman’s parameters, group analysis with calculation of confidence probability of intergroup differences using Mann Whitney test, medians, and percentiles). The data were processed using Statistica v.10 software.

**Results**

Preoperative characteristics of CSF circulation in patients with FMR meningiomas.

We used MRI to visualize CSF movement through the third ventricle, cerebral aqueduct, large cistern, and spinal canal. **Fig. 9** shows an example of the preoperative examination of patient S., 46 years old, who was diagnosed with FM meningioma. **Table 2** shows the average and median values of CSF circulation parameters in 38 patients.

**Fig. 4. Total resection of FM meningioma.**

a, b — preoperative contrast enhanced T1-weighed MRI of the brain (sagittal and axial projections); d, e — contrast enhanced T1-weighed MRI of the brain after total resection (gross-total resection, sagittal and axial projection); c — overall view of the tumor after opening of the dura mater and arachnoid membranes; f — after total removal of the tumor node (1 — cerebellum, 2 — arachnoid, 3 — tumor, 4 — caudal group of cranial nerves, 5 — resected tumor bed, 6 — medulla oblongata, 7 — loop of the posterior inferior cerebellar artery).
Comparative analysis of quantitative characteristics of CSF circulation at C2—C3 in apparently healthy individuals and patients with CSF meningiomas showed CSF circulation disorders in the form of statistically significant increase in all investigated parameters ($p<0.05$) in patients with meningioma.

The relationship between meningioma size and CSF circulation parameters

We found no correlation between meningioma size and CSF circulation parameters. Examples of various relationships between tumor size and CSF circulation parameters are shown in Fig. 10 and 11.

The relationship between CSF circulation and location of meningiomas

CSF circulation parameters were compared in three groups of patients depending on tumor location (ventral, anterolateral, and dorsal) based on Mann-Whitney test. The analysis found that tumor location, as well as FM meningioma size, has no significant effect of CSF circulation parameters.
Clinical manifestations and their correlation with CSF circulation parameters

Clinical presentation of FM meningoicas consists of various symptoms. We combined these symptoms into several characteristic syndromes:

1) cerebellar syndrome — dizziness, cerebellar ataxia, impaired statics, gait, and coordination;
2) cerebral symptoms are caused by increased intracranial pressure. They manifest in the forms of headache, dizziness, nausea, and vomiting;
3) bulbar syndrome — hoarseness, nasal voice, decreased palatal and pharyngeal reflexes, choking when swallowing, tongue deviation toward the affected muscle, atrophy and fibrillar twitching of a half of the tongue. This syndrome is associated with a direct effect of the tumor on the medulla oblongata and exiting roots of the IX, X, and XII pairs of cranial nerves;
4) pyramidal disorders — symptom resulting from tumor compression of the pyramidal pathways at the level of medulla oblongata and spinal cord and manifesting in the form of various severity of conduction motor disorders;
5) sensitivity disorders. These disorders are mainly caused by direct effect of meningiomas on the afferent pathways of the medulla oblongata and superior cervical spinal cord;
6) cervical syndrome — presents with restricted neck mobility, pain in the cervico-occipital area, head tilt;
7) dysfunction of the XIth pair of cranial nerves presents with paresis, plegia, atrophy of sternocleidomastoid and trapezius muscles.

Preoperative and postoperative distribution of the incidence of the aforementioned syndromes and their relationship to the CSF circulation parameters, as well as the significance of differences in the subgroups are summarized in Tables 3 and 4.

Preoperative positive and negative volume and stroke volume significantly differ \((p<0.05)\) in the subgroups of patients with/without pyramidal symptoms. In the subgroup of patients having pyramidal symptoms, these values are significantly lower compared to patients without pyramidal disturbances. In our opinion, this may be due to the characteristics of the tumor node configuration. Local effect on the anterolateral surface of the medulla oblongata is characterized by more pronounced clinical manifestations in the case of smaller tumor compared to larger tumor volume, having no direct contact with the anterolateral surface of the medulla oblongata. Positive and negative peak velocity and range of maximum velocity amplitude do not depend on the neurological symptoms \((p>0.05)\).

Postoperative values (29 patients) of the positive and negative peak velocity and range of the maximum velocity amplitude are significantly higher \((p<0.05)\) in patients having sensory disorders and dysfunction of the XIth pair of cranial nerves. No statistically significant correlation

| Table 1. Quantitative characteristics of CSF circulation at C2—C3 in healthy volunteers |
| CSF circulation parameter according to PC-MRI | Values |
| Amplitude range of the maximum linear velocity, cm/s | 7.2±0.68 |
| Stroke volume, ml | 1.04±0.37 |
Table 2. Preoperative quantitative characteristics of CSF circulation at C2—C3 in patients with FM meningiomas

<table>
<thead>
<tr>
<th>CSF circulation parameter</th>
<th>Median</th>
<th>Std. Dev.</th>
<th>Median 25,000 th</th>
<th>Median 75,000 th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive peak velocity, cm/s</td>
<td>10.97</td>
<td>4.7</td>
<td>12.2</td>
<td>6.67</td>
</tr>
<tr>
<td>Negative peak velocity, cm/s</td>
<td>9.89</td>
<td>4.59</td>
<td>9.77</td>
<td>5.33</td>
</tr>
<tr>
<td>Positive volume, ml</td>
<td>0.99</td>
<td>0.48</td>
<td>0.93</td>
<td>0.75</td>
</tr>
<tr>
<td>Negative volume, ml</td>
<td>0.84</td>
<td>0.49</td>
<td>0.92</td>
<td>0.38</td>
</tr>
<tr>
<td>Amplitude range of the maximum linear velocity, cm/s</td>
<td>20.86</td>
<td>8.61</td>
<td>21.38</td>
<td>16.23</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>1.83</td>
<td>0.83</td>
<td>1.83</td>
<td>1.43</td>
</tr>
</tbody>
</table>

Comparative analysis of preoperative and postoperative medians of the main CSF circulation parameters showed that positive peak velocity, negative peak velocity, and amplitude range of the maximum linear velocity are significantly lower after surgery. There is no significant difference in the positive and negative volume and stroke volume ($p>0.05$). Therefore, CSF circulation improves after surgery in terms of velocity characteristics and remains unchanged in terms of volumetric characteristics (Table 7).

The effect of the extent of surgical intervention on the recovery of CSF circulation

We compared the medians of all significantly varying parameters of CSF circulation (peak positive velocity, peak negative velocity, amplitude range of maximum linear velocity) between the four groups of patients according to completeness of tumor resection (Table 8, Fig. 12).

The resulting values demonstrate that significant improvement of CSF circulation parameters was achieved in the case of total resection; they were better than postoperative values after almost total and subtotal tumor resection. The group with partial resection was the second best in terms of recovery of CSF circulation parameters.

Comparative analysis of the medians of the main parameters of preoperative and postoperative CSF circulation has shown that surgery results in significantly reduced positive peak velocity, negative peak velocity, amplitude range of the maximum linear velocity. There was no significant changes in the positive and negative volume and stroke volume ($p>0.05$). Therefore, CSF circulation improves after surgery in terms of velocity characteristics.
characteristics and remains unchanged in terms of volumetric characteristics (Table 7).

It should be noted that postoperative velocity characteristics of CSF circulation improve according to PC-MRI, but does not reach normal values, regardless of the completeness of resection.

**Discussion**

Publications dealing with investigation of CSF circulation based on PC-MRI studies are dominated by studies in patients with Chiari malformation [13—16] and hydrocephalus [22, 27]. Available literature provides no studies of CSF circulation in patients with FM meningioma.

Chiari malformation is the most similar to FM tumors in terms of the pathogenetic basis of CSF circulation changes. Analysis of the literature demonstrates conflicting data on CSF circulation parameters at the superior cervical level in both healthy volunteers and patients with type I Chiari malformation before and after the operation [13—16, 28, 29]. This may be caused by the following reasons: different specifications of MR imager; measurements at different levels; heterogenous age composition of the patients under study; the study did not take into account the degenerative-dystrophic changes affecting CSF circulation processes; many authors provide not all CSF circulation parameters, which makes it difficult to compare the results.

---

**Fig. 10.** Anterolateral FM meningioma sized 24 mm. All CSF circulation characteristics are 2—3-fold higher than normal.

a — contrast-enhanced T1-weighed MRI, sagittal view; B — contrast-enhanced T1 MRI, axial view.

**Fig. 11.** Anterolateral FM meningioma sized 38 mm. All CSF circulation characteristics are within the normal range.

a — T1-weighed MRI, sagittal view; b — T2-weighted MRI, axial view.
Table 3. Preoperative neurological symptoms in 38 patients with FM meningiomas. Medians of CSF circulation parameters at C2—C3 depending on the presence/absence of a certain symptom complex, as well as the significance of differences between the subgroups.

<table>
<thead>
<tr>
<th>Symptom complex</th>
<th>Peak positive velocity</th>
<th>Peak negative velocity</th>
<th>Positive volume</th>
<th>Negative volume</th>
<th>Amplitude range, max.</th>
<th>Stroke volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>Median+</td>
<td>Median−</td>
<td>p</td>
<td>Median+</td>
</tr>
<tr>
<td>Cerebellar syndrome</td>
<td>26 68,4</td>
<td>10,20</td>
<td>14,65</td>
<td>0,25</td>
<td>9,64</td>
<td>0,95</td>
</tr>
<tr>
<td>Cerebral syndrome</td>
<td>16 42,1</td>
<td>10,74</td>
<td>13,45</td>
<td>0,99</td>
<td>10,94</td>
<td>0,48</td>
</tr>
<tr>
<td>Bulbar syndrome</td>
<td>6  15,8</td>
<td>11,77</td>
<td>12,20</td>
<td>0,78</td>
<td>10,71</td>
<td>0,83</td>
</tr>
<tr>
<td>Pyramidal disorders</td>
<td>10 26,3</td>
<td>11,65</td>
<td>12,54</td>
<td>0,84</td>
<td>11,90</td>
<td>0,62</td>
</tr>
<tr>
<td>Sensory disorders</td>
<td>11 28,9</td>
<td>14,70</td>
<td>10,20</td>
<td>0,41</td>
<td>13,60</td>
<td>0,15</td>
</tr>
<tr>
<td>Cervical syndrome</td>
<td>10 26,3</td>
<td>11,63</td>
<td>12,19</td>
<td>0,45</td>
<td>8,09</td>
<td>0,49</td>
</tr>
<tr>
<td>Dysfunction of XI</td>
<td>5  13,2</td>
<td>12,99</td>
<td>11,29</td>
<td>0,60</td>
<td>13,30</td>
<td>0,35</td>
</tr>
</tbody>
</table>

Note. In Tables 3 and 4: n — the number of patients, % — syndrome occurrence rate; median+ — median of respective indices in patients having the complex of symptoms; median− — median of respective indices in patients without symptom complex; p<0.05.

Table 4. Postoperative neurological symptoms in 29 patients with FM meningiomas. Medians of CSF circulation parameters at C2—C3 depending on the presence/absence of a certain symptom complex, as well as the significance of differences between the subgroups.

<table>
<thead>
<tr>
<th>Symptom complex</th>
<th>Peak positive velocity</th>
<th>Peak negative velocity</th>
<th>Positive volume</th>
<th>Negative volume</th>
<th>Amplitude range, max.</th>
<th>Stroke volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>Median+</td>
<td>Median−</td>
<td>p</td>
<td>Median+</td>
</tr>
<tr>
<td>Cerebellar syndrome</td>
<td>11 37,9</td>
<td>8,21</td>
<td>9,7</td>
<td>0,6</td>
<td>8,5</td>
<td>9,68</td>
</tr>
<tr>
<td>Cerebral syndrome</td>
<td>7  24,1</td>
<td>9,8</td>
<td>9,63</td>
<td>0,85</td>
<td>9,65</td>
<td>9,65</td>
</tr>
<tr>
<td>Bulbar syndrome</td>
<td>9  31</td>
<td>8,21</td>
<td>9,7</td>
<td>0,6</td>
<td>8,5</td>
<td>9,68</td>
</tr>
<tr>
<td>Pyramidal disorders</td>
<td>4  13,8</td>
<td>11,85</td>
<td>8,88</td>
<td>0,1</td>
<td>10,25</td>
<td>8,92</td>
</tr>
<tr>
<td>Sensory disorders</td>
<td>8  27,6</td>
<td>11,55</td>
<td>7,46</td>
<td>0,03</td>
<td>11,65</td>
<td>8,35</td>
</tr>
<tr>
<td>Cervical syndrome</td>
<td>3  10,3</td>
<td>13,6</td>
<td>9,63</td>
<td>0,34</td>
<td>12,9</td>
<td>9,65</td>
</tr>
<tr>
<td>Dysfunction of XI</td>
<td>14 48,3</td>
<td>10,79</td>
<td>6,19</td>
<td>0,01</td>
<td>10,15</td>
<td>8,34</td>
</tr>
</tbody>
</table>
We used the technique that was previously developed at the Burdenko Neurosurgical Institute and demonstrated in the article of N.V. Arutyunov reporting the study of CSF circulation in patients with type I Chiari malformation [26]. According to the findings of N.V. Arutyunov et al. (2009), all preoperative CSF circulation parameters in patients with type I Chiari malformation were significantly lower than normal values. After surgery, all CSF circulation characteristics significantly increase and reach normal level. In our study, the reverse trend was observed in patients with FM meningiomas before surgery: all CSF circulation parameters were above normal. Our data, demonstrating increase in velocity values of CSF circulation, are in agreement with hydrodynamic continuity law (Castelli’s law), whereby the flow rate of the fluid in pipes is inversely proportional to their cross-section. In our opinion, increase in volumetric characteristics of CSF circulation is due to turbulent motion of the CSF below meningiomas (C2—C3). After surgery, velocity characteristics of CSF circulation (peak positive and negative velocity, amplitude range of the maximum linear velocity) in patients with FM meningiomas significantly decreased, but did not reach normal values; volumetric parameters (positive and negative volume, stroke volume) did not change. Since the follow-up study was conducted 3—6 months after the operation, these CSF circulation characteristics can be attributed to the development of postoperative cicatrical changes.

**Conclusion**

According to PC-MRI, all preoperative CSF circulation parameters in patients with FMR meningiomas exceed normal values. The relationship between these parameters and tumor size and location was not established. We found only correlations between some parameters and clinical manifestations of the disease, which can indirectly indicate the role of tumor configuration in CSF circulation disorders. After the operation, velocity characteristics of CSF circulation decrease, volumetric characteristics remain unchanged.

**Table 5. Quantitative characteristics of CSF circulation at C2—C3 in 28 patients with FM meningiomas before tumor resection**

<table>
<thead>
<tr>
<th>CSF circulation parameter</th>
<th>Median</th>
<th>Std. Dev.</th>
<th>Median</th>
<th>25,000 th</th>
<th>75,000 th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive peak velocity, cm/s</td>
<td>12.12</td>
<td>4.35</td>
<td>14.20</td>
<td>10.05</td>
<td>15.05</td>
</tr>
<tr>
<td>Peak negative velocity, cm/s</td>
<td>10.85</td>
<td>4.47</td>
<td>11.90</td>
<td>6.46</td>
<td>14.52</td>
</tr>
<tr>
<td>Positive volume, ml</td>
<td>1.06</td>
<td>0.47</td>
<td>1.01</td>
<td>0.82</td>
<td>1.44</td>
</tr>
<tr>
<td>Negative volume, ml</td>
<td>0.85</td>
<td>0.51</td>
<td>0.97</td>
<td>0.46</td>
<td>1.16</td>
</tr>
<tr>
<td>Amplitude range of maximum linear velocity, cm/s</td>
<td>22.97</td>
<td>8.16</td>
<td>23.70</td>
<td>17.27</td>
<td>29.26</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>1.92</td>
<td>0.80</td>
<td>1.91</td>
<td>1.56</td>
<td>2.28</td>
</tr>
</tbody>
</table>

**Table 6. Quantitative characteristics of CSF circulation at C2—C3 in 28 patients with FM meningiomas after tumor resection**

<table>
<thead>
<tr>
<th>CSF circulation parameter</th>
<th>Median</th>
<th>Std. Dev.</th>
<th>Median</th>
<th>25,000 th</th>
<th>75,000 th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive peak velocity, cm/s</td>
<td>8.96</td>
<td>3.95</td>
<td>9.75</td>
<td>4.66</td>
<td>12.45</td>
</tr>
<tr>
<td>Peak negative velocity, cm/s</td>
<td>8.88</td>
<td>3.87</td>
<td>9.67</td>
<td>4.96</td>
<td>11.40</td>
</tr>
<tr>
<td>Positive volume, ml</td>
<td>0.80</td>
<td>0.48</td>
<td>0.78</td>
<td>0.42</td>
<td>1.18</td>
</tr>
<tr>
<td>Negative volume, ml</td>
<td>0.70</td>
<td>0.51</td>
<td>0.66</td>
<td>0.21</td>
<td>1.14</td>
</tr>
<tr>
<td>Amplitude range of maximum linear velocity, cm/s</td>
<td>17.84</td>
<td>7.65</td>
<td>19.56</td>
<td>9.71</td>
<td>24.05</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>1.50</td>
<td>0.90</td>
<td>1.27</td>
<td>1.04</td>
<td>2.15</td>
</tr>
</tbody>
</table>
Table 7. Median of preoperative and postoperative quantitative characteristics of the CSF circulation at C2 —C3 and probability values in patients with FM meningiomas

<table>
<thead>
<tr>
<th>CSF circulation parameter</th>
<th>Median 25,000 th</th>
<th>75,000 th</th>
<th>Median 25,000 th</th>
<th>75,000 th</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive peak velocity, cm/s</td>
<td>14,20</td>
<td>10,05</td>
<td>15,05</td>
<td>9,75</td>
<td>4,66</td>
</tr>
<tr>
<td>Peak negative velocity, cm/s</td>
<td>11,90</td>
<td>6,46</td>
<td>14,52</td>
<td>9,67</td>
<td>4,96</td>
</tr>
<tr>
<td>Positive volume, ml</td>
<td>1,01</td>
<td>0,82</td>
<td>1,44</td>
<td>0,78</td>
<td>0,42</td>
</tr>
<tr>
<td>Negative volume, ml</td>
<td>0,97</td>
<td>0,46</td>
<td>1,16</td>
<td>0,66</td>
<td>0,21</td>
</tr>
<tr>
<td>Amplitude range of maximum linear velocity, cm/s</td>
<td>23,70</td>
<td>17,27</td>
<td>29,26</td>
<td>19,56</td>
<td>9,71</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>1,91</td>
<td>1,56</td>
<td>2,28</td>
<td>1,27</td>
<td>1,04</td>
</tr>
</tbody>
</table>

Table 8. Quantitative characteristics of CSF circulation (median and percentiles) at C2—C3 as a function of the extent of surgical intervention

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Extent of tumor resection</th>
<th>Total</th>
<th>Near-total</th>
<th>Subtotal</th>
<th>Partial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive peak velocity, cm/s</td>
<td>7,15 (4,39—11,7)</td>
<td>10,63 (5,15—12,6)</td>
<td>11,7 (6,71—13,2)</td>
<td>9,63 (3,93—9,88)</td>
<td></td>
</tr>
<tr>
<td>Peak negative velocity, cm/s</td>
<td>6,36 (4,77—10,56)</td>
<td>9,3 (4,9—10,1)</td>
<td>10,2 (9,65—14,30)</td>
<td>9,68 (3,25—10,4)</td>
<td></td>
</tr>
<tr>
<td>Amplitude range of maximum linear velocity, cm/s</td>
<td>13,53 (9,25—22,13)</td>
<td>20,53 (9,88—21,5)</td>
<td>23,4 (16,36—27,4)</td>
<td>19,31 (7,27—20,28)</td>
<td></td>
</tr>
</tbody>
</table>

Decrease in these values does not depend on the completeness of tumor resection.

The small number of patients and differently directed changes in the velocity and volumetric parameters complicate interpretation of the results and indicate that routine use of PC-MRI in the treatment of FM meningiomas is inappropriate at this stage.

REFERENCES

15. Haughton VM, Korosec FR, Medow JE, Dolar MT, Iskandar BJ. Peak systolic and diastolic CSF velocity in the foramen magnum in adult patients.

The lack of correlation between the completeness of tumor resection and recovery of CSF circulation parameters pathogenetically justifies the use of palliative surgery (partial resection, dural plasty, decompression of the craniovertebral junction) in the case of inoperable FM meningiomas.

There is no conflict of interest.


doi: 10.1097/00006123-199408000-00006


doi: 10.1148/radiology.161.3.3786732


doi: 10.1148/radiology.178.2.610204


doi: 10.1148/radiology.183.2.1561340


doi: 10.2214/ajr.05.0003


doi: 10.3174/ajnr.a1308

**Commentary**

In this article, the authors focus on a rare pathology, namely meningioma of the foramen magnum (FM) region, which accounts for 3.2% of all meningiomas, and CSF circulation status after surgical treatment, which is scarcely described in the literature.

The Materials and Methods summarizes the experience in 38 patients with anterolateral (29 patients), ventral (5), and dorsal (4) FM meningiomas. A total of 29 patients were operated on. All operated patients were examined before and after surgery. CSF circulation was studied using phase contrast MRI (PC-MRI).

The study demonstrated that the size and location of FM meningiomas did not significantly affect the characteristics of CSF circulation. Neurologic deficit correlated with CSF circulation parameters. Most importantly, the dynamics of recovery of CSF circulation parameters is the same regardless of the completeness of surgery. In all groups of operated patients, CSF circulation characteristics do not reach normal values as evidenced by PC-MRI, which pathogenetically justifies the use of palliative surgery (partial resection, dural plasty, decompression of the craniovertebral junction) in the case of inoperable meningiomas.

The article as a whole, references, and summary provide detailed presentation of the matter under investigation. This study included a sufficient number of patients, which makes it statistically significant, summarizes the experience with PC-MRI and the influence of radical surgery on the CSF circulation parameters in patients with FM meningiomas, and proves the possibility of palliative surgery.

*L. M. Zaytsev (Moscow, Russia)*
Application of Resorbable Plates for Fixation of a Laminotomy Flap

YU.V. KUSEL’, YU.D. BELOVA, A.R. TEKOEV

Burdenko Neurosurgical Institute, Moscow, Russia

The paper describes a new technology — application of resorbable plates and pins for securing a laminotomy flap in children’s neurosurgery. Four patients were operated on at our clinic. We describe in detail a surgical technique and compare it with a traditional fixation technique using ligatures.

Keywords: fixation, resorbable plates and pins, ultrasonic tip, laminotomy.

Laminotomy is widely used for surgical access to pathologies of the spinal canal [1]. The duration of laminotomy, especially in case of multilevel access, is rather short (much shorter than standard laminectomy). However, the process of fixing the laminotomy flap can take a lot of time, often as much as the time required for all previous stages of the surgery. The technology used for fixing the laminated flap is either ligatures through each arch or titanium mini-plates [1, 2]. We deliberately did not use titanium mini-plates in our practice for several reasons: difficulty of achieving good fixation of screws in children’s thin and soft vertebrae arches and issues with relaminotomy in the event of relapse of the disease. Therefore, until recently our main method of fixation was ligatures [1, 3].

Resorbable plates and pins (biodegradable plates and special screws for them) are made of amorphous polymer consisting of D-lactide and L-lactide in equal proportions [4, 5]. Biodegradation requires about 90 days and occurs by hydrolysis. The screws used for this method differ from the “true” ones by the absence of threads and therefore there is no need use a screwdriver. In essence, they are pins that can be softened using a special ultrasonic nozzle and subsequently “flow into” the bone’s diploque, which allows them to become fixated in it once the ultrasonic action is stopped and they solidify. The technology is simple and convenient. In addition, the plate itself is also softened by heating at a temperature of 60 °C and can be modeled “in situ”. The manufacturer positions these products for cranial and maxillofacial surgery [5, 6]. Our experience with the use of resorbable plates and screws in the surgery of craniosynostosis and complex skull defects in children led to the idea of using the same fixation technology for laminotomy.

Material and Methods

Resorbable plates and screws were used to fix laminotomy flaps in 4 patients aged 4 to 11 years (at 3, 4, 5, and 9 levels). In total, the fixation was performed at 21 levels. The operations were performed for intradural tumors and cysts of the spinal cord. The average time of fixation was 15 minutes (which is approximately 2.5 times shorter than the duration of traditional fixation by ligatures). There were no complications, flap displacements or tissue reactions. The minimal follow up period was 3 months.

Operation technique

In all cases laminotomy was performed after subperiosteal dissection, following the procedure described previously by the first author [1]. The intradural stage of the surgery was performed using microsurgical techniques and depended on a specific pathology. The stage of fixing the flap began after tight sealing of the dura mater. We used 1-mm thick plates with 4 holes in all cases (the length and arrangement of holes was always sufficient for our purpose) and pins with a diameter of 2.4 mm and a length of 5 mm. Plates were bent “in situ” to produce the required configuration, just before they were fixed. The fixation of all plates to the flap was carried out immediately afterwards (Fig. 1).

Further, the flap was put in place and, if necessary, the plates were additionally bent to ensure their optimal contact with the base of the arches. Then most cranial and caudal arches were fixed, which ensured correct position of the flap in the wound. Finally, all the other plates were fixed (Fig. 2). The wound was sutured layer by layer in accordance with general surgical principles.

A schematic depiction of the method for fixing a laminated bone flap is shown in Fig. 3.

Discussion

Literature search for use of resorbable plates and screws in neurosurgery produced only results related to cranial application [4, 6—8]. Therefore, it was not possible to compare our experience with the literature data. Nevertheless, it should be noted that resorbable materials are gradually getting traction in traumatology, orthopedics and spinal surgery and there are already relevant publications. However, the main issues that are discussed in these papers are mechanical strength and
reliability of fixation in comparison with metallic analogs [5].

In our clinical study, this comparison is not determinative. It is well known that the purpose of laminotomy and fixation of the flap is not so much immediate “stabilization” as restoration of the place of fixation of the paraspinal musculature and prevention of gross epidural fibrosis. In this situation, the main goal of fixation is to position the flap “in situ”, where the mechanical load on it is minimal, so even ligature fixation is sufficient. We have been successfully using ligatures to fix the laminotomy flaps since 2003 (more than 270 laminotomies were performed), and we have never noted any issues related to insufficient rigidity of fixation or flap displacement. The only significant drawback of this technique is that it is labor-intensive and time-consuming, especially in case of laminotomies of more than 3 levels. For example, the process of fixing a 5-level flap in the thoracic spine can take up to 40 minutes. This procedure becomes even more time-consuming in case of narrow canal and thick arches. In addition, the process of drilling holes in the roots of the arches often leads to additional venous bleeding from the epidural veins, which also leads to unnecessary waste of time and resources. The use of resorbable plates is more promising in this situation. The use of standard titanium plates in children is less desirable for reasons we have already mentioned above: difficulty in achieving good fixation of screws in thin and soft arches of children’s vertebrae and issues with relaminotomy in the event of relapse of the disease. In addition, the classical technology of drilling holes and tightening the screws does not provide any benefits in terms of technology or convenience (in a narrow and deep wound it is even more difficult) than imposing ligatures.

Therefore, we became interested in resorbable plates with ultrasonic “welding” of “screws”. Our preliminary experience with the use of resorbable plates and pins was positive. This technology provides reliable and fast fixation for fixing a laminotomy flap. In addition, by bending the plates in a specific manner, one can slightly increase the transverse dimension of the spinal canal to ensure decompression. The biggest drawback and the main obstacle to the wide application of the described technology, are the price of implantable products and special equipment required for their installation.

**Conclusion**

The paper presents the initial experience of using resorbable plates and pins (screws) for fixing a laminotomy flap. We describe the surgical technique and provide comparative evaluation of the proposed technology with those already commonly used in practice.

The local ethical committee of the Burdenko Neurosurgical Institute of the Ministry of Health of the Russian Federation at the meeting of 09.06.16 (protocol No 06/2016) approved the publication of this paper in a specialized medical journal.

**There is no conflict of interest.**
REFERENCES


Commentary

This work is devoted to the use of resorbable plates and pins for laminoplasty in children. The process described by the authors was previously used only for cranioplasty, so its application in spinal surgery is off-label.

The laminoplasty is widely used in treatment of cervical spondylogenic myelopathy in Japan (Hirobayashi, Kurokava), and in Russia (A.O. Guscha, O.A. Drepal). At present, there are titanium plates of special shape for fixing the arches available for carrying out this operation. Of course, the use of resorbable products is an attractive alternative to metal ones, especially when ultrasonic “welding” is used for fixing pins in place.

It remains unclear whether it is possible to use these products in the elderly, given the frequency of laminoplasty in the stenosis of the spinal canal at the cervical level and the frequent sclerosis and fragility of the arches in this category of patients.

A.O. Guscha (Moscow, Russia)
Minipterional Craniotomy in Surgery for Anterior Circle of Willis Aneurysms

R.S. DZHINDZHIKHADZE, O.N. DREVAL', V.A. LAZAREV, R.L. KAMBIEV

Russian Medical Academy of Postgraduate Education, Moscow, Russia; Inozemtsev City Clinical Hospital, Moscow, Russia

One of the significant events in aneurysm surgery was promotion of a microneurosurgical technique by G. Yasargil. Despite its versatility, pterional craniotomy is associated with extensive osteotomy and a significant incision of the skin and temporal muscle, which may lead to the adverse cosmetic effects, risk of temporomandibular joint dysfunction, injury to the frontal branch of the facial nerve, and facial and scalp numbness. We present our experience with minipterional craniotomy in surgery for anterior circle of Willis aneurysms in 40 patients. There were no serious complications or deaths. Also, there were no intraoperative aneurysm ruptures. All patients experienced expected transient hypesthesia in the temporal region, which was not considered as a complication. In this case, hypesthesia was significantly milder compared to that in the classical pterional craniotomy. Patients assessed the postoperative cosmetic outcome as excellent.

Keywords: minipterional craniotomy, keyhole, minimally invasive surgery, aneurysms.

The traditional pterional approach in surgery of cerebral aneurysms was proposed by G. Yasargil. The approach includes an arcuate incision of the skin from the tragus to the midline along the hairline, followed by an extensive dissection of the temporal muscle and craniotomy of the frontotemporal region [1, 2].

This classical extensive approach is often associated with various postoperative complications, unsatisfactory cosmetic results, prolonged stay of patients in a hospital, and prolonged postoperative recovery at the outpatient stage, which entails great economic costs. Later, J. Hernesniemi et al. [3] modified pterional craniotomy (PC) and proposed a lateral supraorbital approach that differed (in the authors' opinion) from PC by the subfrontal trajectory facilitating an approach to the parasellar space and causing less damage.

The modern concept of keyhole surgery involves reducing the aggressiveness of surgery by minimizing a surgical approach. Modified keyhole approaches were initially proposed in surgery of anterior circulation aneurysm and parasellar space-occupying lesions [4—23]. We have used a differentiated approach for surgical accesses and the concept of keyhole surgery for anterior circulation aneurysms and anterior and middle cranial fossa tumors since 2014.

In this work, we present the experience of using the minipterional craniotomy (MPC) in surgery of anterior circle of Willis aneurysms.

Material and methods

In the period between March 2014 and December 2015, 40 aneurysms were clipped using the minipterional craniotomy. The aneurysm location was as follows: 30 middle cerebral artery (MCA) aneurysms, 7 internal carotid artery (ICA) aneurysms in the area of the posterior communicating artery orifice, and 3 ophthalmic aneurysms. The male:female ratio was 1:2.5. The mean age of patients was 53.7 years. Thirty patients had unruptured aneurysms. Ten patients had subarachnoid hemorrhage (SAH): 7 of these were operated on in the acute period. The condition of these patients was assessed using the Hunt—Hess scale, and the amount of SAH was assessed using the Fisher scale. Four patients underwent surgery in the early period. Three patients underwent clipping in the long-term period. All patients had a Hunt—Hess grade of I or II and Fisher grade 1 or 2 SAH.

Preoperatively, all patients underwent two-dimensional and 3D-CT angiography. The surgical approach was chosen after a thorough evaluation of the anatomy of intracranial structures and aneurysms. All aneurysms clipped using MPC were of small or medium size, no more than 15 mm in diameter. In the case of complex large and giant aneurysms, the method of choice involved more extended approaches ranging from the classical pterional craniotomy to the orbitozygomatic approach and its different modifications. Also, we did not consider MPC as an acceptable technique in patients in a decompensated state (Hunt—Hess grade IV—V) as well as in the case of massive subarachnoid hemorrhages and large parenchymal hematomas accompanied by brain edema and intracranial hypertension. Along with clipping, most of the patients underwent extensive decompressive trepanation.

Surgical technique

Surgery is performed under general anesthesia, with the patient in a supine position with the head turned in the opposite direction at an angle of 30—60°, depending on the lesion location. The neck is maximally extended to provide gravitational retraction of the frontal lobe from the skull base and adequate venous drainage. A 4—5 cm arcuate incision of the skin and soft tissues is performed in the temporal region, starting from the
zygomatic process, 1 cm anterior to the superficial temporal artery, and to the hairline or not reaching the superior temporal line (Fig. 1).

Next, the classical interfascial temporal muscle dissection is performed, with the frontal branch of the facial nerve being preserved. An incision of the temporal fascia is performed by monopolar coagulation with preservation of the myofascial cuff. After a subperioseal dissection, the temporal muscle is expanded by a small retractor or reduced by hook tensioners. This enables full exposure of the pterion area. A burr hole is placed superior to the frontozygomatic suture. A craniotomy, 2—3 cm in size, includes the lateral sphenoid bone, a portion of the frontal bone below the superior temporal line, and a minimum portion of the temporal bone. Like in the classical PC, the sphenoid crest is resected until the meningo-orbital artery in the superior orbital fissure is visualized (Fig. 2).

The dura mater (DM) is opened by a semi-oval incision, with its base directed towards the pterion. The intradural stage of surgery is performed under a microscope (Fig. 3).

The subsequent technique depends on the aneurysm location. In the case of MCA aneurysms, the Sylvian fissure is dissected anteriorly to the superficial Sylvian veins that should be preserved from damage. The Sylvian fissure is sharply dissected. Usually, small bridging veins coming from the temporal lobe to the frontal lobe can be coagulated without consequences. Of great importance is a dissection in the subarachnoid space area to preserve the cortex and minimize its damage. However, this is not always possible in patients after massive subarachnoid hemorrhage accompanied by brain edema and obliteration of the Sylvian fissure. In the case of MCA M1 bifurcation aneurysms, the transsylvian approach, without dissection of the parasellar cisterns, may be sufficient. In this situation, identification of the M1 segment to provide proximal control is the priority, and then, the MCA branches (M2 segment) and aneurysms are identified. After dissection, the aneurysm is clipped with temporary clipping or without it. In the case of ICA aneurysms, the classical microsurgical technique with early brain relaxation by opening of the optic nerve and carotid artery cisterns is used. Further, a limited dissection of the medial Sylvian fissure is performed to provide moderate traction of the frontal lobe and visualization of the ICA bifurcation. The posterior communicating artery is visualized through the optic-carotid triangle. Arachnoid adhesions of the ICA are sharply dissected, and then the anterior choroid artery is identified. The microsurgical technique is dictated by the aneurysm location. In the case of carotid-ophthalmic aneurysms, intradural resection of the anterior clinoid process may be necessary to provide proximal control and visualization of the ophthalmic artery.

In the case of adequate brain relaxation after draining the cerebrospinal fluid from the subarachnoid cisterns and/or after pharmacological exposures, there is no need for significant retraction of the parenchyma. In the case of hemorrhage, the brain may be edematous. In these cases, the carotid cistern is first opened for adequate relaxation, which then enables more comfortable and less traumatic dissection of the Sylvian fissure. Early placement of a lumbar drain may be an alternative in SAH patients.

After clipping the aneurysm and verifying its complete exclusion (it is optimal to use intraoperative indocyanine green (ICG) angiography, followed by opening of the aneurysm), hemostasis is performed. The DM is tightly closed. A bone flap is fixed with craniofixes or miniplates. The temporal fascia/muscle, subcutaneous tissue, and skin are sutured in layers (Fig. 4). Given a small wound size, wound drainage is not performed, which is also an undoubted advantage of minimally invasive surgery.

Below, we provide an example of surgery in a female patient with a carotid-ophthalmic ICA aneurysm. The microsurgical stage of surgery was performed without retractors (Fig. 5).

**Results and discussion**

All aneurysms were completely excluded from the cerebral circulation, which was confirmed by
intraoperative opening of aneurysms and subsequent monitoring using intraoperative indocyanine green angiography and control 3D-SCT angiography in the postoperative period. There were no serious complications or lethal cases in patients. Also, there were no intraoperative aneurysm ruptures. All patients experienced transient hypesthesia in the temporal region, which was expected and, therefore, was not regarded as a complication. It should be noted, that the hypesthesia area was significantly smaller when compared to the outcomes of classical pterional craniotomy.

Fig. 2. Minimal pterional craniotomy.
a — an intraoperative view: a skin-aponeurotic flap is moved anteriorly, and the temporal muscle is spread by a retractor; b — the size of a bone flap.

Fig. 3. Stages of microsurgical treatment of a left MCA aneurysm.
a — SCT-angiography: a saccular aneurysm of the left MCA M1 segment is seen; b — an intraoperative view after minipterional craniotomy and opening of the DM; the center of craniotomy is situated over the Sylvian fissure; c, d — stages of Sylvian fissure dissection; e — the saccular aneurysm of the MCA M1 segment; f — clipping of the aneurysm; g, h — intraoperative indocyanine green angiography: the aneurysm is excluded from blood flow, the MCA branches, not stenotic, are visualized; i — a view after clipping of the aneurysm and opening of the aneurysmal sac.
Patients assessed the postoperative cosmetic result as excellent. In 2 patients, a follow-up examination at up to 10 months revealed minimal dysfunction in the temporomandibular joint area and symptoms of temporal muscle atrophy in the craniotomy area.

The traditional approach in surgery for intracranial aneurysms of the anterior circulation is the pterional craniotomy proposed by M. Yasargil in 1975 [1, 2]. Pterional craniotomy is associated with a quite extensive osteotomy and a significant incision of the skin and temporal muscle, which may lead to the following side effects: temporal muscle atrophy, scar formation, facial asymmetry, risk of temporomandibular joint dysfunction, chewing pain, discomfort when wearing glasses, damage to the frontal branch of the facial nerve, scalp numbness, and scar alopecia. Exposure of the cortex at the intradural stage, more significant in size, may be accompanied by damage to the cortex due to the influence of the non-physiological environment, retractor trauma, etc [21—25].

The concept of keyhole is not new. Since its introduction by A. Perneczky et al. [10, 11, 21—25], considerable experience in surgery of aneurysms and intracranial tumors has been accumulated. Keyhole surgery is a modern concept that significantly reduces injury caused by surgery. The size of keyhole craniotomy is 2—3 cm, on average. However, this is not just a reduction in the trephination window size. Keyhole means the creation of an optimal surgical corridor in each particular case to access a certain lesion with minimal injury to both soft tissues, including the temporal muscle, and brain tissue. This goal is achieved through the use of small incisions of soft tissues, minimal DM opening, and exposure of the cortex with minimal retraction of the brain. This enables achieving the main goals of minimally invasive neurosurgery: minimization of surgical invasion, improvement of the cosmetic effect compared to that of classical surgery, shorter surgery time, reduction in blood loss, postoperative pain, and postoperative complications, and shorter total hospital stay, which reduces financial and economic costs for treatment of patients. It is also important to assess the outcomes of minimally invasive microsurgery of aneurysms in terms of patient satisfaction with surgery.

The keyhole approaches used for anterior circulation aneurysms are primarily supraorbital and minipterional ones. B. Chehrazi [6] was one of the first researchers who described a temporal transsylvian approach to aneurysms as an alternative to the classical pterional craniotomy, which was accompanied by a decrease in the trephination...
Later, many authors [5—16] used the minimally invasive approach in aneurysm surgery, calling it a modified pterional craniotomy. E. Figueiredo et al. [10, 11] compared the minipterional approach and the pterional craniotomy in two groups of patients. Despite the similar treatment outcomes, the authors noted that the minipterional approach was associated with less damage to soft tissues and less craniotomy, which reduced the time of surgery and recovery period and improved cosmetic results. A necessary support in keyhole surgery of aneurysms is the use of an additional imaging technique, intraoperative indocyanine green fluorescence angiography [4, 26—28].

Keyhole surgery is based on a thorough preoperative assessment to determine the trephination window position depending on the pathological process and individual patho-anatomic picture. We associate the good results of surgical treatment in our group with careful preoperative selection of candidates for minimally invasive surgery and exclusion of patients being at the decompensated stage (Hunt—Hess grade IV—V). Patients with unruptured aneurysms are ideal candidates for keyhole surgery, except for patients with large and giant aneurysms. Among patients with the clinical presentation of SAH, the most favorable candidates for minimally invasive surgery are patients with Hunt—Hess grade I—II aneurysms. For subcompensated and decompensated patients, we consider the classical pterional approach with its modifications (orbitopterional or orbitozygomatic craniotomy) as the method of choice.

**Fig. 5. Stages of microsurgical treatment of a carotid-ophthalmic ICA aneurysm.**

a — SCT-angiography: a carotid-ophthalmic aneurysm on the right is visualized; b — an intraoperative image after minipterional craniotomy and opening of the DM; the Sylvian fissure is indicated by the arrow; c — intradural resection of the anterior clinoid process by a 2 mm diamond burr; d, e — stages of aneurysm isolation; f — aneurysm clipping; g — a view of the surgical wound at the end of surgery.
Conclusion
The minipterional craniotomy is the method of choice for most MCA and some ICA aneurysms. The main goal of keyhole surgery is not only to reduce the trephination window but also to decrease traction brain injury. An important support in minimally invasive surgery of aneurysms is the use of ICG-angiography and endoscopic assistance, which greatly enhances visualization and control in a narrow deep wound.

There is no conflict of interest.

REFERENCES
Pterional craniotomy with transsylvian dissection provides a wide viewing angle for manipulations with intracranial structures and is used as a standard approach for clipping of anterior circulation and upper basilar artery aneurysms. A modification of the pterional craniotomy in terms of minimally invasive surgery, called minipterional craniotomy, is characterized by reduced iatrogenic trauma. High safety of surgery is achieved by reducing the length of a skin incision, length of temporal muscle dissection, size of a bone flap, and time spent on performing the approach and closing the wound.

Any desire to minimize a surgical approach to intracranial structures requires a comparative evaluation of the safety of the new technique, degree of its versatility (applicability), duration of surgery, cosmetic results, etc. In the presented work, R.S. Dzhindzhikhadze and co-authors analyze the experience of using minipterional craniotomy in treatment of 40 saccular aneurysms of the carotid territory, with 30 of them being middle cerebral artery aneurysms.

In the discussion of minimally invasive approaches in surgery of aneurysms, the authors refer to studies devoted to a supraciliary approach. The supraciliary approach is a variant of the supraorbital subfrontal approach and, being significantly different, provides significantly less freedom of surgical manipulations in the Sylvian fissure compared to the minipterional approach.

The indications for minimally invasive surgery, including minipterional craniotomy, in treatment of arterial aneurysms are determined not only by the aneurysm size but also by the aneurysm neck configuration. The use of a relatively narrow intracranial corridor reduces visualization and hampers arachnoid dissection of the vascular structures as well as limits the use of complex configuration clips and clip holders with large swing flexible heads.

The minipterional approach is most appropriate for clipping of middle cerebral artery and supraclinoid internal carotid artery aneurysms with a simple neck configuration directed perpendicular to the axis of a planned approach. Exposure of the Sylvian fissure within a relatively small trephination window enables its safe dissection in the lateromedial (distal-proximal) direction, which is usually sufficient for clipping of middle cerebral artery aneurysms. In my opinion, this approach can not be used for complex middle cerebral artery and anterior communicating artery aneurysms and, if necessary, for contralateral dissection in multiple aneurysms. All similar cases require extensive arachnoid dissection with retraction of the frontal lobe and the standard pterional craniotomy, the size of which enables insertion of instruments and clips into the depth of the wound at different angles.

The presented good results of minipterional craniotomy in surgical treatment of aneurysms of the carotid territory are associated with careful analysis of the relationship among the aneurysm location, the direction and shape of the aneurysm neck, the presence of hemorrhages and edema of brain tissue that have been considered by the authors at the preoperative planning stage. Experience of R.S. Dzhindzhikhadze and co-authors emphasizes the important point about the need for selecting not only a surgical approach but also its minimally invasive modification to ensure both the primary goal of surgical intervention (safe clipping of the aneurysm) and reduce the total injury rate and duration of surgery.

Yu.A. Grigoryan (Moscow, Russia)
A Giant Hyperostotic Parasagittal Meningioma in a Child with Neurofibromatosis Type II. A Case Report and Literature Review


Burdenko Neurosurgical Institute, Moscow, Russia

Large parasagittal meningiomas, in particular hyperostotic ones, in children are rare and problematic in the differential diagnosis. The literature reports only single clinical cases related to this issue; opinions about the indications, surgical treatment options, and prognosis are contradictory. This paper presents a clinical case of a hyperostotic parasagittal meningioma with intra- and extracranial growth in a 10-year-old boy with neurofibromatosis type II, which significantly worsened the prognosis. We discuss the epidemiological and clinical features of childhood meningiomas and issues of their diagnosis, treatment, and prognosis.

Keywords: parasagittal, meningioma, hyperostosis, children, neurofibromatosis.

Meningiomas diagnosed in children under the age of 15 years form a special group and have a number of principal differences from meningiomas in adults. Parasagittal meningiomas are less common in children than in adults and account for only 4% of all brain tumors [1]. Hyperostosis can occur in association with convexity and parasagittal meningiomas [2]. In childhood, 25―49% of meningiomas are associated with hyperostosis [3―6], while in adults, this figure amounts to 4.5% [2]. In children, 33―40% of meningiomas are associated with neurofibromatosis type II (NF-2) [3, 6―8], which is a factor worsening the disease prognosis [1, 3, 9].

In this article, we present a rare clinical case of hyperostosis associated with a giant parasagittal meningioma with intra- and extracranial growth in a child with NF-2.

Clinical case

A 10-year-old boy L. applied to the Neurosurgical Institute (August 31, 2015) with complaints of a bulging in the parietal region. Eleven days before hospitalization, the patient had acutely developed right-sided hemiparesis and hemihypesthesia that completely regressed within 8 days of conservative treatment, including osmodiuretics and glucocorticoids. Careful taking of a family history revealed that the child’s grandmother had bilateral neurinomas of the vestibulocochlear nerve (absolute diagnostic criterion for NF-2 [10]), and his mother died of an unspecified brain tumor (she refused surgery, so there was no histological verification). MRI of the brain detected a large parasagittal tumor with intra- and extracranial growth, perifocal edema, and involvement of the parietal bones, which invaded the middle third of the superior sagittal sinus (Fig. 1).

At admission, there were no focal neurological and intracranial hypertension symptoms. The Karnofsky scale score was 100. On examination, a tight elastic bulging in the temporal parasagittal region, mostly on the left, was found. No subcutaneous neurofibromas were found. SCT of the brain revealed a parasagittal contrast enhanced tumor as well as a hyperostotic lesion of both parietal bones, 11×8.5 cm in size, with a marked periosteal reaction (Fig. 2). According to total selective cerebral angiography, the afférents feeding the tumor were multiple small branches of the ICA and ECA; the superior sagittal sinus was not enhanced at the tumor site (Fig. 3).

Given the history, examination, and radiographic findings, including intra- and extracranial components of the tumor and the bone lesion, the diagnosis was...
differentiated between primary Ewing’s sarcoma of the parietal bone and hyperostotic parasagittal meningioma.

To determine the tactics of treatment, an open biopsy of the extracranial portion of the tumor was performed (03.09.15). The biopsy revealed meningotheliomatous meningioma, WHO Grade I, with a Ki-67 labeling index of 5—7%. An attempt to resect the tumor was made (10.09.15). Resection of the extracranial tumor component and resection trepanation of the skull with removal of hyperostosis were performed through a horseshoe-shaped skin incision in the projection of the affected calvarial area. This procedure exposed the intracranial tumor portion, but surgery was terminated due to a high blood loss and a high risk of further massive bleeding. At the second stage, 8 days later, the intracranial tumor portion was removed. The superior sagittal sinus walls occurred to be the initial site of tumor growth. Because of marked venous bleeding from the sagittal sinus, a drop in arterial pressure, and the risk of impairment of venous outflow from large vessels of the parietal region, total removal with resection of the ICA was not performed. The ICA wall was strengthened with tachocomb and artificial DM. The extent of tumor resection was Simpson grade 4 [11]. According to the pathology report, the resected intracranial meningioma portion was identified as atypical meningioma, WHO Grade II. On September 23, 2015, the patient underwent duraplasty (artificial sheath) and bone defect reconstruction using Palakos (Fig. 4). The patient was discharged home 2 weeks after surgery. By that time, the child was active, walked around the department, played, communicated with others, and was capable of self care. The Karnofsky scale score was 100.

One month later, control MRI of the brain revealed small residuals of the meningioma in the superior sagittal sinus region (Fig. 5). Given the family history, MRI of all parts of the spinal cord was also performed, which revealed a space-occupying lesion at the C6—C7 space level on the left, most likely neurinoma, which did not clinically manifest itself (Fig. 5, 6). Thus, the child had a combination of the intracranial meningioma, neurinoma of the C6—C7 spinal nerve, and family history (a direct relative with NF-2), which was the basis to diagnose neurofibromatosis type II.

Three months after tumor resection, the patient underwent a course of stereotactic radiation therapy at a dose of 60 Gy in 30 fractions for the residual meningioma. Control MRI of the brain at 6 and 12 months after surgery did not detect continued growth. Further radiation treatment for the neurinoma at the C6—C7 level was under discussion.

Discussion

The annual incidence rate of meningiomas increases with age and peaks at 8.4 per 100,000 population by the eighth decade of life [12]. Meningiomas account for 13—25% of all adult intracranial tumors [13]. At the same time, the occurrence of these tumors in children is much lower and is only 0.4—4.6% [1, 3, 14]. Adult meningiomas are more common in females [9, 12]; on the contrary, pediatric meningiomas are more common in boys [1]. However, according to some studies [4], the primary incidence of meningiomas is approximately the same in children of both genders. Pediatric meningiomas are associated with hyperostosis in 25—49% of cases [3—6], while this parameter is 4.5% for adult tumors [2].

The topography of pediatric and adult meningiomas is also different. Convexity meningiomas account for 41% of pediatric meningiomas [1] and only 19% of adult meningiomas [12].
Meningiomas [15]. Parasagittal pediatric meningiomas are rare (about 4% of cases [1]) in contrast to adult tumors (25% of cases [15]). In addition, pediatric meningiomas are often (about 15% of cases) found in the ventricle cavity [1, 4].

Y. Liu et al. [1] (2008) analyzed a large number of pediatric meningiomas and concluded that the prognosis was primarily affected by the following factors: the extent of initial resection (total resection is associated with a better prognosis), location of the tumor (affects the completeness of resection and, indirectly, the prognosis), presence of NF-2, and previous radiation treatment for other tumors (worsens the prognosis). In 33—40% of cases, pediatric meningiomas are associated with neurofibromatosis type II [3, 6—8]. Neurofibromatosis type II is believed to increase the risk of recurrence and death in meningiomas [1, 3, 9, 16]. At the same time, the degree of anaplasia is a less significant factor [1].

Bilateral neurinomas of the VIIIth nerve are the absolute diagnostic criteria for NF-2 [10, 17]. Also, the diagnosis of NF-2 is established if there is a direct relative having this disease in a combination with either unilateral neurinoma of the VIIIth nerve or two or more of the following signs: neurofibroma, meningioma (one or more), glioma (one or more), schwannomas (including one or more spinal schwannomas), and juvenile posterior subcapsular lenticular cataract [10, 17]. Cafe-au-lait spots occur in approximately 80% of NF-2 patients but have no diagnostic significance [10].

The main method to diagnose meningiomas is MRI. Meningiomas sometimes invade vital vascular structures, so direct selective cerebral angiography is an important...

Fig. 2. Preoperative SCT images of the 10-year-old patient L. Periosteal hyperostosis of both parietal bones and an irregular surface of the affected bone are presented.

Fig. 3. Angiography of the 10-year-old patient L. The afferents are small branches of the ICA and ECA. The superior sagittal sinus is not enhanced in the tumor area.
adjunctive diagnostic technique in the preoperative period. In addition, in the presence of large feeding vessels, the vessels can be embolized to reduce blood loss at the main stage of treatment [3, 18].

As early as 1987, K. Kim et al. [19] emphasized the importance of spiral computed tomography for the diagnosis of tumors associated with hyperostosis. The authors noted that hyperostosis associated with convexity or sphenoid wing meningiomas may often be confused with bone changes associated with other pathological processes, such as fibrous dysplasia, osteoma, or sarcoma. All 9 cases presented in the study had one or more CT features typical of hyperostosing meningiomas, namely: a pronounced periosteal reaction, inward bulging of the bone in the lesion area, an irregular eroded surface of the affected bone, and intracranial changes. The authors [19] argue that high-resolution computed tomography is the method of choice for evaluation of hyperostosis and differential diagnosis of hyperostosing meningiomas and other diseases. The literature [18, 20, 21] reports only single cases of meningiomas associated with hyperostosis in children. The presented clinical case is rare and of great interest because of the medical history features and the complexity of differential diagnosis. Before the tumor biopsy, one of the presumptive diagnoses was a meningioma in the setting of neurofibromatosis type II. However, the patient did not fully meet the diagnostic criteria: having a direct relative with bilateral neurinomas of the VIIIth nerve, the patient himself had a single tumor and no neurinomas by the time of hospitalization. A giant meningioma in the child without neurofibromatosis was unlikely. MRI and CT findings might equally indicate hyperostosing meningioma and Ewing’s sarcoma. Therefore, the second potential diagnosis was primary Ewing’s sarcoma of the cranial vault. This diagnosis was favored by a short history of just 11 days after the onset of symptoms and location of the tumor — the parietal and frontal regions that are typical primary sites of Ewing’s sarcoma growth [22]. In addition, bone changes associated with this tumor can be characterized either by lysis of the inner and outer bone plates or by sclerosis of bone tissue with a periosteal reaction in the form of spicules, which is hardly distinguishable from hyperostosis in meningioma on CT images.

In the world practice, both tumor resection and neoadjuvant chemotherapy are used as the primary treatment for Ewing’s sarcoma [22—25]. Chemotherapy can be selected as primary treatment in the absence of symptoms of intracranial hypertension [25]; in our case, there was no intracranial hypertension. If treatment starts with chemotherapy, the 5-, 10-, 15-, and 20-year overall

---

Fig. 4. A CT image of the 10-year-old patient L. after duraplasty and bone defect reconstruction.

Fig. 5. Postoperative MRI scans of the 10-year-old patient L. Tumor residuals in the sagittal sinus area are indicated by arrows.
survival of patients with Ewing’s sarcoma is 57.2, 49.3, 44.9, and 38.4%, respectively [26].

The standard of treatment for meningiomas is surgical resection. However, total resection is achieved only in 80—90% of patients [3]. The surgeon should strive for total resection of convexity and olfactory meningiomas as well as meningiomas of the anterior third of the cerebral falk and the superior sagittal sinus.

*Fig. 6. MRI scans of all parts of the spinal cord of the 10-year-old patient I. A neurinoma at the C6—C7 level on the left is indicated by arrows.*
At the same time, if the tumor is located in the medial sphenoid wings, posterior superior sagittal sinus, clivus, or orbit, subtotal resection is safer treatment [18, 27]. Based on these factors and the diagnosis, a treatment approach is chosen. After an open biopsy and receiving the results of a histological study, the diagnosis and the need in maximally radical surgery became apparent.

According to the literature [28], adjuvant radiation therapy significantly improves local tumor control in atypical and malignant meningiomas, especially in cases of subtotal resection. Despite the fact that the difference in disease-free survival after surgical and combined treatment of meningiomas was not statistically significant in most studies [28], some authors have still found a significant difference confirming the positive effect of radiotherapy on disease-free survival [29]. For example, I. Pisciević et al. [29] (2015) reported the following results: out of 88 meningioma patients, 58 patients had recurrence within a mean follow-up period of 5.6 years. Five-year disease-free survival (DFS) in patients who underwent tumor resection followed by radiotherapy at a dose of 55/60 Gy (n=34) was 65%, and that in patients who underwent surgery alone (n=24) was 13%. The differences were statistically significant (Log rank=31.9; p=0.001).

For atypical meningiomas, the DFS difference was even more significant (Log rank=34.1; p=0.001): the 5-year DFS in combined and surgical treatment groups was 75 and 12%, respectively. It should be noted that the literature lacks studies devoted to the efficacy and safety of radiation therapy in pediatric meningiomas, and patients with neurofibromatosis have been excluded from most similar studies.

Unlike patients with sporadic tumors, patients with NF-2 often have multiple or extensive tumors and a high risk of recurrence [1, 3, 9, 16], in which some cases limits the capabilities of surgery and radiotherapy. Pharmacological therapy with proven efficacy in meningiomas is currently not available. However, a better understanding of the molecular mechanisms of NF-2 pathogenesis opens the opportunity for application of targeted therapy.

Tumor growth is often accompanied by neovascularization, therefore tumors produce angiogenic factors, such as the vascular endothelial growth factor (VEGF) [30]. A VEGF inhibitor is the medication bevacizumab [30]. This is a humanized monoclonal antibody that prevents binding of all VEGF isoforms to VEGF receptors. A study by F. Nunes et al. [31] (2013), which evaluated a meningioma response to bevacizumab treatment in NF-2 patients, demonstrated that a partial response (a decrease in the tumor size by more than 20%) was received in 30% of the patients. A gradual decrease in the tumor in patients on treatment lasted for 3.7 months, on average, and then the size remained stable. The mean duration of remission was 15 months. Despite the fact that bevacizumab is effective only in a third of patients, targeted therapy may be used in meningioma patients in the setting of NF-2 if other anti-recurrence treatments fail.

Conclusion

In the presented case, the cause to use staged surgery was poorly controlled bleeding at all stages of soft tissue manipulations and tumor resection, which may lead to a significant blood loss and serious complications. The staged surgical treatment enabled resection of the extra- and intracranial tumor portions, followed by reconstructive closure of the bone defect without negative somatic and neurological effects, as well as good and rapid functional recovery of the patient.

In conclusion, it is necessary to emphasize the importance of a careful taking of family and hereditary history as well as MRI of not only the head but all parts of the spinal cord in children operated on for meningiomas. In the presented case, this facilitated identification of an asymptomatic neurinoma at the cervical level, establishment of the diagnosis of NF-2 (negatively affecting the prognosis), and adjustment of the treatment.

There is no conflict of interest.

REFERENCES


Commentary

The paper describes and discusses a rare clinical case that is also of great theoretical importance. The work is easy to read and well illustrated. The discussion of the case and comparison with the literature data provide the reader with an adequate view of the issue and the current state of the problem. The article is of great interest to a wide range of neurooncologists and neuropediatricians.

V.A. Khachatryan (Saint Petersburg, Russia)
Commentary

The presented observation is a rare case of neurofibromatosis type II combined with parasagittal meningioma in a child and is devoted to solving topical issues of neurosurgery, in particular, modern treatment options for primary brain tumors. This problem is important for several reasons related to improvement of diagnostic methods, new capabilities of the modern microneurosurgical complex, and an increase in the resectability of this complex group of patients. Undoubtedly, surgery is believed to be the main modern technique in complex treatment and is surgical, but the tactics of surgical treatment, choice of an operative approach and methods that increase the radicalness of tumor resection still remain controversial, which causes increased interest in this clinical case and confirms the topicality of the problem.

The tumor nature of hyperostosis in meningiomas is now generally recognized. However, invasion of the dura mater and bone by the tumor and formation of hyperostosis are not considered as signs of biological aggressiveness, and hyperostosis associated with parasagittal meningiomas has no effect on recurrence. Only an increased number of recurrences in the case of bone destruction or hyperostosis combined with destruction have been observed. Head soft tissue invasion by meningioma is considered as an indicator of biological aggressiveness of the tumor.

The literature emphasizes a high recurrence rate of parasagittal meningiomas, which is associated with anatomic limitations of surgical radicalness in this area. Parasagittal meningiomas affect the superior sagittal sinus in 15—50% of cases, which sometimes objectively complicates one-stage resection of the tumor. In these cases, surgery should be broken up into several stages. Anatomical data should be considered when planning and evaluating outcomes of surgical treatment.

The presented work provides a detailed, critical, and chronological analysis of the literature data on neurofibromatosis type II associated with meningiomas. The authors rightly put emphasis on insufficiently resolved issues of this complex pathology.

This clinical case is of considerable scientific and practical interest and is devoted to the solution of topical issues of neurosurgery and neurooncology. The work is well illustrated and written in a good literary language and may serve as a guide for both novice neurosurgeons and experienced specialists.

V.V. Timirgaz (Chisinau, Moldova)
Spinal Stroke in a Pregnant Female with an Endodermal Cyst of the Cervical Spinal Cord (a Case Report and Literature Review)

M.A. MARTYNOVA1, N.A. KONOVALOV1, A.YU. LUBNIN1, A.V. SHMIGEL’SKII1, I.A. SAVIN1, T.F. TABASARANSKIY1, K.N. AKHVLEDIANI2, E.V. SINBUKHKOVA1, R.A. ONOPRIENKO1
1Burdenko Neurosurgical Institute, Moscow, Russia; 2Moscow Regional Research Institute of Obstetrics and Gynecology, Moscow, Russia

Spinal stroke, especially at the cervical level, poses a serious danger to the patient’s life and health. In our practice, we were faced with a similar situation where the patient was a female with incomplete pregnancy. This article discusses the experience in treatment of the patient and associated problems.

Clinical case

A 24-year-old female patient M. was transferred from a regional hospital at the place of residence to the Burdenko Neurosurgical Institute (BNI). The patient was at 20 weeks gestation. According to a medical history, the patient suffered from neck pain since the end of August 2015 and received pain relievers. In the evening of September 05, 2015, she noted numbness and growing weakness in the upper and lower extremities. In the morning, she could not move the extremities. The patient was transported by an ambulance team to a regional hospital; after examination by a neurologist and neurosurgeon, she was immediately transferred to the Critical Care Department. The patient’s condition at admission was evaluated as serious. The patient was clearly conscious and complained of neck pain, especially during head movements. Breathing was spontaneous and adequate. Bilateral anesthesia of all kinds of sensitivity, starting at the C3—C5 level of the spinal cord, and flaccid tetraplegia were present. Reflexes in the upper and lower extremities were absent. There was acute urinary retention.

Within 1 day of hospitalization, the patient’s condition began to deteriorate rapidly: respiratory failure worsened, which required intubation of the trachea and ventilation. On the second day of stay at the hospital, after stabilization of the vital functions, the patient underwent spiral computed tomography (SCT) of the cervical spine, which revealed a space-occupying lesion in the vertebral canal at the C3—C5 level, which was located extramedullary and markedly compressed the spinal cord (Fig. 1). Blood test indicators were without significant abnormalities, except for hypokalemia (3.0 mmol/L).

Ultrasound of the uterine cavity confirmed a normally developing pregnancy at 20 weeks. There were no obstetric indications for abortion.

On the 3rd day after the development of focal symptoms, the patient was transferred to the BNI for surgical treatment. The patient’s condition at admission was serious: she was in the supine position in a passive pose. Ventilation was performed through an orotracheal tube. The patient followed simple instructions (she answered simple questions by nodding of the head, articulated, and closed the eyes on command) but quickly exhausted; there were no movements in all the extremities; there was a loss of all types of sensation, starting at the C5—C6 level of the spinal cord and below. The patient had hyperthermia of up to 38.7 °C and arterial hypotension that required intravenous infusion of vasopressors (norepinephrine), and worsening respiratory failure (acceptable SpO2 figures were reached only at FiO₂=0.8). X-ray of the lungs revealed bilateral infiltrative shadows in the lower lobes and perilobar portions. The patient underwent therapeutic fibrobronchoscopy.
accompanied by removal of a small amount of viscous purulent sputum. Given the episodes of desaturation and desynchronization with the respirator, elevation of the CRP level, fever, pulmonary radiographic findings, nature of the underlying disease, and expected need for prolonged ventilation, a puncture tracheostomy was performed on the second day of stay at the Critical Care Department of the BNI. On ventilation with positive end expiratory pressure of 10 cm and FiO₂=0.6 as well as norepinephrine infusion, the patient’s condition was stabilized, after which (on the 5th day of stay at the BNI), she underwent magnetic resonance imaging (MRI) of the cervical spinal cord (Fig. 2) and brain. MRI revealed an extramedullary space-occupying lesion at the C3—C5 level, which was located in the vertebral canal on the right anteriorly, compressing the spinal cord and displacing it to the left posteriorly. The lesion had a high T2 signal (Fig. 2a, c), differing from that of free CSF, and relatively clear smooth contours. T1-weighted MRI revealed signs of parietal hemorrhage in the lesion (Fig. 2b). The spinal cord at the pathology level and I or II vertebra below it, as well as the medulla oblongata, had signs of vasogenic edema. Series of T1 and T2-weighted axial MRI scans of the brain revealed no pathological changes.

The patient repeatedly consulted an obstetrician-gynecologist and underwent daily ultrasound of the uterine cavity, which revealed signs of threatened miscarriage. There were no obstetric indications for abortion. The patient was offered surgery for removal of the space-occupying lesion at the C3—C5 level with preserving pregnancy; the patient and her mother gave a written consent.

On the 7th day of stay at the BNI, the patient underwent surgery: microsurgical resection of the extramedullary space-occupying lesion at the C3—C5 level using ultrasound monitoring of the fetus.

Anesthesia included intravenous propofol (infusion under control of anesthesia depth) + intravenous bolus of fentanyl and rocuronium during surgery. Arterial pressure was monitored directly through a catheter placed in the left radial artery. Continuous intravenous infusion of norepinephrine was performed throughout surgery due to the tendency to arterial hypotension.

The patient was placed in the left lateral position that was considered as the most physiological one, given the gestational age and the need for intraoperative ultrasound monitoring of the fetus. The patient’s head was fixed with a Mayfield clamp; the patient underwent a laminectomy at the C3—C5 level. The dural sac was stretched, not pulsed, and prolapsed into the wound. After opening of the dura mater, about 3 mL of fluid discharge released into the wound, which was collected for testing. The spinal cord was pale and ischemic. After excision of arachnoid adhesions, a pale-gray space-occupying lesion located anterolaterally on the right was found; it grossly compressed and displaced the spinal cord. After identifying poles of the lesion, its capsule was opened. The space-occupying lesion contained viscous yellowish liquid. The space-occupying lesion and its capsule were resected en bloc (Fig. 3).

An urgent biopsy revealed that the resected lesion had an endodermal origin.

Surgery was performed in the presence of an obstetrician-gynecologist, with continuous ultrasound monitoring of the fetal condition (Fig. 4).
The duration of surgery was 1.5 h. The total time of anesthesia, including positioning of the patient, was about 4 h. The amount of intraoperative blood loss was less than 150 mL.

After surgery, the patient was transferred to the Critical Care Department where she continued receiving intensive therapy. No changes in the neurological status occurred.

Postoperatively, the patient’s condition remained unstable: she was conscious; episodes of fever, up to 39 °C, persisted, without any effect of administration of antipyretics; artificial ventilation through the tracheostomy was continued. There was marked production of viscous sputum, requiring sanitation bronchoscopy; the tendency to arterial hypotension persisted, which required continuation of intravenous infusion of norepinephrine; salt-wasting syndrome typical of patients with a high level of spinal cord injury developed [1].

A control MRI study of the cervical spinal cord confirmed complete resection of the space-occupying lesion (Fig. 5).

A histological examination of the lesion capsule revealed the presence of cell-free masses with hemorrhages as well as fibrous tissue with cylindrical epithelium, the morphological structure of which was typical of an endodermal cyst (Fig. 6).

A histological examination of the discharge collected after opening of the dura mater revealed necrotized tissue with hemorrhages (cerebral detritus).

On intensive therapy, the patient’s general condition gradually stabilized: fever, hypoalbuminemia, and anemia regressed. There was no improvement in the neurologic status. According to an examination by an obstetrician-gynecologist, the fetus continued to develop normally; there were no indications for abortion.

Given expected prolonged subsequent treatment and rehabilitation and upon agreement with relatives, the patient was transferred to the Critical Care Department of a regional hospital at the place of residence.

Further information on the fate of the patient and the child was obtained from the doctors of appropriate clinics by phone. The patient’s condition remained relatively stable within a month after surgery; then, an infectious process in the lungs worsened. This fact and the need for antibacterial therapy with high doses of potentially fetotoxic antibiotics, as well as significant intrauterine fetal growth retardation, served as the basis for the decision to terminate the pregnancy. Preterm labor surgery (cesarean section) was performed at 29 weeks gestation, and a premature baby (boy) with a body weight of 780 g, with an Apgar score of 6, was born. The child was intubated and transferred to a specialized perinatal center for artificial ventilation. According to the available information, the child’s condition remained severe by the time of manuscript preparation; the child had several intracranial hemorrhages and was on artificial ventilation. The mother’s condition after cesarean section rapidly deteriorated. In the setting of bilateral pneumonia, sepsis, and progressive multiple organ failure, she died.

**Discussion**

Spinal pathology is the second most common disease after traumatic brain injury among neurosurgical diseases in Russia. Degenerative spine diseases are the most common spinal pathologies. Primary tumors of the spinal cord are relatively rare and account for only 10—15% of all CNS tumors, or 1—2 cases per 100,000 people per year [2]. Manifestations of spinal cord tumors during pregnancy refer to casuistic cases. For example, A. Moles et al. in their recent work on symptomatic vertebral hemangiomas [3] (ones of the most common spinal tumors) in pregnant females note that only 27 similar cases have been reported in the literature since 1948. Spinal cord tumors in pregnant females are even rarer. Our patient had an extremely rare pathology — an endodermal cyst.
An endodermal cyst is a cystic lesion resulting from endogenous dysgenesis; it is often combined with other developmental anomalies [4]. The endodermal cyst wall consists of columnar epithelium with cylindrical, cuboidal, or goblet cells that usually produce mucin. Inside, the endodermal cyst is lined with the ciliated epithelium. Depending on the location, there are intraspinal (intradural extramedullary) cysts, which are most common, and intracranial cysts that are usually located in the posterior cranial fossa, anteriorly to the brainstem. Intraspinal cysts often occur in the lower cervical and upper thoracic spine. The cysts typically have an intradural extramedullary (mainly anterior) location [5]. Endodermal cysts usually have an isointense
or hypointense signal on T1-weighted MR images and a hyperintense signal on T2-weighted MR images and are not contrast-enhanced. The lack of tracer uptake in the cyst wall distinguishes endodermal cysts from other cystic lesions, such as cystic schwannomas, cystic meningiomas, cystic ependymomas, and cysticercosis [6]. Differential diagnosis with arachnoid, epidermal, and dermoid cysts should be performed. Despite the benign nature, endodermal cysts can recur, therefore the main surgical treatment option is total cyst resection [5, 6].

The symptoms of spinal cord space-occupying lesions usually develop slowly and can be represented by pain as well as motor and sensation disorders [7]. An acute onset occurs extremely rare and usually is a consequence of concomitant spinal stroke, as it obviously occurred in the presented case. This is confirmed by the rapid development of a neurological deficit and the presence of hemorrhages in histological specimens. It is important that the rate of deterioration and the severity of clinical symptoms should be considered and profoundly influence the management of these patients.

Examination and, if necessary, surgical intervention should be performed as soon as possible, no later than the “golden” day, and preferably earlier [8—10]. In the presented case, surgery should be performed immediately, even at the place of residence, to provide at least decompression of the spinal cord. Transfer to the BNI and stabilization of the patient’s general condition took some time. The delay in surgery resulted in irreversible changes in the tissues of the spinal cord, as evidenced by the morphological picture of the fluid discharge released after dissection of the dura mater, represented by a necrotic tissue with hemorrhages.

In general, the management of pregnant females with spinal pathology, especially in cases of severe neurological symptoms, is extremely complex, and information on this topic is quite limited [11—14]. Usually, one or two clinical cases with almost full-term pregnancy or in the postpartum period are reported. In this regard, the most interesting is a paper by I. Han et al. [11], which summarizes the experience of managing 10 pregnant patients with different spinal pathologies at one clinic for 13 years, and an article by K. Vijay et al. [14], which describes 10 patients with vertebral hemangiomas. Summarizing the data provided by the authors of these two papers, we believe that two points are of crucial importance: 1) neurological status of the pregnant female and its dynamics and 2) gestational age of the fetus. In the case of life-threatening neurological symptoms, full-term or almost full-term pregnancy (32 weeks or more) almost uniquely necessitates the following approach: cesarean section and subsequent surgical treatment of the mother. In the case of life-threatening neurological

**Fig. 4.** Intraoperative ultrasound examination of the fetus.

**Fig. 5.** Postoperative T1- and T2-weighted MR images of the cervical spinal cord in the sagittal (a) and axial (b) projections; there is no residual cyst; the area of vasogenic edema and ischemia at the cervical level is decreased in size.
symptoms and early pregnancy, the authors of both works suggest abortion because of the risk of fetal exposure to X-rays and potentially fetotoxic drugs during diagnosis and surgery in the first trimester of pregnancy. We consider this recommendation as not quite reasonable, especially given the recommendations of the American Society of Radiologists, which contain the only limitations related to the use of gadolinium as an MRI tracer and a moderate risk of newborn hypothyroidism associated with the use of iodine-containing contrast agents [15].

Parturition in the case of incomplete pregnancy is an approach that always requires serious argumentation. A complication in premature newborns, such as intracranial hemorrhage, is a well-known phenomenon with the rate of occurrence, according to various authors [16], ranging from 35 to 90%. The cause for this high rate of the severe complication is now known: a highly vascularized embryonic matrix is a substrate of the developing brain. It is located in the subependymal space of the lateral ventricles and undergoes a reverse development at the 32—34th week of pregnancy. Capillaries of this embryonic matrix are immature and fragile and lack autoregulation mechanisms, which sets the ground for hemorrhage in the case of even a slight increase in cerebral blood flow [16]. In our opinion, the only solution in our situation was an attempt to preserve pregnancy by all means. Obviously, our colleagues had solid indications for operative delivery in the case of incomplete pregnancy. However, the consequences of prematurity in the form of typical complications affected the further fate of the baby.

**Conclusion**

The presented clinical case is a rare coincidence of unfavorable circumstances: the presence of an extramedullary space-occupying lesion in the patient, lesion-induced spinal stroke, and incomplete pregnancy. All these factors influenced the unsatisfactory outcome of the disease. An endodermal cyst is a rare cystic lesion of the intradural space, which we encountered for the first time in our practice. Spinal stroke caused by an anterior endodermal cyst at the cervical spinal cord level in a pregnant female had not been reported in the literature before, so we tried to present in detail this case and the features of microsurgery, anesthesia, and critical care. Regarding the management of the patient, we believe that the decision of surgery should have been made within the first 12 h after the disease onset. The outcome of later interventions is unfavorable in most cases, and the neurological deficit is irreversible. Treatment of patients with combined pathology requires participation of various specialists. In our case, the fetus condition was controlled by obstetrician-gynecologists. Unfortunately, prolongation of pregnancy up to 37—38 weeks was excluded in the presented situation. Was it possible to avoid this treatment outcome? In our view, under these circumstances, unfortunately not.

**There is no conflict of interest.**
The article describes a rare clinical case of intensive therapy and surgical treatment of a 24-year-old patient who was admitted to the Neurosurgical Institute at 20 weeks gestation with spinal stroke associated with a space-occupying lesion of the cervical spinal cord — an endodermal cyst.

Undoubtedly, the presented clinical case is of great practical importance and real interest. Pregnancy combined with spinal pathology is rarely encountered by the neurosurgeon and neurointensivist in their practical work and is always associated with considerable difficulties in choosing the treatment strategy and tactics. In the present case, the authors encountered a combination of unusual and, unfortunately, extremely unfavorable factors that occurred simultaneously in the patient. These factors included a very rapid development of the clinical and radiographic picture of the tumor in the form of spinal stroke, a rare histological type of the space-occupying lesion, and delayed radical surgery (because the patient had no neurological symptoms. Unfortunately, surgical care, at least decompression of the spinal canal, was not provided in the first hours after admission of the patient to a local hospital. Despite the fatal outcome of the disease for the mother and dubious prospects for the newborn, this clinical case demonstrates high skills of the authors and the coherence of their work.

A.O. Gushchya, A.A. Kashcheev (Moscow, Russia)
Extrapontine Myelinolysis Developed After Aneurysmal Subarachnoid Hemorrhage (a Case Report and Literature Review)


Polenov Russian Scientific Research Institute of Neurosurgery, the Branch of the Almazov Federal North-West Medical Research Centre, St. Petersburg, Russia

**Topicality.** Central pontine and extrapontine myelinolysis is a rare and dangerous form of the demyelinating process of unknown origin, the development of which is associated with abrupt changes in the serum sodium level (hypernatremia).

**Objective** — to describe a rare case of extrapontine myelinolysis complicating the hemorrhagic period of anterior communicating artery aneurysm rupture as well as to demonstrate the ability to intravitally diagnose this condition.

**Conclusions.** Clinical vigilance of extrapontine myelinolysis may promote the timely diagnosis and treatment of this disease that is a potential cause of death. Pulse-therapy with glucocorticoids alleviates neurological symptoms and stabilizes the patient's condition.

**Keywords:** hypernatremia, subarachnoid hemorrhage, extrapontine myelinolysis, glucocorticoids.

The paper is published to describe the development, diagnostic capabilities, and treatment of a rare life-threatening complication of subarachnoid hemorrhage.

**Clinical case**

A 58-year-old female patient was transferred to the Department of Cerebral Vascular Surgery of the Polenov Russian Scientific Research Institute of Neurosurgery (PRSRIN) from a city hospital on the 15th day after subarachnoid hemorrhage (SAH) from an anterior communicating artery (AComA) aneurysm. The patient was admitted with a WFNS grade 1 SAH. Neurological status: the patient had clear consciousness and cerebral symptoms with signs of intracranial hypertension and focal lesions of the frontal lobes. Spiral computed tomography (SCT) of the head revealed narrowing of the subarachnoid spaces in the right cerebral hemisphere. There was no hydrocepalus and deformity of the ventricles. The patient had a concomitant disease, rheumatoid polyarthritis, and constantly received 20 mg of methotrexate per week. Spiral computed tomographic angiography of the brain revealed a saccular aneurysm and diverticula of the AComA (Fig. 1).

The patient underwent urgent osteoplastic craniotomy and microsurgical clipping of the AComA aneurysm. In the postoperative period, there was no worsening of cerebral and focal symptoms. The patient received antibacterial, anti-edematous, and cerebroprotective therapy (medocef, nimotop, cytoflavin, mexidol). In a blood chemistry panel, the sodium level changed between 144—152 mmol/L; there were no other changes. On the 14th postoperative day, the patient’s condition sharply deteriorated: the consciousness level worsened to profound obtundation with development of spastic tetraparesis of up to 1 point. A CT examination revealed signs of right hemisphere edema with a brain displacement of 7 mm to the left. Magnetic resonance imaging (MRI) of the brain detected multiple areas of a hyperintense T2-weighted image (T2-WI) signal, having clear contours in the area of the corpora quadrigemina, both cerebral peduncles, and oral pons (Fig. 2). A blood chemistry panel revealed hypernatremia of up to 170 mmol/L as well as elevated AST (58.5 U/L) and ALT (103 U/L) levels.

The patient’s condition was assessed as the development of pontine and extrapontine myelinolysis. Pulse-therapy with glucocorticoids (solud-medrol for 3 days according to the schedule) provided a pronounced positive effect: recovery of the consciousness, partial restoration of limb movements (up to 4 points), and normalization of natremia. However, a week later (on day 28 of the postoperative period), negative changes again occurred in the patient’s condition: bulbar symptoms, tetraplegia, and locked-in syndrome. An EEG examination revealed gross diffuse changes clearly predominating in the diencephalic brainstem structures. A blood test again detected hypernatremia (172 mmol/L). A cerebrospinal fluid test demonstrated a significant increase in the myelin basic protein level (460 ng/mL, with the normal level being less than 1 ng/mL) as well as a sharp increase in the anti-myelin-associated glycoprotein level (4,850 U/mL, with the normal level being 1000 U/mL); the S100 protein and neuron-specific enolase levels were not significantly increased. Repeated pulse-therapy with glucocorticoids had no significant effect. The patient’s condition progressively worsened, multiple organ failure (bilateral pneumonia and renal, hepatic, and cardiovascular failure) deteriorated, which led to death of the patient.

Autopsy findings: the white matter of the brain was of a pale color, soft elastic in its texture, with bulging over...
the cut surface in the subcortical nuclei area and in the pons; the grey matter of the subcortical nuclei and thalami was of a heterogeneous color, with small yellowish foci (Fig. 3).

A histological examination of fragments of the subcortical nuclei, thalami, and white matter of the hemispheres as well as a cross-section of the pons, staining with hematoxylin and eosin, and Nissl (for detection of the Nissl substance in neurons) and Spielmeyer (for myelin) staining were performed. In all the examined fragments, diffuse foci of complete demyelination were detected; edema in the form of a spongy transformation of the white matter was present in the perifocal area of the foci (Fig. 4).

In the demyelination foci, there was destruction of the brain tissue, disintegration of neuropils, neuronal shrinkage, the presence of eosinophilic bodies, moderate gliosis with the microglial response, and swollen oligodendrocytes (Fig. 5).

Neurons in these foci had dystrophic changes: pericellular edema, moderate neuronophagia, foci of neuronal dropout, and granular disintegration of the Nissl substance (Fig. 6).

Therefore, the patient had diffuse microfocal demyelination in the white matter of the hemispheres and brainstem.

**Discussion**

Central pontine myelinolysis (CPM) was first described by R. Adams et al. [1] (1959) in a patient with chronic alcoholism, which was defined as osmotic demyelination syndrome. Later, CPM was detected in patients with diabetes mellitus, systemic lupus erythematosus, renal failure, pituitary adenoma, and cerebellar astrocytoma [2, 3]. The development of CPM after liver transplantation was reported. As it was demonstrated in an experimental model of CPM in rats, rapid administration of hypertonic saline (rapid hypernatremia) resulted in extracellular edema of the brain, provoking swelling of oligodendrocytes and destruction of the myelin sheath [4]. Damage to the myelin sheath can develop not only in the pons but also in other brain structures, both in combination with CPM and alone [5]. These disorders were called extrapontine myelinolysis (EPM); in this case, demyelination foci can occur in the brain peduncles, thalamus, corpus callosum, geniculate bodies, and other brain structures [5]. Pontine and extrapontine myelinolysis may be caused by other hyperosmolar states [6].

The pathogenesis of this rare demyelinating process has not been sufficiently studied. Currently, its development is believed to be associated with a sharp disturbance of the electrolyte (sodium) balance and blood osmolarity [3, 6].

The major regulator of electrolyte metabolism in the body is the hypothalamus. Studies of researchers guided by Prof. M.V. Ugryumov (neurohistological, neurohistochemical, and ultrastructural studies) at the PRSRIN proved involvement of the hypothalamus in the genesis of the degenerative-dystrophic process in the nervous system and internal organs [7, 8]. The development of the pathological process may involve decreased functional activity of the hypothalamic neurosecretory centers, which leads to deficiency of viscerotropic peptide neurohormones in the general circulation. The hormones maintain homeostasis, change permeability of biological membranes, and affect various aspects of metabolism, which, in turn, may cause gross disturbances of electrolyte metabolism (hypo- and hypernatremia).

The clinical picture of myelinolysis includes spastic tetraparesis, pseudobulbar palsy and mental disorders [9].
Cerebral palsy (CPM) and encephalomyelitis (EPM) are primarily diagnosed based on neuroimaging data. Myelinolysis appears as a high H2O content area on the X-ray film and can resemble infarction on the SCT scan. The method of differential diagnosis of myelinolysis is MRI. Brain lesion areas are characterized by a homogeneous high signal on T2-WI MR images and by a low signal, the absence of perifocal edema, and mass-effect signs on T1-WI MR images. A characteristic feature of this pathology is non-involvement of the pontine tegmentum and anterolateral pontine structures. The affected area can involve the midbrain, periventricular white matter, internal and external capsules, and corpora callosa. MRI findings of bilateral symmetric lesions of the thalami and basal nuclei in combination with brainstem lesions facilitate the correct clinical interpretation of myelinolysis [15].

A significant contribution to the differential diagnosis in the present case was made by the data of chemistry blood and cerebrospinal fluid panels that revealed elevated levels of the demyelination markers — the myelin basic protein (its level was increased hundreds-fold) and antimyelin-associated glycoprotein, with no increase in the S100 protein (a marker of damage and inflammation of the brain) and neuron-specific enolase (a marker of ischemia) levels. This indicates the demyelinating process in the brain, developing without signs of ischemia and inflammation.

In the literature, there are separate reports on the use of high doses of corticosteroid hormones [16] and plasmapheresis for the treatment of EPM [17—19].
use of pulse-therapy with glucocorticoids enabled us to slow down the process in the presented case as well as to achieve pronounced regression of the neurological symptoms. However, the intravital diagnosis of this rare complication did not help stop the development of severe neurodystrophic lesions of internal organs, which led to multiple organ failure that caused patient’s death.

**There is no conflict of interest.**

**REFERENCES**


Commentary

The article presents a case of surgical treatment of a patient during the subacute stage of subarachnoid hemorrhage from an anterior cerebral (communicating) artery aneurysm, which was complicated by the development of pontine and extrapontine myelinolysis in the late postoperative period, discusses this rare complication, and reviews the literature. The article describes the clinical course of the disease, data of CT and MRT examinations in the postoperative period, results of chemistry blood and cerebrospinal fluid panels for demyelination markers, and attention to the problem of pathogenesis of various disturbances and infusion therapy are also discussed. There is also no information about the presence and severity of angiospasm in the preoperative and, particularly, postoperative periods, which may also be a cause of diencephalic disorders, especially given postoperative edema of the right hemisphere and postoperative hyponatremia. It is not entirely clear what led to the patient’s death because it is not indicated on what day after surgery she died, and the cause of death is not cerebral and postoperative hypernatremia. It is not entirely clear what led to the patient’s death because it is not indicated on what day after surgery she died, and the cause of death is not cerebral and postoperative hyponatremia. There is no discussion of a relationship between the revealed changes and the patient’s autoimmune disease as well as long-term therapy with immunosuppressors. There are questions about quality of the morphological study and its description that does not provide an unambiguous confirmation of demyelination and may also indicate ischemia.

However, the article is of undoubted interest, drawing attention to the problem of pathogenesis of various complications in neurosurgical patients and their differential diagnosis. In this regard, of great interest are chemistry blood and cerebrospinal fluid panels for demyelination markers, which are rarely used in neurosurgical practice.

O.B. Belousova, I.A. Savin, O.A. Gadzhieva, L.V. Shishkina (Moscow, Russia)
Extradural Spinal Cord Hemangioblastoma (a Case Report and Literature Review)


Burdenko Neurosurgical Institute, Moscow, Russia

Hemangioblastoma is a rare CNS vascular tumor that develops sporadically and can also be associated with von Hippel—Lindau disease. Hemangioblastomas account for 2—6% of all spinal cord tumors and rank third in the structure of intramedullary space-occupying lesions of the spinal cord. For the first time in our practice, we observed a dumbbell paravertebral hemangioblastoma. The international literature reports only 3 cases of the tumor with this growth type.

Keywords: hemangioblastoma, von Hippel—Lindau disease, extradural dumbbell tumor.

Case report

Patient N., 56 years old, was admitted to the Burdenko Neurosurgical Institute on 03.09.14 with complaints of pain in the lumbosacral region irradiating to the left leg, as well as sensory disorders in the form of hypesthesia along the posterior surface of the left femur and tibia. The history showed that the patient suffered from back pain for a long time, pain gradually increased over time and became permanent. The patient repeatedly received drug therapy aimed at treatment of degenerative disc disease, which did not result in improvement. Since 2006, the pain intensified and occurred in the rest, sitting, and lying positions. In August 2013, the pain became very intense and conservative therapy still was ineffective.

In this regard, MRI of the lumbosacral spine was carried out, which revealed extradural mass lesion having paravertebral spread at L4 —L5 into the intervertebral foramen on the left. The mass was oval-shaped, sized 16x25x10 mm. Spinal angiography with contrasting of tumor’s own vascular network at the level of L4 vertebra was carried out (images are not shown). The patient was admitted to neurosurgical department at the place of residence for surgical treatment. The attempt of tumor resection was unsuccessful. Histological examination of resected fragment led to conclusion that it was ganglioneuroma.

Control MRI 12 months after surgery showed the same MR pattern as preoperative one (Fig. 1).

Resection of extradural paravertebral dumbbell tumor on the left at L4—L5 was carried out at the Burdenko Neurosurgical Institute on 11.09.14.

Operation

Patient’s position on the operating table: prone position under a combination anesthesia with endotracheal ventilation. Tumor level was localized using O-arm intraoperative CT tomograph, images were taken in the lateral and frontal planes in 2D-mode.

Paramedian skin incision was performed a few centimeters to the left from the scar resulting from the previous surgery. Caspar surgical microscope and retractor system were used to approach the tumors. The use of this expander minimized trauma to surrounding tissues. Hemilaminectomy on the left at the level of L4 vertebral arch was carried out using microsurgical instruments and Zimmer high-speed bur. Orange elongated tumor sized 3x2 cm was observed. The tumor was located in the L4—L5 intervertebral foramen and was shaped similar to neurinoma. Extradural portion of the L4 root on the left was determined to be the growth origin. Major arterial vessel supplying the tumor was detected during tumor separation along its perimeter. It was coagulated and transected. Proximal part of the tumor and root were ligated and then the tumor and nerve root were coagulated and removed en bloc. Hemostatic material was placed to the bed of resected tumor (Fig. 2). The wound was closed using the standard scheme.

In the postoperative period, pain regression was observed. The patient was aroused on day 1 after the operation. After 7 days, the patient was discharged home in satisfactory condition. Histological diagnosis: hemangioblastoma. Follow-up MRI study was carried out 3 months after the operation (Fig. 3).

The histological characteristics of the tumor

Histological examination (Fig. 4) confirmed the microscopic diagnosis of hemangioblastoma. Tumor consisted of two types of cells: stromal cells with optically empty cytoplasm and a large number of vascular cells. The tumor was surrounded by a thin layer of fibrous tissue closely bordered by nervous tissue fragments and clusters of ganglion cells (Fig. 5).

During the study, adjacent nerve stem was discovered (Fig. 6); the same finding was reported by R. Pluta et al. [2].

Comparative analysis of the results of surgical treatment of hemangioblastomas

Spinal hemangioblastomas belong to the group of highly vascularized tumors, which are often characterized by intramedullary localization. Hemangioblastoma
CASE REPORTS

account for 2—6% of all spinal cord neoplasms and rank third in the structure of intramedullary space-occupying lesions of the spinal cord [1]. In our case, the tumor was paravertebral, dumbbell-shaped, and was not connected to the dura mater. In the international literature [2—4], we found three case reports describing patients with similar localization of a space-occupying mass. The Table shows some information about these patients, in particular, clinical status and results of surgical treatment (cases 1—3) and compares these data to the case described in our study (case 4).

When evaluating data shown in the Table, it is clear that there were certain differences in the clinical presentation of the disease. Thus, case 3 was characterized by acute onset of the disease, where strong pain evolved within 2 weeks, followed by admission of the patient to neurosurgical hospital. In two other cases, (cases 1 and 2), as well as in our patient (case 4), there was a 2—20 years-long history. The tumor mainly manifested in the form of radiculopathy characterized by pain in the lumbosacral spine radiating to the leg, and also radicular sensory disorders. Dysfunction of pelvic organs (urinary incontinence) was observed in the case 3, possibly due to compression of the roots of “cauda equina”.

The Table shows that preoperative clinical and X-ray examination suggested correct histological diagnosis

---

**Fig. 1. Hemangioblastoma of L4 root.**

The series of T2-weighed MRI scans in the sagittal, frontal and axial projections (a, b, c) shows extradural hypointense space-occupying mass at L4—L5 vertebrae characterized by hyperintense foci and dumbbell-shaped paravertebral growth to the left (the tumor is shown by white arrows). The sagittal and frontal views (a, b) show pronounced vasculature (indicated by red arrows), which corresponds to multiple areas of hypointense signal in T2-weighed mode.

---

**Fig. 2. Operation stages.**

a, b — exposure and mobilization of the solid part of the tumor; c — ligation of the neck of the tumor of the L4 root; d — tumor resection along with the root. 1 — solid portion, 2 — L4 root, 3 — gaine radiculaire, 4 — tumor bed.
only in one case (case 1) owing to the fact that this patient with von Hippel—Lindau disease was diagnosed with multiple CNS hemangioblastoma. In 2 cases (cases 2 and 3) preoperative MRI study led to a presumable diagnosis of radicular neurogenic tumor, neuroma (schwannoma). In our case (case 4), the tumor was considered as paravertebral ganglioneuroma of the L4 root, corresponding histological diagnosis was made after the first operation at the place of residence.

Our analysis of X-ray data led to the following conclusions. Firstly, the studies should be contrast-enhanced. Second, detection of pathologically dilated tortuous vessels within the spinal canal around the neoplasm is a pathognomonic sign of hemangioblastoma. The vessels are best visualized in T2-weighted mode. Thirdly, the solid component of the tumor has hypo-intensive or iso-intensive T1-weighed MR signal, and cystic cavities have T1- and T2-weighed signal similar to that of the CSF or brighter T2-weighed signal. At least one of the above MRI features suggests a vascular tumor, and in this connection selective angiography can be recommended [4, 5].

When evaluating the outcomes of surgical treatment, we should note that tumors were completely resected in all four cases (see Table). This was accompanied by regression of pain syndrome. Possible occurrence of minor neurological deficit should be considered as an inevitable consequence of the operation rather than a complication, since the tumor is most often removed together with the root, where it originates from.
CASE REPORTS

!!! Обзор публикаций о хирургическом лечении корешковых гемангиобластом спинного мозга

<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>Case No</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Anamnesis mo, months</th>
<th>Location</th>
<th>HL (Von Hippel–Lindau)</th>
<th>Presumable preoperative diagnosis</th>
<th>AG with embolization</th>
<th>Clinical presentation</th>
<th>History, months</th>
<th>Treatment outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryszard M. Pluta, 2003</td>
<td>1</td>
<td>F</td>
<td>38</td>
<td>120</td>
<td>EL S1-S2 left</td>
<td>+</td>
<td>Hemangioblastoma</td>
<td>+</td>
<td>RPS at S1—S2, SD</td>
<td>12</td>
<td>Regression RPS</td>
</tr>
<tr>
<td>Masaaki chazo NO, 1999</td>
<td>2</td>
<td>F</td>
<td>48</td>
<td>24</td>
<td>EL-DS L5 left</td>
<td>—</td>
<td>Neurogenous tumor (Neurofibroma, schwannoma)</td>
<td>—</td>
<td>MD, SD</td>
<td>12</td>
<td>Regression MD</td>
</tr>
<tr>
<td>María Román-de Aragón, 2014</td>
<td>3</td>
<td>M</td>
<td>48</td>
<td>1</td>
<td>EL-DS L4 right</td>
<td>—</td>
<td>Neurinoma</td>
<td>+</td>
<td>PS, RPS, SD, DPO</td>
<td>36</td>
<td>Regression PS, RPS, SD, DPO</td>
</tr>
<tr>
<td>N.A. Konovalov, 2016</td>
<td>4</td>
<td>F</td>
<td>56</td>
<td>240</td>
<td>EL-DS L4 left</td>
<td>—</td>
<td>Paragangioma</td>
<td>—</td>
<td>PS, RPS</td>
<td>3</td>
<td>Regression PS, RPS</td>
</tr>
</tbody>
</table>

Footnotes. EL — extradural location, DS — dumbbell-shaped tumor, PS — pain syndrome, RPS — radicular pain syndrome, SD — sensory disorders, MD — motor disorders, DPO — dysfunction of pelvic organs.

Discussion

Extradural hemangioblastomas are a fairly rare pathology and there are no standards for their resection. Since the aforementioned case was the first case of extradural hemangioblastoma in our practice, we applied microsurgical resection technique similar to that used for resection of dumbbell tumors. Unfortunately, we did not embolized the vessel supplying the tumor, which resulted in bleeding from that vessel, the radicular artery, during separation of the paravertebral portion of the tumor, going beyond the intervertebral foramen. The bleeding was successfully stopped using bipolar coagulation.

As the second stage, we exposed tumor poles, while maintaining the dilated tumor draining veins, since we believe that it is a string requirement. Hemangioblastomas are well encapsulated and can be easily separated from the surrounding tissue. Manipulations inside the tumor capsule are dangerous since pronounced bleeding is possible, which is usually difficult to control and can completely obscure the entire field of view. Next, we exposed the part of the tumor adjacent to the dura; the root entering the tumor was ligated to prevent liquorrea from the gaine radiculaire. In our case, hemangioblastoma could not be separated from the root because they were adhered to each other. Therefore, hemangioblastoma has been removed together with the L4 root. Despite the transection of the root, no negative symptoms in the form of increasing muscle weakness were observed in patient’s left foot in the postoperative period. Tumor resection resulted in formation of a deep bed. We carefully examined the bed and suppressed hemorrhage from small blood vessels. In this situation, hemostasis should be carried out with hemostatic material without the use of bipolar coagulation.

Conclusions

Extradural hemangioblastoma is a very rare disease. However, in the cases, where MRI signs of a vascular tumor are detected, further examination in required, which may include CT perfusion study, as well as selective angiography, when necessary. In the case of hemangioblastoma with clearly differentiated supplying vessels, embolization is advisable to reduce the risk of intraoperative hemorrhage.

In our view, resection technique for extradural hemangioblastomas is similar to operations carried out for other tumors characterized by mostly paravertebral dumbbell growth.

There is no conflict of interest.
REFERENCES


Hemangioblastoma is a highly vascularized benign tumor, consisting of clustered thin-walled vessels of various calibers, whose interstitial cells contain lipid-rich cytoplasm. In most cases, spinal hemangioblastomas are intramedullary and account for 2 to 8% of all intramedullary neoplasms, being exceeded in incidence only by ependymomas and astrocytomas. Spinal hemangioblastoma account for up to 20% of all CNS hemangioblastomas. In rare cases, these tumors can be extramedullary, and, in exceptional cases, even extradural. Despite the preferential location of the tumor within the central nervous system, no histological relationship between this tumor and glial tissue was found. This explains the fact that the disease occurs not only in the boundary zone between the central and peripheral part of the nervous system (intradural extramedullary hemangioblastomas are usually connected with the dorsal surface of the spinal cord or intradural portion of the posterior root), but also in the distant areas. The literature describes hemangioblastomas of radial and sciatic nerves.

Cases of extramedullary tumors are extremely rare, which complicates the choice of correct diagnosis and surgical treatment of this pathology.

In the present article, the authors describe the clinical presentation, diagnostic algorithm, and preoperative preparation of patients with extradural hemangioblastomas, taking into account available literature. Special attention is paid to the surgical techniques of tumor node resection.

The article is of great interest to a wide range of neurosurgeons.

G. Yu. Evzikov (Moscow, Russia)
Infant Form of Alexander Disease (Clinical Case and Literature Review)

R.A. VASIN, M.A. KRASNIKOV, S.V. VASINA

Regional Children’s Hospital, Lipetsk, Russia

We present a case of the infant form of Alexander disease. The case is unique because the patient’s examination was started at the preclinical stage and continued during the manifestation and fastigium of the disease. We present rare images obtained during neurosonography at the preclinical stage of the disease as well as the unique findings of MRI studies. The MRI findings at disease onset and 3 years later indicate that the infant form of Alexander disease is characterized by clinical stages.

Keywords: Alexander disease, leukodystrophy, hydrocephalus.

Alexander’s disease is a rare hereditary disease, characterized by progressive degeneration of white matter of the brain. The disease is caused by mutation in a gene, which encodes GFAP (glial fibrillar acidic protein) protein. Russo et al. (1976) distinguish three forms of the disease based on the time of its manifestation: infant form, which manifests at the age from 0 to 2 years, adolescent form, from 2 to 12 years, and adult form, after 12 years of age [1]. Some authors [2—4] also describe neonatal form. The infant form accounts for 63 to 80% of all cases [3, 5, 6].

Recently, another classification scheme has been gaining traction which is based on the localization of the lesion and clinical presentation. Prust et al. (2011) identify types I and II of the disease. Type I includes early forms with predominantly frontal leukodystrophy, while type II includes mainly cerebellar lesions and lesions of stem structures. The median survival for type I is 14 years, for type II, 25 years [1]. It is believed that the earlier the disease manifests, the more malignant is its course. This is especially true of the neonatal form [2, 3]. At the same time, some experts note unpredictable course of the disease at any age and do not consider age-based classification to be relevant [2].

S. Marjo van der Knaap et al. [7] offer five MRI criteria for establishing the diagnosis of Alexander's disease:
- extensive changes in the white matter of the cerebral hemispheres, mainly in the frontal lobes;
- periventricular rim with high intensity T1 signal and low level of T2 signal;
- changes in basal ganglia and thalamus;
- damage to the brainstem;
- increase the contrast of gray and white matter.

Four of the five criteria are sufficient for the diagnosis [7]. Some patients develop hydrocephalus due to compression of the Sylvian aqueduct; therefore these patients require neurosurgical intervention [1—3, 8].

Clinical observation
We present the clinical case of the girl T., who first came to the attention of neurologists and neurosurgeons at the age of 2 months.

The child was from the first pregnancy, with urgent delivery at 42 weeks, which proceeded on its own, without complications. Body weight at birth, 3310 g, height, 53 cm. No anomalies were observed before the age of 2 months, the child grew and developed normally. At the age of 2 months, preventive neurosonography (NSG) was prescribed. At the time of the examination, the mother had no complaints, noting only minor episodes of the child's anxiety.

The results of the NSG are shown in Fig. 1. Frontal standard projection. The arrows indicate cloudy hyperechoic zones in the periventricular sections of the anterior horns of the lateral ventricles. The ventricular system is not enlarged. There is a narrowing of the anterior horns of the lateral ventricles at the point of contrast with areas of increased echogenicity due to mass effect of pathological foci.

Given the unusual nature of the NSG findings, were in-hospital examination to clarify the diagnosis was proposed to the parents. On June 28, 2011 the baby was admitted to the nursing department. The NSG data were regarded as possible ischemic lesion of the natal period or expansive process. The child’s state drastically deteriorated in the hospital: she lost ability to hold her head, there were choreoid movements in the facial musculature and athetoid movements in the distal parts of the limbs, she suffered from expressed anxiety attacks. On July 07, 2011 magnetic resonance imaging (MRI) of the brain without contrast and with contrast enhancement by Magnevist was performed. The results are shown in Fig. 2 and 3.

In general, focal changes identified by MRI coincided with those identified by NSG. A focus in the quadrigeminal plate area is clearly visible. The beginning of
Ventriculomegaly can already be clearly seen from these pictures. The mass effect of pathological foci on the anterior horns of the lateral ventricles is observed and its lumen is practically invisible.

From July 26, 2011, there was further worsening of the condition in the form of increase in anxiety, vomiting, and fits of “fading”. According to the NSG, there is a progressive expansion of the ventricular system. On July 27, 2011, ventriculoperitoneostomy was performed. The surgery had certain features dictated by the disease: due to the narrowing of the anterior horns of the lateral ventricles, caused by mass effect of the pathological foci, it was decided to perform ventriculostomy not from the Kocher point but through the horn (Dandy point) by moving a catheter beyond the vascular plexus using ultrasound control. Improvement was noted in the postoperative period. General cerebral symptoms regressed, hyperkinesis decreased. Genetic analysis (genetic laboratory of the Russian Children’s Clinical Hospital, Moscow) revealed a mutation.

Fig. 1. Patient T. NSG at the age of 2 months.

Fig. 2. Patient T., age 2.5 months. MRI of the head without contrast enhancement in T1 and T2-modes. The primary lesion of the white matter of the frontal lobes with the involvement of the subcortical ganglia is visible. There is a moderate expansion of the lateral ventricles.
c1117C>a(pClu373Lys) in the gene GFAP (Alexander’s disease), which is described in the mutation database (cm023075) in the heterozygous state.

Later the child was observed by a neurologist and received anticonvulsant therapy. A repeated in-depth examination was conducted at the age of 3 years. The general condition of the child was regarded as satisfactory. There was marked delay in psychomotor development. The child experienced epileptic seizures 1—2 times a week in the form of a short-term “fading”. At the time of the examination the child was sane, had speech at the level of babbling, reacted to the examination positively, could ‘fixate’ the eyesight, was interested in toys, took them in hands and examined them for long time, sat without support, did not walk. Exotropia. Choreoid-like movements in the extremities. Pronounced muscular hypotension.

Discussion

This case is interesting in several aspects. Since the first description of the disease back in 1949 and until 2011, there were less than 100 described cases, and only ca. 50 of them were described with the use of modern neuroimaging. In 2011, S.V. Serkov et al. [8] described two cases of juvenile form of the disease for the first time in Russia. Our case, perhaps, is the third case identified in the Russian Federation.

We had a rare opportunity to obtain neuroimaging of Alexander disease using NSG at the preclinical stage. It should be noted that such NSG findings are difficult to interpret, but they can point the clinician in the right...

Fig. 3. Patient T., age 2.5 months. MRI of the head with contrast enhancement. Symmetrical accumulation of contrast in the frontal lobes, visual cusps and quadrigeminal plate.

MRI without contrast and with contrast enhancement was performed. The results are shown in Fig. 4.
Fig. 4. Patient T., age 3 years 2 months. MRI of the head. The condition after ventriculo-peritoneal bypass (VPS).

a — MRI without contrast. The affected zones retain the former localization, but are less extensive. There are no indications of mass effect of pathological foci. The luminaire of the anterior horns is visible together with the cavity of the transparent septum; b — MRI of the brain with contrast. There are not foci of contrast accumulation.
direction. Localization of foci in the frontal lobes with spreading into the visual cups and their mass effect is probably pathognomonic for Alexander’s disease. We have not found similar neurosonographic findings in the literature.

The second important observation is the data obtained with MRI with contrast enhancement. The nature of the accumulation of contrast and the period of the disease in which this accumulation occurs are important. Intense accumulation of the contrast was recorded in the lesions at the onset of clinical symptoms. In addition to the intensity of contrast accumulation, the symmetry of the foci is also notable. Another feature is the lack of accumulation 3 years after the manifestation of the disease during the stabilization period. It can be assumed that the accumulation of contrast in the leukodystrophy foci is typical for onset and height of the disease, and that the period of remission can be characterized by the absence of such accumulation. In case of juvenile form of the disease described by S.V. Serkov et al. [8], the intensity of contrast accumulation was constant. The change in contrast accumulation observed in our case has not been described in the literature and may be characteristic of the infant form of the disease.

During the manifestation of the disease, MRI presentation fully complied with the criteria proposed by Marjo S. van der Knaap et al. [7], however, during the stabilization of clinical symptoms, no more than 3 out of the 5 described criteria were present.

The third important fact concerns the course of the infant form of the disease. The disease can last from several months to 8 years. The average duration of the disease is 2—3 years [8]. Our case demonstrates long period of stabilization. It can be assumed that timely shunt surgery in other cases can contribute to the stabilization of the patient’s condition and the prolongation of his or her life.

Analysis of the described observations allows proposal that there are distinct stages of the infant form of Alexander’s disease.

**Conclusions**

Focal changes detected in neurosonography in the form of hyperechoic cloud-like foci that spread from the periventricular sections of the anterior horn of the lateral ventricles to the basal ganglia can be specific for the infant form of Alexander’s disease. Leukodystrophy foci in the period of onset and height of the disease present as mass process. Leukodystrophy foci identified during MRI examination can intensively accumulate contrast during the onset of the disease, and, on the contrary, do not accumulate contrast during the period of the absence of clinical manifestations, which may indicate the presence of at least two distinct stages of the disease.

The infant form of the disease does not always lead to a fatal outcome. At the same time, the severity of white matter lesions inevitably leads to disability of the patient. A timely shunt surgery is likely to prolong the life of these patients.

**There is no conflict of interest.**
REFERENCES


Commentary

The work is devoted to a rare genetic disease. The observations are unique due to good neuroimaging of various stages of the development of the disease and rare data of neurosonography with the observed pathology. The literature review cited by the authors in the discussion is also interesting. Undoubtedly, the work is worthy of publication in the neurosurgical journal, as it broadens the horizons of neurosurgeons in terms of differential diagnosis. In addition, as the authors have shown, the presented disease sometimes requires neurosurgical interventions to alleviate the patient’s condition.

Yu.V. Kushel (Moscow, Russia)
Use of Surgical Approaches to the Posterior Cranial Fossa in Patients in a Lying Position

V.N. SHIMANSKIY1, V.V. KARNAUKHOV1, S.V. TANYASHIN1, V.K. POSHATAEV1,2, K.V. SHEVCHENKO1, D.A. ODAMANOV1, S.V. KONDRAHKOV2

1Burdenko Neurosurgical Institute, Moscow, Russia; 2Clinical Hospital №1 (Volynskaya) of the Presidential Administration of the Russian Federation, Moscow, Russia

Background. Various suboccipital approaches are extensively used in modern neurosurgery for treatment of posterior cranial fossa disorders. The main patient’s positions on the operating table during surgery are the half-sitting and lying ones.

Material and Methods. The article provides a detailed description and the methodology of the suboccipital retrosigmoid and median suboccipital approaches in the lying position.

Conclusion. The suboccipital retrosigmoid and median suboccipital approaches in the lying position, when used correctly, provide a good view of the operating field with the minimal risk of complications associated with the patient’s position on the operating table.

Keywords: suboccipital retrosigmoid approach, median suboccipital approach, posterior cranial fossa tumors, skull base surgery, skull base tumors.

Materials and Methods

More than 450 surgeries for PCF pathologies are performed annually at the Department of Peri-brainstem Tumors (Burdenko Neurosurgical Institute). The main approaches used are the suboccipital retrosigmoid and the median suboccipital approaches.
This ensures the required position of the body axis by compensating for spine rotation around its axis as a roll is placed. A foam pad is placed between the legs to prevent soft tissue atrophy. The arm is placed on the patient’s chest ipsilaterally to the approach side. The surgeon and surgeon’s assistant perform head fixation using the Mayfield skull clamp: while one of them holds the patient’s head raised, the other one places the pins. Pin positioning is performed as follows: a single pin is ipsilaterally placed onto the frontal protuberance, while the paired ones are contralaterally positioned into the superior temporal line and the occipital bone above the asterion (see Fig. 1a, b). The pins are tightly secured in the outer table of skull; one should avoid placing the pins above thin regions of calvarial bones (above the frontal sinuses, mastoid air cells, and along the anterior margin of the temporal muscle). Pin position must provide an unencumbered view of the operative field and leave a possibility for bone skeletonization to a required extent.

The surgeon then rotates the patient’s head secured with the Mayfield–Kees skull clamp 30 degrees towards the side contralateral to the pathological process and maximally bends it forward, leaving no less than the thickness of two transverse fingers between the patient’s chin and chest. One needs to make sure that the sagittal suture is parallel to the floor (see Fig. 1a, b). This position of the head ensures the best view of the structures of the cerebellopontine angle. When rotating or bending the head, it is also important to maintain the longitudinal body axis (the line running through the external occipital protuberance and the apices of spinous processes of cervical vertebrae must be straight). Allowance should be made for the risk of compression of jugular veins associated with excessive head flexion, which is particularly topical in hypersthenic overweight patients having a short thick neck.

**Description of the surgical approach.** The SRSA is performed in the cervico-occipital region below the superior nuchal line. Blood is supplied to this region from the occipital and posterior auricular arteries. Blood outflows from the soft tissues of the occipital region via the veins accompanying the aforementioned arteries and draining into the external jugular vein. Soft tissues of the occipital region are innervated by the greater occipital nerve accompanying the occipital artery [1].

The mastoid notch and the line of transition of the occipital squama into the horizontal part are the landmarks for incision of the soft tissues. In SRSA, skin incision is often made parallel to the auricular concha, 1.5–2.5 cm posterior to the mastoid notch (see Fig. 1d). The upper one-third of the skin incision is made above the transverse sinus projection line. The border between the middle and the lower one-thirds of the incision runs at the level of the mastoid notch (see Fig. 1d).

Once skin and subcutaneous fat were dissected, muscles are transected at a point where they are attached to the superior nuchal line and the occipital plane. It is reasonable to perform the musclectomy stage using

---

*Fig. 1. Suboccipital retrosigmoid approach in the supine position with a roller placed under the ipsilateral shoulder.*

a, b — positions of rigid fixation pins. The sagittal sinus is parallel to the operating room floor: 1 — the coronal suture; 2 — the sagittal suture; c — lateral view of the positions of the patient and the rigid fixation system. Landmarks for skin incision (d): 1 — mastoid notch, 2 — incision running parallel to the auricular concha.
monopolar coagulation, which allows one to significantly reduce capillary hemorrhage. The portion of the occipital bone, from the mastoid process to the median line in a medial direction (tentatively until the anticipated midpoint of the cerebellar hemisphere is reached) and from the superior nuchal line down to the foramen magnum, needs to be skeletonized.

When dissecting the soft tissues, one should not forget about the occipital artery whose injury causes profound bleeding. It is reasonable to begin with identifying the occipital artery in the soft tissues and to transect it only after precoagulation. Skeletonization of the occipital squama is typically accompanied by opening the emissaria located lateral and superior to the mastoid notch and, in the inferior regions, in the foramen magnum area. The opened emissaria need to be sealed with wax.

Asterion, the point where the lambdoid, the occipitomastoid, and the parietomastoid sutures meet, is a landmark for making the burr hole. Transition between the sigmoid sinus and the transverse sinus is located in the projection of this point (Fig. 2a). The asterion most typically lies 3—4 cm above the mastoid notch. The burr hole is made 5 mm below the asterion. After dura mater is separated from the bone around the burr hole, osteoplastic trepanation is performed using a pneumatic trephine (see Fig. 2b). In some cases, when there is significant coherence between the dura mater and the bone (which is often observed in patients older than 60 years), resection trepanation using bone-cutting forceps followed by closing the bone defect with a graft is performed.

Special care is needed when cutting the bone above or near the transverse and sigmoid sinuses, since injury to these structures causes profound venous bleeding. The injured sinus should be sealed with a hemostatic sponge or the TachoComb material by placing them on the surface of the injured sinus wall. By no way should the hemostatic agents be placed into the cavity of an opened sinus, since this may result in sinus thrombosis and severe neurological deficit or even death.

In order to prevent injury to venous sinuses, the bone should be cut 5 mm away from the tentative inferior border of the transverse sinus and 5 mm medial to the sigmoid sinus. The craniotomy is usually followed by additional lateral resection of the bone to expose the margin of the sigmoid sinus. Mastoid air cells often become opened as a result of additional resection of the lateral margin of the trepanation window. The disruption of their continuity may cause nasal liquorrhea during the postoperative period, which, in its turn, is associated with the risk of meningitis. Therefore, they need to be sealed with autotissue at the final stage of surgery. Adipose tissue harvested from the patient’s hip or fragments of muscle tissue from the surgical wound on the neck can be used for this purpose. TachoComb material or fibrin sealant can be additionally used.

Most often, a trepanation window up to 4 cm in diameter is sufficient for managing cerebellopontine angle tumors. The borders of the trepanation window correspond to the following structures: the upper border, to the inferior margin of the transverse sinus; the lower border, to the line of transition from the vertical portion of the occipital bone to its horizontal portion; the lateral border, to the medial margin of the sigmoid sinus; and the medial border, to the midline of the cerebellar hemisphere [1]. Craniotomy size varies depending on the type of the pathological process;
however, visualization of the site of transition of the sigmoid sinus to the transverse sinus is a prerequisite.

*Lateral positioning on the operating table.* The key indication for this positioning is the hyperstenic body habitus of a patient, namely, the short neck and broad shoulders.

After the patient had been intubated, a surgeon and surgeon's assistant roll him/her laterally onto one side contralateral to the surgery side; the anesthetist is simultaneously controlling the head position. Patient's arms are secured using specialized holders (Fig. 3b, c); the ipsilateral leg is bent at knee and hip joints to an angle of 30° and rotated inward. The surgeon's assistant places a support under the lumbar region. Soft pads are placed between the patient's legs and underarms to prevent soft tissue atrophy. Maximum head flexion is achieved similar to the position described previously; the distance between the chest and chin is supposed to be equal to at least two thicknesses of fingers in the transverse direction. The head is then secured by the surgeon using a Mayfield skull clamp (see Fig. 3a).

If needed, patient's shoulders can be stabilized using adhesive tape (Fig. 4b). One should not forget about the risk of stretch injury to the brachial plexus.

One should also bear in mind that the sagittal suture must be parallel to the floor (see Fig. 3a). This head position ensures the optimal approach angle for manipulations within the cerebellopontine angle during surgical intervention.

**Description of the surgical approach.**

The landmarks for incision and the principles of performing craniotomy are similar to those used for supine positioning (see Fig. 2).

The median suboccipital approach. The key indications for using the median suboccipital approach are as follows:

— PCF neoplasms of median and craniovertebral localization, including tumors of the fourth ventricle and the brainstem;

— decompression of the craniovertebral junction in patients with Chiari malformation and acute circulatory failure in the brainstem; and

— vascular disorders of the vertebrobasilar basin.

Different positions on the operating table are used to perform the median suboccipital approach in lying patients: the prone and the three-quarter prone positions.

First, let us discuss the prone position, patient's position on the operating table that is used most frequently when performing this surgical approach.

Patient's position on the operating table. The patient is intubated and anesthetized while lying on a patient transport cart. Next, the surgeon and the surgeon's assistant rotate the patient into the prone position onto the operating table (the anesthetist is simultaneously controlling the head position).

The patient's posterior head is flexed, and the patient is usually placed by rolling onto a specialized foam frame, with its position controlled by a nurse anesthetist (see Fig. 4a). The foam frame ensures proper chest excursion during mechanical ventilation (see Fig. 4a, 1). Additional corrugated foam rollers or underpads are placed under the sites where the patient's body and limbs may be subjected to positional compression (see Fig. 4a, 2). An additional roller can be placed under patient's chest to ensure physiologically adjusted neck flexion. The head is then secured with a Mayfield skull clamp, with the longitudinal body axis strictly maintained. The skull clamp pins need to be positioned in such a manner as to ensure unencumbered view of the operating field and leave a possibility for skeletonizing the occipital bone to a required extent.

There are two modifications of the median suboccipital approach: the inferior and the superior median approaches (see Fig. 4c, d). The key difference is that both transverse sinuses and the confluence of sinuses are exposed when the superior median approach is performed (see Fig. 4d). The foramen magnum and the arch of the C1 vertebra are not affected by craniotomy performed through this modification of the approach. In the case of the inferior median approach, the upper border of trepanation runs along the inferior margin of both transverse sinuses and the confluence of sinuses until the foramen magnum, and is accompanied by laminotomy of the posterior semi-ring of C1 vertebra if necessary (see Fig. 4c).

The inferior median suboccipital approach is used most frequently.

Description of the surgical approach. Skin incision is made along the median line. It provides a minimally invasive access to the target PCF structures.

The upper border of the incision lies 1—2 cm above the external occipital protuberance (the inion); the lower border lies in the projected point of the spinous process of C3 vertebra (Fig. 5, a).

First, an incision of skin and subcutaneous fat is made. A wound retractor device is placed, with its handle facing upward. Dissection must be conducted along the cervical white line in the avascular zone. The occipital arteries and greater occipital nerves remain intact.

Once the soft tissues were prepared, the occipital bone squama, the posterior arch of C1 vertebra, and the spinous process of C2 vertebra are skeletonized. Deep cervical and occipital muscles are separated from the nuchal line using monopolar coagulation or a bone scraper and moved downward and sideways.

Venous bleeding from the hypertrophied emissaria may take place as the occipital bone squama is skeletonized. In this case, they need to be closed with bone wax. When skeletonizing the posterior semi-ring of C1 vertebra, one should keep in mind the close proximity of vertebral arteries that run in the posterior portion of the occipital membrane. Bleeding from the venous plexuses of vertebral arteries is stopped using hemostatic sponge.

Two burr holes are made below the inion, on both sides from the external occipital crest (see Fig. 4c). “Pear-shaped” craniotomy is then performed with a craniotome...
(see Fig. 4c). If needed, the trepanation window can be made wider: sideways to the maximum extent allowed by the operating field and to the required extent, and downward until the foramen magnum is reached. Sometimes craniotome cannot pass through thickening in the occipital bone near the margin of the foramen magnum. This bone portion can be ground with a burr or continue trepanation downwards and sideways using bone-cutting forceps. This approach can be either combined with laminotomy of the posterior semi-ring of C1 vertebra (see Fig. 5b) or performed individually. Indications for laminotomy of the arch of C1 vertebra are determined by pathology location, the degree of descent of the cerebellar tonsils and, therefore, by the need to decompress the craniovertebral junction and CPF structures. If decompression of the craniovertebral junction is not required, the posterior semi-ring of C1 vertebra is returned to its original place and tightly secured with silk sutures. The borders of laminotomy of the C1 cervical vertebra lie no further than 1.5 cm sideways from the median line; i.e., its full absolute size is no more than 3 mm (see Fig. 5b) due to the close proximity of vertebral arteries and the risk of damaging them upon bone manipulation.

When performing the median suboccipital surgical approach to a patient in the three-quarter prone position, he/she is rolled sideways into the lateral position; the patient’s body is inclined by approximately 45 degrees. Supports preventing trunk shifting with respect to the operating table are placed at the level of the chest and lumbar area. Patient’s arms are secured with special supports; the ipsilateral leg is bent at knee and hip joints to an angle of 30° and rotated inward. Soft pads are placed between the legs and in the underarm area to prevent the development of soft tissue atrophy. The head is bent to a maximum possible extent and then secured using a Mayfield skull clamp (see Fig. 4b). Taking into account the manipulation angle required to access the anatomical structures of the fourth ventricular area and the craniovertebral junction, no additional rotation of the patient’s head is required (see Fig. 4b).

Discussion

When choosing patient’s position on the operating table and performing the suboccipital approaches, a number of questions may arise pertaining to the risks for a patient, which are related only to his/her position rather than to the existing neurosurgical pathology. Having evaluated the experience of performing suboccipital approaches to the patient in the lying and semi-sitting positions that has been gained over the many years, we have arrived at conclusion that performing these approaches to the patient in the lying position is the most safe procedure, since it allows one to avoid such life-threatening complication as air embolism. An analysis of 200 vascular decompression procedures performed in patients in different positions demonstrates that the semi-
sitting position increases the risk of air embolism 25-fold [9]. Nevertheless, it is reasonable to use the suboccipital approaches in some patients in the semi-sitting position using intraoperative transesophageal Doppler to control possible development of air embolism. This category includes obese patients (in whom the lying position blocks chest excursion), patients with giant-size tumors and cervical osteochondrosis that prevents adequate head rotation and/or flexion.

The use of the "lying" position makes it necessary to accurately follow the landmarks when making a skin incision and osteoplastic trepanation, since a deviation from the trepanation performing standards narrow the operating field and make the main surgical stage infeasible. In its turn, this fact discredits the idea of using the lying position that is safe if performed properly. Hence, when using the suboccipital retrosigmoid approach, proper mapping of the operating field ensures patient's safety.

The methods for sealing sinuses if damaged during a surgery are often of concern. If a sinus was injured in the "semi-sitting position", one should prevent the contact between the sinus defect and air by all means, since the sinus defect will become a source of air embolism in this case. In this situation, a surgeon's assistant or a nurse must continuously irrigate the sinus defect with normal saline and subsequently seal its wall using a hemostatic sponge or TachoComb.

Furthermore, a frequent question often is "what type of trepanation should be performed, the resection or the osteoplastic one?" When using the suboccipital retrosigmoid approach, one should always prefer the osteoplastic craniotomy. However, if pronounced cohesion between the dura mater and the bone (especially in elderly patients) is detected when a burr hole is drilled, resection trepanation can be performed to avoid the emergence of defects in the dura mater and sinuses; the bone defect can be subsequently closed with a graft. Osteoplastic trepanation should be preferred when using the median suboccipital approach, excluding the cases when decompression of the PCF structures are needed, e.g., in surgeries for Chiari malformation [10].
Conclusion

When used properly, the suboccipital retrosigmoid and median suboccipital surgical approaches in the patient in a lying position provide a good view of the operating field, while leaving the risks of complications associated with the patient's position on the operating table minimal. A neurosurgeon must have a perfect command of these approaches. The proper use of the approaches ensures a broad view of the cerebellopontine angle and the craniovertebral junction area, while the traction of the cerebral tissue is minimal and usually causes no complications associated with their application.

Authors declare no conflict of interest.

REFERENCES


The article by V.N. Shimanskiy et al. is highly relevant, since the approaches being analyzed (the suboccipital retrosigmoid and the median suboccipital approaches) are most commonly used in surgical treatment of subtentorial pathological neoplasms. While being rather simple, these approaches ensure direct and the most convenient access to all the posterior cranial fossa structures. However, only the meticulous adherence to all the procedure nuances, starting from proper patient positioning, allows one to achieve the objectives of surgical management. It is the analysis of all miniscule details of the aforementioned approaches that makes this paper a thorough manual for using them in a patient in the lying position. The criteria for selecting the patients for whom these approaches are recommended were properly justified and clearly stated. The authors placed special focus on prevention of complications, in particular, postoperative liquorrhea. Numerous schemes and figures that meticulously demonstrate proper patient’s position on the operating table as well as the features of skin incision and skull trepanation are provided in addition to description of the sequence of actions of an operating surgeon.

This work is important, especially for young neurosurgeons, since it teaches them how to perform a proper surgical approach, which, along with good microsurgical skills, is a prerequisite of successful surgery.

V.I. Smolanka (Uzhgorod, Russia)
Navigation Systems in Neurosurgery

V.A. SHURKHAY1,2, S.A. GORYAYNOV3, E.V. ALEKSANDROVA1, A. SPALLONE2, A.A. POTAPOV1

1Burdenko Neurosurgical Institute, Moscow, Russia; 2Moscow Institute of Physics and Technology, Moscow, Russia; 3NCL-Neuromed, Department of Biomedical Sciences University di Roma ‘Tor Vergata, Via Orazio Raimondo, Rome, Italy

When preparing the review, we analyzed publications available in the Medline database; a total of 1,083 publications related to the review’s subject were analyzed. After more careful analysis, we selected 117 publications devoted to the development of neuronavigation in craniocerebral surgery, its historical background, current trends, and future prospects of the technique.

Keywords: neurosurgery, neuronavigation, stereotaxis, computer-assisted neurosurgery.

At the initial stage, the development of neurosurgery was limited by technical level of that time. The lack of accurate and objective anatomical assessment of the relationship between paraplasma and surrounding structures in each individual patient [1—3] was another major limitation. Fundamental studies on the functional brain mapping, which were started as early as in the XIX century by Broca, Wernicke, Exner, and Dejerine, provided data on the architectonics of the key functional systems and their topological representation in the cerebral cortex [4, 5]. W. Penfield significantly contributed to this work [6]. Nevertheless, it was difficult to assess the individual characteristic features of the anatomy and neurophysiology of each individual patient. There was an urgent need to integrate these data and present them to neurosurgeons. This problem could not be solved until 1970s due to the absence of direct brain imaging methods, possibility of mathematical processing and alignment of various data.

The instruments for frame-based stereotactic navigation laid the basis for the development of neuronavigation systems. In 1873, H. Dittmar et al. [7] used the instrument, which provided approach to the neoplasms in the medulla oblongata of laboratory animals for the first time in a neurophysiological laboratory. The pioneering work of D.N. Zemtsov 1889 [8] marked the beginning of stereotactic surgery on the human brain. Further development of the method was associated with the studies of Clarke and Horsley, who developed the device to study the brain of monkeys of in 1906—1908. Ranson and Ingram obtained basic information about the functions of the reticular formation, hypothalamus, and midbrain, using frame-based stereotaxis and modified Horsley-Clarke apparatus [10]. Kirshner has overcome the difficulties of the use of stereotaxis in humans associated with variability of the relationship between the skull bones and brain structures, which enabled thermal ablation of the trigeminal ganglion in a patient with trigeminal neuralgia for the first time, using originally designed stereotactic device [11]. In the second half of the 1940s, E. Spiegel and H. Wyck [12] used the stereotoxic atlas, which they previously developed, in combination with the data of contrast ventriculography and position of the pineal gland to localize intracranial anatomical structures and describe the use of frame-based stereotaxis during neurosurgery. L. Leksell significantly contributed to the development of these techniques [13]. In 1949, he developed his own construction of stereotactic apparatus. Later on, J. Talairach, E. Monnier, T. Riechertand, and F. Mundinguer [14—16] developed original stereotoxic devices for functional interventions. The articles of Russian authors E.I. Kandel and V.V. Peresedov [17—19] reported the results of the use of the original stereotactic apparatus in the cryosurgery of the subcortical structures, as well as clipping of cerebral arterial aneurysms.

The development of X-ray diagnostic technique significantly expanded the possibilities of neurosurgical pathology diagnosis. In 1908, F. Krause et al. [20] devoted a separate chapter of their multi-volume neurosurgery guide to radiodiagnosis of neurosurgical diseases and identified characteristic features of some of them. The development of pneumoventriculography was the next milestone [21]. The capabilities of the contrast cerebral angiography proposed by E. Moniz [22, 23] greatly improved neurosurgeon’s knowledge about the individual anatomy and pathological anatomy of patient’s cerebral structures.

The use of metabolic navigation was based on the discovery of the phototoxicity phenomenon in the early XX century and was associated with the studies of Raab and von Tappeiner [24]. In 1924, Policard showed that some malignant human tumors fluoresce in the orange-red spectral range when irradiated with ultraviolet light [25]. This effect is due to the formation of endogenous porphyrins in tumors, which have been confirmed by fluorescence of experimental tumors in the red spectral region in animals pre-administered with hematoporphyrin [26]. The first study on the use of fluorescein dye during neurosurgical operations in patients with brain tumors was published by G. Moore in 1947 [27]. Fluorescein is not widely used in neurosurgical practice due to its toxicity and low specificity of the method. The paper of B.A. Samotokin et al. [28] reported the use of organic dyes for intraoperative imaging of brain tumors. F.A. Serbinenko et al. [29] used the technique of superselective intravascular injection of dyes in tumor-supplying vessels. However, this method cannot be used in routine practice due to insufficient specificity and reproducibility of the results and toxicity of preparations.

Since the mid-1990s, idocyanin green dye, which is fluorescent in the infrared range, is used for intraoperative visualization of blood vessels (both in normal brain tissue and in tumors). The possibilities of modern surgical microscopes (e.g., Zeiss OPMIpentero) enable color mapping, determining the direction of blood flow [30, 31].

Pioneering studies of the metabolism of porphyrins and visualization of leukemic cells using 5-aminolevulinic acid were reported by Z. Malik et al. [32] in 1979. It was shown that 5-aminolevulinic acid is metabolized by enzyme systems that

e-mail: vash.nsi@gmail.com

© Group of authors, 2016
are active only in tumor cells to produce protoporphyrin IX, which is fluorescent under external light source having certain wavelength [33]. In the late 1990s, the first reports on the possibility of using 5-aminolevulinate in neurosurgery were published [34]. Later studies showed that the use of metabolic navigation improves the extent of tumor resection and increases disease-free and overall survival of patients with malignant gliomas [35]. The studies of A.A. Potapov et al., S.A. Goryaynov et al. [36, 37] have shown that metabolic navigation using 5-aminolevulinate acid can be applied not only in gliomas, but also in meningiomas. Currently, the ways to improve sensitivity of fluorescence diagnosis in the surgery of low-grade gliomas and metastases are being investigated [36, 38]. In the absence of visible fluorescence, the authors suggested laser spectroscopy method to estimate the concentration of amino-levulinic acid in the tumor tissue and thus differentiate it from the healthy brain [24, 37, 38].

Along with fluorescence, high resolution mass spectroscopy is another promising method for ultrafast real-time intraoperative identification of tissues. The method provides molecular “fingerprints” based on the analysis of lipids and proteins produced in the ionization mass spectra, which enables characterizing various brain tumor [39].

Radioisotope-based diagnostic techniques are being used since the mid 1950s — early 1960s [40]. Various isotopes were used, such as iodine(I131, I125), bismuth, mercury, gold, technetium, copper, and labeled serum albumin [41]. In 1964, the article of E.V. Koltayev [42] reported the results of the use of radioactive phosphorus for intraoperative localization of brain tumors. The study of M. Fischer et al. [43] published in 1977 showed that radioangiography is more sensitive than scintigraphy, when determining the histological structure of the tumor. At the same time, the latter enables more reliable assessment of tumor vascularization. The study of A.N. Konovalov [44] published in 1980 notes very high sensitivity of peroperative beta-radiometry, which enabled tumor localization in 98% of cases. Later studies showed that positron emission tomography with 11C-methionine involved in the metabolic pathways in tumor cells is more specific for glial tumors. The data on the accumulation of methionine enable determining the degree of anaplasia, selecting the target for stereotactic biopsy, differentiating between radiation necrosis and continued tumor growth, developing a predictive model for the patient [45, 46]. F.M. Lyass and E.Ya. Shcherbakov [47—49] investigated the role of radionuclide studies in the diagnosis of CSF system diseases, intracranial inflammation, and the consequences of traumatic brain injury. Currently, single-photon and positron emission tomography are mainly used for differential and topical diagnosis of various pathological processes; these methods have significant limitations [46] in intraoperative navigation.

X-ray computed tomography (CT) is based on the studies of Oldendorf, Hounsfield, and Cormack. The first ever in vivo image of patient’s brain was obtained in 1972 [50, 51]. In 1976, L. Jacobs et al. [52] compared the results of computed tomography and 75 autopsies, the accuracy of intracranial pathology diagnosis was 86.2%. Today, CT with intravenous contrast and perfusion techniques enable assessing the condition of the blood flow in the mass lesion and perifocal zone in different parts of the brain, including its deep structures and brainstem [53—57]. The study of J. Maroon et al. [58] focusing on the use of CT to navigate the puncture emptying of tumor cysts and brain abscesses was an important milestone in neurosurgery. In 1979, R. Brown [59] presented the results of successful use of CT and three-dimensional computer graphics for stereotactic localization of targets in a phantom with installed special stereotactic frame. Later on, the results of clinical application of CT to calculate stereotactic surgery (functional neurosurgery and tumor biopsy) were reported in the articles of J. Boethius, B. Czerniak, and Z. Krzyzolik [60—62].

Intraoperative CT was developed in various fields of neurosurgery to specify the completeness of tumor resection, eliminate intraoperative complications, intraoperatively correct navigation information, and provide more accurate implantation of stabilization system elements in spinal neurosurgery [63—66].

The studies of F. Cope and R. Damadian [67], who used magnetic resonance to determine the concentration of potassium ions in a bacterial cell in 1970, provided the basis for magnetic resonance imaging (MRI). Obtaining information about tumors in vivo was made possible through the use of a field-focusing nuclear magnetic resonance, FONAR [68]. The first magnetic resonance image of the human chest was obtained in 1977 [69]. The first commercially available magnetic resonance imager (MRI) was produced in 1980 [70]. When comparing CT and MRI for stereotactic interventions, W. Birg et al. [71] noted high accuracy of the latter, better visualization of brain structures located close to the bone tissue, as well as the absence of necessity for contrast ventriculography during functional operations.

Intraoperative MRI also enables intraoperative correction of navigation data and improves the completeness of surgery. However, it requires special equipment in the operating room, non-magnetic devices and instruments [72]. Low-field portable MR scanners require longer scan time due to low resolution, which lengthens the operation time and does not enable perfusion or spectroscopic studies during the operation. High-field MRI scanner, providing better image quality and wider visualization capabilities due to larger number of sequences, are difficult to integrate into existing operating rooms, requiring either major modernization of the operating unit or its reconstruction with allowance for MRI placement. In addition, the use of high-field scanners is associated with image artifacts and requires long-term personnel training.

Furthermore, intraoperative use of CT and MRI is very expensive and it is not available in all hospitals.

Intraoperative use of ultrasonound (US) is the most available and simple method for navigation and localization of neoplasms and correction for brain displacement [73]. Application of three-dimensional US-navigation, such as Sonowand Invite system, improved surgeon’s orientation, provided adequate assessment of the completeness of paraplasm resection and identification of intraoperative complications, including those in ventriculendoscopic surgery [74—76]. Along with Sonowand system, a combination of a separate expert-level ultrasonic scanner, control computer, and neuronavigation system were used for intraoperative three-dimensional US-scanning and navigation [77, 78].

The effect of brain displacement reduces the accuracy of intraoperative navigation [79, 80]. Reliable prediction of the magnitude and direction of brain displacement is not possible [81]. Correction for brain displacement can be achieved using intraoperative computed tomography or MR imaging, as well as ultrasound study.

The development of neuronavigation systems, which made all of the above methods as much applicable as possible from the neurosurgeon’s viewpoint, was the logical
continuation of the studies of intraoperative visualization of paraplasms and other brain lesions. Currently, the most accurate and sparing approach to the pathological lesion is possible in each particular patient.

Since the inception of neuronavigation systems, they developed along two parallel lines determined by the used monitoring techniques, optical (active or passive) or electromagnetic.

In the first report of A. Kato et al. [82] on the frameless electromagnetic navigation, the system which enables monitoring of inclination and spatial arrangement of the surgical instrument equipped with electromagnetic sensor to within 4 mm was described. ISG Magic Wand system produced in 1992 was the first commercially available neuronavigation system. It was a manipulator consisting of six segments, where a special pointer, rigid endoscope, or biopsy needle can be installed. This system was used for navigation in brain tumors, epilepsy surgery, ventriculoscopy operations, stereotactic biopsies, pathology of the skull base, posterior fossa, clivus, and superior cervical vertebrae [83—85]. This system could not be used for functional neurosurgery due to inability of rigid fixation of navigation manipulator and relatively high error (>2.2 mm) [86].

The operation principle of electromagnetic navigation systems is based on the fact that a special generator (running on DC or AC) creates an electromagnetic field around the patient’s head, which is the coordinate system where the reference and surgical instrument equipped with a built-in electromagnetic sensor or special adapter are positioned. Spatial movement of the sensor changes the characteristics of the field at this point, which allows the navigation system to determine the coordinates of the instrument. The dimensions and placement of the sensor on the instrument may vary, affecting the functionality of the system: for example, Medtronic Stealth Station 7 navigation system (Medtronic, USA) incorporates a separate external electromagnetic navigation module and DC electromagnetic field generator; sensors in disposable instruments are located in the handle, which prohibits changing the length of the instrument during the operation or its bending. At the same time, Fiagon navigation system (Fiagon GmbH, Germany) includes an electromagnetic field generator operating on alternating current, and instruments contain two sensors: one of them is located on the working end of the instrument and the other is located on the handle, which allows the surgeon to model (bend) the instrument depending on the operating situation, while preserving navigation accuracy. Application of direct current to generate electromagnetic field is an earlier technology. It requires the use of larger sensors and the resulting field is more vulnerable to various factors that can change its shape, such as the presence of large quantities of metal or a source of electromagnetic interference near the patient’s head [87]. Using AC overcomes these limitations [88]. Electromagnetic field generator can be fixed to the operating table using a special bracket (Stealth Station 7, Fiagon), as well as integrated into the universal head support for an operating table (Fiagon). A separate module for electromagnetic navigation that requires connection to the main system increases the overall size and floor space occupied by the system. The advantages of the last generation electromagnetic navigation system include their portability and compactness, the possibility of integration into existing operating room system, very small sensor, which enables its integration into an instrument without increasing its size and, more importantly, changing tool geometry during operation without loss of navigation accuracy. According to C. Hayhurst et al. [89], the use of electromagnetic navigation in most cases enables avoiding rigid fixation of patient’s head, for example, during neuroendoscopic interventions, bypass surgery, awake craniotomy. Compatibility with intraoperative neurophysiological monitoring is an important factor.

The use of the most portable and mobile electromagnetic navigation systems, which are not only a module in the basic optical navigation system, but rather can be effectively integrated into the workspace of the operating room, do not require any special infrastructure owing to full compatibility with existing equipment and instruments, and are easy to master for the staff, is the most promising direction.

Most neuronavigation systems developed in the 1990—2000s were based on optical monitoring technique. Historically, its earlier version involves the use of diodes emitting light in the IR range, which is detected by the receiving camera of the system. The LEDs are located on the reference, which is placed as close to the patient’s head as possible. They form the basis of the coordinate system and can also be placed on the instruments using special adapter or directly integrated into the instruments. Passive techniques involve the installation of reflective spheres, which are located in the field of view of the camera equipped with an infrared light source, on the reference, instruments, and adapters. The article of K. Roessler et al. [90] describes the results of clinical application of this system in spinal and cranial neurosurgery. System accuracy averaged 3.4 mm in 36 craniotomies and 11.3 mm in 4 cases of spinal operations. The large error during spinal operations was associated with difficulties in the registration of images and the use of cutaneous registration markers. The development of computer graphics and new data processing capabilities have led to the use of “augmented reality” concept in neurosurgery, which enabled direct real-time alignment of paraplasm modeling results, functional areas, and anatomical landmarks (based on CT or MRI data) with the surgical field [91].

New features of intraoperative neuronavigation were associated with combining different modalities of neuroimaging: CT, conventional MRI, diffusion-tensor and functional MRI, as well as magnetoencephalography and electrophysiological mapping of speech, sensory, and motor areas of the cerebral cortex [92]. This improved the results of surgical procedures for pathological processes at the functional areas, hydrocephalus, ventriculodendoscopic interventions, and epilepsy [93, 94]. Many authors noted a positive effect of intraoperative navigation on completeness of paraplasm resection, duration of hospital stay, overall survival, and functional outcome [95—97].

The use of data provided by diffusion-tensor MRI, magnetoencephalography, functional MRI in a navigation system with simultaneous recording of cortical somatosensory evoked potentials enabled successful reconstruction of conductive paths of the brain at different levels and assessing the impact of the pathological process on these pathways [98, 99]. Computer modeling facilitated understanding of the anatomical relationships between the paraplasms and intact structures of the brain [100]. The use of neuronavigation significantly improved the resolution of transcranial magnetic stimulation [101].

Comparative analysis of various neuronavigation system (ISG Magic Wand, Cygns PFS, SMN) by E. Benradette et al. [102] in the laboratory showed that, regardless of the used technique (mechanical manipulator, electromagnetic or
optical monitoring, respectively), the average precision of the systems did not differ significantly and ranged 1.67 to 2.6 mm. According to the authors, selection of navigation system was mainly determined by portability, ease of use, and compatibility with the operating microscope. The study of M. Cartellieri et al. [103] comparing six different navigation systems also showed no fundamental difference between the systems, since their precision was comparable (error ranged 0 to 6.7 mm). For a long time, precision of neuronavigation systems compared to conventional frame-based stereotactic devices was the subject for discussion. R. Steinmeier et al. [104] analysed the factors (technical precision of the system, registration process, voxel size and/or the presence of images distortions, intraoperative situation) that have a direct impact on navigation precision. It has been shown that imaging modality has minimal effect on the accuracy of navigation. The number of registration markers and the nature of their placement are the most important factors. The authors concluded that the accuracy of neuronavigation systems (as exemplified by a robotic microscope MKM Carl Zeiss and optical system Stealth Station Sofamor-Danek) is comparable to that of conventional stereotactic frame-based devices. Particular attention was paid to the fact that registration error calculated by each navigation system does not reflect the real error. U. Spetzger et al. [105] analyzed 10 years of experience in the application of neuronavigation and came to conclusion that system accuracy is mainly affected by the human factor. At the same time, S. Poggi et al. [106] concluded that the parameters of CT or MRI images also have an impact on the accuracy of neuronavigation.

The accuracy of target localization based of CT data was higher than when using MRI data; the presence of image distortions was an important parameter that reduces the accuracy of MRI navigation. At the same time, Y. Enchev et al. [107] found no statistically significant differences in accuracy of neuronavigation with CT and MRI. There was also no significant differences in the navigation accuracy when using registration based on anatomical landmarks or fiducial markers. For this reason, W. Pfisterer et al. [108] recommended to use registration based on anatomical markers as more economic and less costly.

Comparative analysis of systems with active (Stryker) and passive (BrainLab Vector Vision) tracking technology conducted by D. Paraskevopoulos et al. [109] at the anthropomorphic model of the head showed that the accuracy was similar for both systems (<1.5 mm), and accuracy data calculated by the systems do not always fit the actual values and always require rechecking by surgeon. In all options, optical technique is characterised by following limitations: a) the need for placing the camera at a distance of at least 1 meter from the spheres or diodes; b) placing the camera on a separate bracket or stand, increasing the size of the system and reducing its portability and mobility; c) dependence of navigation accuracy on the state of reflecting spheres or diodes; d) “visions line” problem of the camera, leading to cessation of navigation when closing diodes or spheres with some object; e) bulky adapters for reflective spheres or diodes to be mounted on surgical instruments; e) inability to provide navigation of instrument with variable length, curvature, or made of soft materials (silicone catheters); f) the need for rigid fixation of patient’s head, which limits the use of navigation in children [110]. It was also shown that infrared radiation from the optical navigation system tracker camera can substantially affect the performance of pulse oximeters, causing errors in the quality of signal and assessment of saturation level [111]. In 2001, M. Zaaroor et al. [110] published the paper, where the experience with electromagnetic navigation system Magellan (Biosense Webster) was analyzed. The electromagnetic sensor was located at the working end of the instrument, which enabled using the system for installation of flexible catheters, navigation of endoscopes and other instruments.

The advantages of the use include high operation speed, high precision, small size, the possibility to navigate flexible instruments, greater freedom of movement of the surgeon, which does not depend on the viewing field of the recording camera, no need for rigid fixation of the head, which enables operating children from the second week of life [110, 112, 113]. At the same time, T. Rodt et al. [114] noted that the interference of the magnetic field might affect the performance of the navigation system.

Comparative analysis of the accuracy of optical and electromagnetic navigation systems conducted by J. Rosenow et al. [115] revealed no significant differences (the target point location error ranged 0.71 to 3.51 mm). A. Sieskiewicz et al. [116] also compared optical and electromagnetic navigation systems (Medtronic Stealth Station and Digipointeur, respectively) and concluded that electromagnetic navigation is faster and easier to configure, provides greater freedom of surgeon’s hands, and its accuracy is similar to that of the optical system; the small number of instrument supported for navigation was the imitation of that specific electromagnetic system.

Recently, intraoperative robot assistance became one of the main trends in surgery, improving safety and accuracy of surgery due to high-precision intraoperative navigation. In neurosurgery, such systems have been tested in preserving craniotomy, precise approach to deep brain structures for the purpose of biopsy of tumors, inflammatory and other lesions, implantation of shunt systems, electrodes and others. [117, 118]. Robotic systems are essentially a further option of the development of navigation systems.

**Conclusion**

The analysis of the literature over the past 100 years revealed preconditions for the development of neuronavigation and traced the evolution of this trend from both technical and clinical point of view. The advantages of using navigation systems in modern neurosurgery are obvious. Neuronavigation is one of the most popular high-tech methods, which enables combining various studies to evaluate the anatomical and functional situation in the preoperative and intraoperative periods. All this enables conducting highly accurate and safe surgical procedures much faster than conventional methods. Application of neuronavigation systems is highly valuable from both clinical and scientific viewpoint. Integrative nature of neuronavigation enables combining different modalities of data, including anatomical, neuroimaging, molecular, and neurophysiological, which improves the efficiency, effectiveness, and conclusiveness of clinical studies carried out using this technique. Furthermore, it is undoubtedly highly promising as an educational method. Currently, neuronavigation should not be a luxury for neurosurgical clinics; its application should be as widespread and routine as possible. We believe that, although neuronavigation does not replace the expertise and clinical thinking of neurosurgeon, it is a necessary complement, which enables neurosurgeons to maximize the use of their skills.
REFERENCES

doi: 10.1007/bf01401819
doi: 10.1008/0964704060700245
doi: 10.1227/01.neu.0000249205.58601.05c
doi: 10.1227/01.neu.0000249205.58601.05c
doi: 10.1007/174_2012_540
doi: 10.1126/science.106.2754.349
doi: 10.1007/174_2012_540
doi: 10.3171/jns.2000.93.6.1003
24. Potapov AA, Goryainov SA, Golbin DA, Zelenkov PV, Kobaykov GL, Okhlopkov VA, Zuzov VL, Shishkina LV, Loshinov BK, Savelyeva TA, Kuzmin SG, Chumakova AP, Spallone A. Intraoperatsionnaya fluorescence navigatsii diagnostika i lazernaya spectrukskopiya pri povtornykh fluorescence tissues using multidimensional molecular profiles database as the main element of data processing system of the intelligent neurosurgical scalpel". There is no conflict of interest.
92. Krombach GA, Spetzger U, Rohde V, Gilsbach JM. Intraoperative local-
95. Nazarenko GI, Minasyan AM, Cherkashov AM, Nazarenko AG. doi: 10.3171/FOC/2008/25/9/E7
97. Krivoshapkin AL, Kanygin VV, Semin PA. Rezul’taty radikal’nogo
93. De Almeida AN, Wheatley BM, Olivier A. Advanced surgical approach for doi: 10.1007/s10143−010−0302−5
107. Enchev YP, Popov RV, Romansky KV, Marinov MB, Bussarsky VA. Effect of the type of image study (CT or MRI) on some parameters of neuronavi-
118. Mullin JP, Smithason S, González-Martínez J. Stereo-Electroencephalo-
120. Cavarschio M, Langlotz F, Nolte LP, Hauser R. Impact of a self-
Prevention and Treatment of Postoperative Epidural Scar Adhesions

D.M. ZAV’YALOV, A.V. PERETECHIKOV

Navy Clinical Hospital 1469, Severomorsk, Russia

Postoperative epidural scar adhesions remain one of the most common late complications of microdiscectomy, which worsens the overall outcome in treatment of herniated lumbosacral discs. Despite a large number of conservative and surgical treatment options for epidural scar adhesions, the treatment outcome not always satisfies patients and doctors. The review was aimed at systematizing the available data on this complication and facilitating the choice of appropriate treatment strategy.

Keywords: epidural scar adhesion, epidural fibrosis, microdiscectomy, disc herniation, degenerative disc disease.

Despite the development of new techniques and achievements in the surgical treatment of herniated discs, the number of poor postoperative outcomes in the form of persistent radicular pain syndrome still remains high and accounts for 5—20% according to different authors [1—4].

The development of adhesive process known as epidural scar adhesions or epidural fibrosis is the most common cause of persistent radicular pain syndrome. The incidence of epidural scar adhesions among the other reasons of so-called “failed back surgery syndrome” is up to 8—70% [3, 5—9].

The causes of excessive formation of connective tissue in the epidural space after surgery are still not fully understood. It is still not clear, why the pronounced epidural fibrosis develops in the postoperative period in some cases, while it is less pronounced or absent in other cases under identical conditions.

The relationship between the severity of epidural fibrosis and discectomy technique still remains a debatable issue. Several authors suggest that the incidence of this postoperative complication is lower in the case of minimally invasive interventions, application of gel materials and insulating membranes, various surgical techniques preserving ligamenta flava, and intraoperative irrigation of nerve structures with steroidal and non-steroidal anti-inflammatory drugs. In the last few years, there were publications describing the prevention of scar-adhesions in the following way: the affected root and dural sac at the area of surgical trauma are enveloped with fat injected with methylprednisolone solution. The experimental studies showed that this method reduces the activity of prostaglandins E1 and E2 and leukotriene B, which are the triggering factor in the development of peridural fibrosis. There are significantly different opinions on the effectiveness of this method. Some authors [3, 5, 10—15] believe that it is useful; on the contrary, others believe that it increases scarring.

Many authors [16—21] believe that immuno-infiltrative aseptic inflammation form the basis for discogenic epidural scar adhesions, others note the important role of preoperative values of fibrinolytic activity of the blood in the development of epidural fibrosis, since decrease in fibrinolysis and anticoagulant mechanisms and increase in blood coagulation in the postoperative period increase the risk of epidural scar adhesions [6, 22, 23].

Pain syndrome caused by the development of epidural fibrosis is not characteristic of the early postoperative period, and patient’s quality of life worsens due to persistent pain caused by fibrotic changes in the epidural space only 2—18 months after discectomy [6, 24, 25].

Clinical and neurological examination, including medical history, local status, and neuroimaging techniques is the main diagnostic method to verify the postoperative epidural scar adhesions. Magnetic resonance imaging (MRI), whose effectiveness is improved when using contrast enhancement (Magnevist, Gd-DTPA), is the most popular and informative imaging technique [26—32]. Electrophysiological methods of investigation (somatosensory evoked potentials, eletroneuromyography) are no less informative [33].

Despite the fairly large number of treatment methods for epidural fibrosis after microdiscectomy, most authors [34—37] note that all of them lack clinical effectiveness. General treatment regimen should be based of general principles of vertebral pathology treatment, including pathogenetically oriented complex and stage-by-stage sparing therapeutic modalities with allowance for the individual characteristics of patients [28].

Medicinal treatment with nonsteroidal anti-inflammatory drugs was suggested as a conservative treatment, limiting the development of fibrous tissue in the postoperative period [38—40]. According to some researchers [41], the use of corticosteroids for the purpose of anti-inflammatory therapy in the treatment of epidural fibrosis is well founded. In the case of persisting long-term intractable pain syndrome caused by epidural fibrosis, epidural block is effective [42, 43]. Physiotherapy (amplipuls, magnetotherapy, electrophoresis with caripazim) is widely used as the non-drug treatments for pain [44]. Outcomes of reoperations carried out due to ineffective conservative therapy do not always satisfy patients and surgeons [45, 46].

Epidural scar adhesions are still quite common in today’s neurosurgical practice. It is highly significant medical and social problem: recurrence of radicular pain in the postoperative period makes patients to feel desperate, destroying their social adaptation. The need for timely treatment and prevention of epidural scar adhesions is undoubted and dissatisfaction with clinical outcomes makes it a pressing problem.

There is no conflict of interests
REFERENCES


doi: 10.1016/s0039-1904(01)00677-2

doi: 10.3171/spi.2001.95.2.0179

doi: 10.1097/00007632-199110000-00005


20. Omar R. Bolevye korreksionnye sindromy na smeznykh urovnyakh u bol’nykh, ranee operirovannykh po povodu degenerativno-distrophiceskikh zabolevanii poezvonochno-kresttsovoj otdel poezvonochnika: Dis. ... kand. med. nauk. SPb. 2006. (In Russ.)


doi: 10.1007/BF02278130


doi: 10.1007/s0023496000144


doi: 10.1007/s005860000144

doi: 10.1007/978-3-7091-9419-5_25


doi: 10.1007/s00586-007-0580-y

doi: 10.1007/s00586-007-0344-8
Literature review “Prevention and treatment of postoperative epidural scar adhesions” focuses on the topical problem: scarring processes, developing after neurosurgical interventions for spinal pathology, in particular after microsurgical discectomy. It is well known that these processes to some extent develop in all the operated patients and can significantly reduce patient’s quality of life and even destroy the results of formally successful surgery. The authors present data on the importance of epidural scar adhesions in the development of neurological symptoms, summarize the data obtained from Russian and international literature on the diagnosis and possible methods to prevent these processes.

Given the complexity and multidimensionality of these problems, it would be interesting to determine risk factors for adhesive processes in the case of decompressive and stabilities interventions, including their relationships with the type and extent of stabilizing structure. The authors rightly pay attention to MRI and contrast-enhanced MRI in the diagnosis; it would be useful to mention the role of other techniques, such as percutaneous minimally invasive diagnostics, in particular flexible endoscopy (epiduroscopy and thecaloscopy). Among possible prevention methods, the use of type 3 collagen, and, more importantly, limited aggressiveness of discectomy, in particular by applying portal endoscopic techniques, are worth noticing.

A.O. Gushcha (Moscow, Russia)