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SURGICAL TREATMENT OF GANGLIOGLIOMAS IN FUNCTIONAL AREAS OF THE BRAIN IN CHILD: A LITERATURE REVIEW AND CLINICAL CASES

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Surgical treatment of tumors located near functional areas involves the use of technologies such as awake craniotomy, cortical and subcortical stimulation. The introduction of these and other technologies makes it possible to achieve maximum resection of the tumor without compromising the functional status of the patient. The use of this technologies has been well studied in adults, but this not about pediatric patients.

Aim of the work is to present two clinical cases of successful treatment of low-grade gliomas of functional areas of the brain in children and literature review.

In clinical cases, damage of functionally significant areas were noted: the sensory speech cortex and the corticospinal tract. The involving speech cortex in the first case was also confirmed by functional magnetic resonance imaging. In the first case, an operation was performed with awake craniotomy, using cortical and subcortical mapping, in the second, using subcortical mapping and metabolic navigation. Total tumor resection was achieved in both clinical cases with a good functional outcome.

Achieving an optimal balance of functional outcome and the degree of radical removal of low-grade tumors of functional areas is possible using an integrated approach based on the analysis of multimodal data.

Keywords: functional areas, awake craniotomy, cortical stimulation

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BACKGROUND

Currently, it is undeniable that maximal resection of glial tumors plays a crucial role in treatment of both adults and children [1–4]. However, increased resection volume can be associated with persistent neurologic deficit and significantly worse quality of life [2]. Achieving a balance between oncological utility and functional outcome is the priority of modern neuro-oncology. This statement is especially important in cases of gliomas of functionally critical areas (FCA). The problem of surgery of FCA tumors is sufficiently studied in the adult population which is reflected in a large number of observation series, but it is not applicable to neurosurgery in children [2, 5, 6].

It is hard to accurately estimate the incidence of FCA tumors of the cerebral hemispheres in children. However, in Russia 1000–1200 new cases of brain tumors in children are registered annually, 25 % of which are located supratentorially [7]. According to international literature, about 40 % of brain tumors in children are located in the supratentorial area, among them 20 % in FCA [8].

Successful treatment of FCA gliomas requires awake craniotomy (AC), various neuromonitoring and neuroimaging techniques. Selection of the technology directly depends on the area of interest and the function it governs.

Use of AC allows to decrease the risk of permanent neurologic deficit after surgical treatment of both low- and high-grade glial tumors [8–11]. Meta-analysis of a series of operations with awakening showed that the frequency of neurologic deficit was decreased by 58 % and radicality was increased compared to procedures without intraoperative mapping [12]. A review encompassing 951 cases showed that awake surgery leads to shorter hospital stay (4 days *versus* 9 days) and lower number of neurologic complications (7 % *versus* 23 %) compared to similar surgeries without awakening [13]. However, despite growing experience of AC, this approach is still rarely used in children which is reflected in a low number of case series [5, 6, 14–17]. Nonetheless, AC in children is possible and demonstrates similar level of effectiveness compared to AC in the adult population in some conditions [5].

The aim of this study is to describe 2 clinical cases of successful treatment of pediatric patients with low-grade FCA gliomas and to present a literature review of this problem.

SURGICAL TREATMENT OF LOW-GRADE GLIOMAS OF FUNCTIONALLY CRITICAL AREAS OF THE BRAIN IN CHILDREN

The technique of AC in children, as well as patient selection criteria, are well described (despite insufficient number of case series), which cannot be said about cortical stimulation mapping.

Pediatric practice does not have a universal protocol of language zone stimulation. Data based on the available case series vary in stimulation parameters. Thus, in the L.N. Lohkamp et al. study, starting current of 1 mA and maximal of 7 mA is recommended [17], but J.A. Balogun et al. used stimulation intensity between 3 and 14 mA [6].

Subcortical stimulation is considered the gold standard of corticospinal tract identification. However, this technique is still not standardized [18–20]. In some studies, motor evoked potentials during stimulation of the corticospinal fibers with 1–2 mA current are considered crucial [19, 20]. Other data shows that if responses with such current are achieved, operation can be continued if the surgeon is confident that the tumor can be completely removed [21].

Meanwhile, results of analysis of 294 surgeries with subcortical stimulation showed that white matter tracts can be identified when resection margin is already inside in the tract of interest or at a distance of 2–3 mm which significantly increases the risk of their damage [22].

Subcortical stimulation allows to identify white matter tracts intraoperatively, but information on the location and direction of the tracts is necessary at the planning stage.

Diffusion tensor images became the main technique for tract identification during preoperative planning. In the brain, unidirectional movement of water molecules is called anisotropy. In the white matter, water molecules move in parallel to the axons, therefore this movement can be observed and give information on the location of the tracts [23].

Comparison of tractography and subcortical stimulation data showed quite optimistic results. In some studies, to compare the results of preoperative tractography and intraoperative subcortical stimulation the distance between subcortical stimulation point and neuronavigation station data was used [24, 25]. This distance is about 8.7 mm [26, 27].

The use of tractography data and neuronavigation systems demonstrated good practical results. J.S. Wu et al. showed that neuronavigation with tractography based on diffusion tensor imaging without subcortical stimulation allow to significantly decrease postoperative motor deficit in patients with maximally resected gliomas [28]. A. Romano et al. evaluated the use of tractography both at the planning stage and intraoperatively in a study with 28 patients. They showed that tractography affected the selection of approach in 25 % of cases, identification of resection margin in 64 % of cases. Similar results were obtained in other studies of patients with tumors [29].

In general, the majority of studies showed that tractography based on diffusion tensor imaging is a sufficiently accurate method of identification of motor, speech, and visual pathways. However, tract identification becomes difficult in cases of significant edema, crossing of the fibers [24, 30]. So-called brain shift can also limit the use of tractography with neuronavigation. This restriction can be partially resolved by using real-time ultrasound scanning in combination with neuronavigation [31].

Apart from identification of white matter tracts at the planning stage, information on the location of the FCAs themselves is necessary. For this purpose, functional magnetic resonance imaging (fMRI), a technique based on the changes of cerebral blood flow in areas of increased neural activity, is used. The BOLD (blood oxygenation level-dependent) phenomenon underlying this technique is associated with different magnetic characteristics of 2 modifications of iron-containing hemoglobin molecules – oxy- and deoxyhemoglobin. Increased metabolic activity of the neurons leads to increased blood blow intensity which is observed in fMRI. During the exam, cortical response to speech or voluntary finger movement, etc., is detected [32]. This technique has its limitations associated with movement artifacts, as well as signal distortion by tumor-supplying vessels [17, 32]. Currently, fMRI at rest is being used with increasing frequency as it also recommended itself as a good technique for preoperative FCA identification. The advantages of this method include the ability to fully identify the network of a certain FCA and not only its part responsible for performing a task. This method also does not require a task which is especially important for the pediatric population [33, 34].

Special attention should be paid to the use of metabolic navigation as an additional method to simplify orientation at the intraoperative stage.

5-aminolevulinic acid (5-ALA) is widely used in surgery of high-grade gliomas [35]. However, the role of 5-ALA in surgery of low-grade gliomas is still under debate [36]. According to data from M. Jaber et al. who presented results of the largest case series ($n = 82$), visible fluorescence was observed in only 13 (16 %) cases [37]. Similar results were demonstrated in other studies [38, 39]. However, in a case series by S.A. Goryaynov et al., visible fluorescence was observed in 52 % of cases. The authors explain these results by higher 5-ALA dose (25 mg/kg body weight) and histological characteristics of the tumors in the sample. The researchers assumed that the presence of visible intraoperative fluorescence is associated with the presence of malignant lesions in low-grade gliomas [40]. Therefore, the role of 5-ALA in optimization of surgical treatment of low-grade gliomas is ambiguous and requires further analysis.

Below we describe treatment algorithm for children with tumors of individual FCAs based on 2 clinical cases: 16-year-old patient with ganglioglioma of the speech area and 9-year-old patient with ganglioglioma of the basal parts.

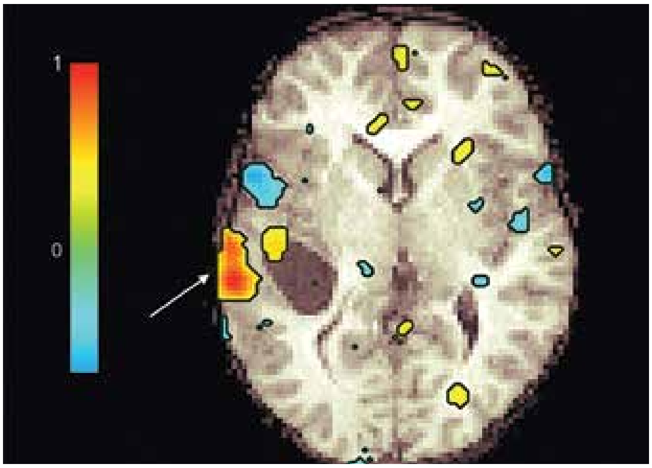

Fig. 1. *Preoperative state functional magnetic resonance imaging of the lingual network demonstrates the proximity of the tumor to the speech zone (arrow)*

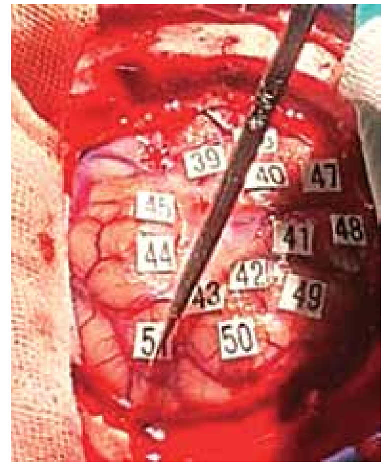

Fig. 2. *Intraoperative photo of cortical stimulation. The position of the speech cortex corresponds to the mark "44" (there was a failure to complete the language task). At other points, there are no violations during the performance of the language task*

CLINICAL CASE 1

Patient, *16 years old, right-handed, was admitted to the clinic of the V.A. Almazov National Medical Research Center, Ministry of Health of Russia, complaining of a single seizure with speech impairment in the postictal period, headache, easy fatigability. Magnetic resonance imaging (MRI) showed a cystic tumor of the posterior parts of the temporal lobe. fMRI at rest reflecting activation of the lingual network (Fig. 1) showed close proximity of the tumor to the sensory speech zone, tractography – to the arcuate fasciculus.*

Neuropsychological exam showed slight impairment of sound analysis and synthesis, phonemic awareness, moderately decreased volume of short-term auditory and verbal memory, slight abnormalities in nominative speech function.

The essence of the surgery was explained to the patient and his parents. The talk was focused on the fact that the child will have to actively participate in the most important stage. In the patient»s room, position of the child on the operating table and limits of his visual contact with the environment were modeled. During visits with a neuropsychologist, the patients carefully studied the tasks of intraoperative testing. Additionally, prior to surgery the patient met all members of the surgery and anesthesiology teams.

Tumor resection was performed with intraoperative awakening. As a language task, we used the naming and sentence completion tests [41]. At the start of stimulation, 1mA current was used; if language test was performed without mistakes, current was uncreased by 1 mA. During Penfield cortical stimulation with 4 mA current at point "44" (Fig. 2), sentence completion test was failed. Stimulation was performed 3 times during reading of the task. During tumor resection, dynamic subcortical stimulation per the Taniguchi»s method with 300 Hz frequency and starting current 10 mA was performed. In close proximity to the arcuate fasciculus – 4 mm per neuronavigation data which corresponded to the resection margin (Fig. 3) – at current 6 mA, the patient displayed paraphasia during the sentence completion and naming tests. For lower currents, no mistakes during testing were observed.

Fig. 3. *On the screen of the neuronavigation station, the arrow indicates the distance between the resection border and the fibers of the arcuate fascicle according to the data of the navigation station. The marked point corresponds to the zone of occurrence of paraphasia during subcortical stimulation with a current of 6 mA*

In the early postoperative period, elements of afferent motor aphasia were observed which regressed on day 4. Control contrast-enhanced MRI confirmed total tumor resection (Fig. 4). Histological examination showed that the tumor was a grade 1 ganglioglioma.

Per contrast-enhanced MRI of the brain 6 months after the surgery, no signs of tumor tissue were found. Neurological exam did not show any neuropsychological abnormalities.

CLINICAL CASE 2

Patient, *9 years, was admitted to the clinic complaining of headache, weakness in the right arm. Neurological exam showed paresis of the distal musculature of the right hand up to 4 points. MRI showed a tumor of the basal parts of the left hemisphere. Magnetic resonance tractography showed that the tumor was attached to the left corticospinal tract (Fig. 5).*

Fig. 4. *Postoperative magnetic resonance imaging T2 mode (axial plane): in the left temporal lobe there is a resection cavity surrounded by a zone of edema (indicated by an arrow). Complete resection of the tumor is confirmed*

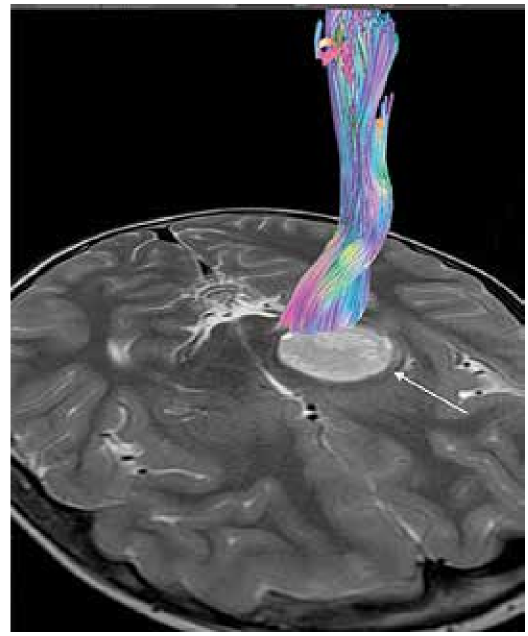

Fig. 5. *Preoperative magnetic resonance imaging in T2 mode (axial section): tumor of the basal ganglia (posterior leg of the internal capsule, globus pallidus), thalamus of the left hemisphere and lateral parts of the left brain stem (indicated by an arrow) is adjacent to the left corticospinal tract*

The control of size sufficiency and location of craniotomy was performed using a neuronavigation station with integrated microscope (Fig. 6, 7).

During tumor resection using dynamic stimulation per the Taniguchi»s method with 8 mA current, the left corticospinal tract was identified. Further from the tumor and closer to the motor fibers, response was achieved at 3 mA current which corresponded to a distance of 4 mm per neuronavigation data (Fig. 8). Individual parts of the tumor showed visible 5-ALA-induced fluorescence (Fig. 9). After visually total resection of the tumor, registration of motor responses was observed at current 3 mA.

Histological examination showed that the tumor was a grade 1 pilocytic astrocytoma.

Postoperative T2-weighted MRI and magnetic resonance tractography (Fig. 10) confirmed total tumor resection with preservation of the left corticospinal tract.

In the early postoperative period, increased paresis of the distal musculature of the right hand to 2 points was observed with paresis in the proximal musculature up to 3 points. Despite therapy, no significant dynamics were observed in the early postoperative period. However, after rehabilitation treatment positive dynamics in the form of partial regression of paresis of the distal musculature of the right hand to 3 points, paresis in the proximal musculature to 4 points were observed.

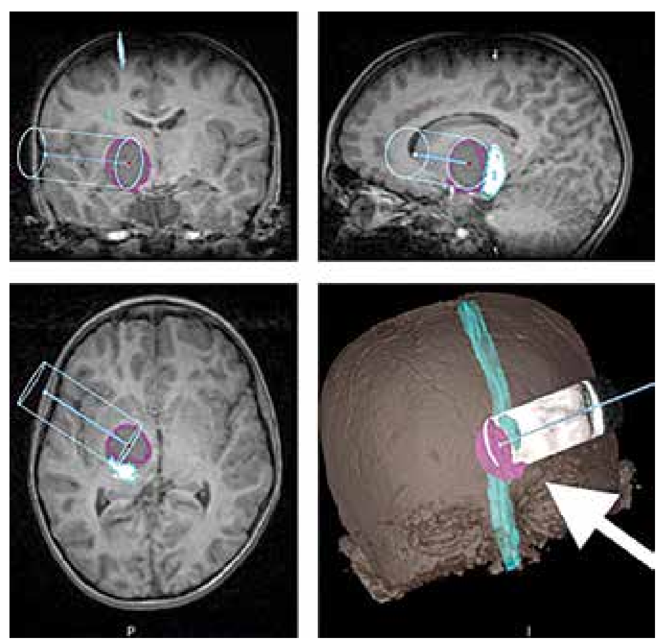

Fig. 6. *The screen of the neuronavigation station reflects the stage of access planning (shown by an arrow), taking into account the location of the tumor (marked with a crimson outline) and the left corticospinal tract (turquoise outline)*

DISCUSSION

One of the main aspects of successful use of AC in children is careful psychological preparation of the patients and their relatives (parents) to form positive attitude towards the procedure which was demonstrated by us in clinical observation 1. Special attention should be paid to modeling of the operating room, which will allow to overcome the fear of closed space and head fixation. This careful preparation allows to make AC safe in children of even younger age [16].

During cortical stimulation in clinical observation 1, we successfully used 4 mA current which corresponds to data of large case series.

In clinical observation 2, during subcortical stimulation total tumor removal was achieved with motor responses at 3 mA current. However, this led to neurologic deficit (which

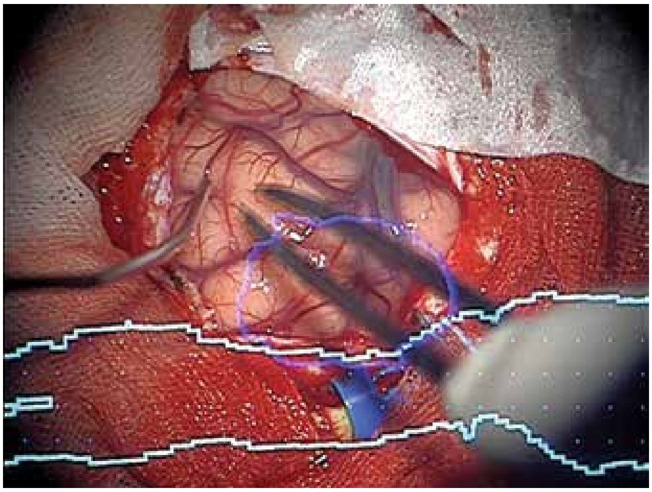

Fig. 7. *In the microscope (during the operation), the border of the tumor projection onto the cortex is marked with a crimson outline, the projection of the left corticospinal tract is marked with turquoise*

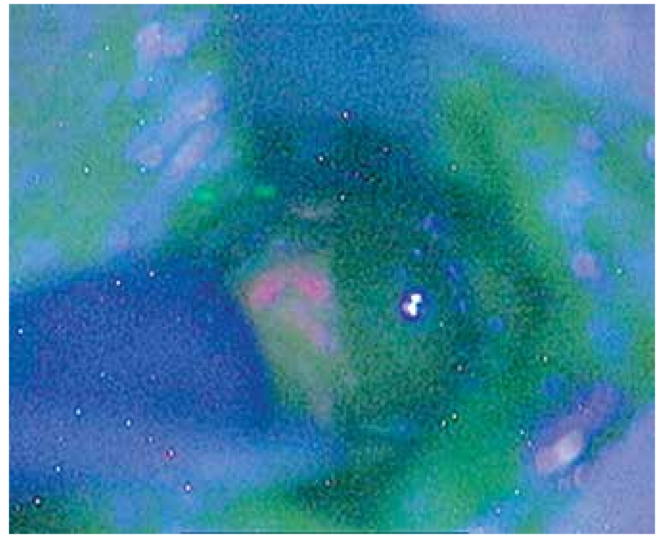

Fig. 9. *Intraoperative photo. Fluorescent glow of individual tumor areas induced by 5-ALA*

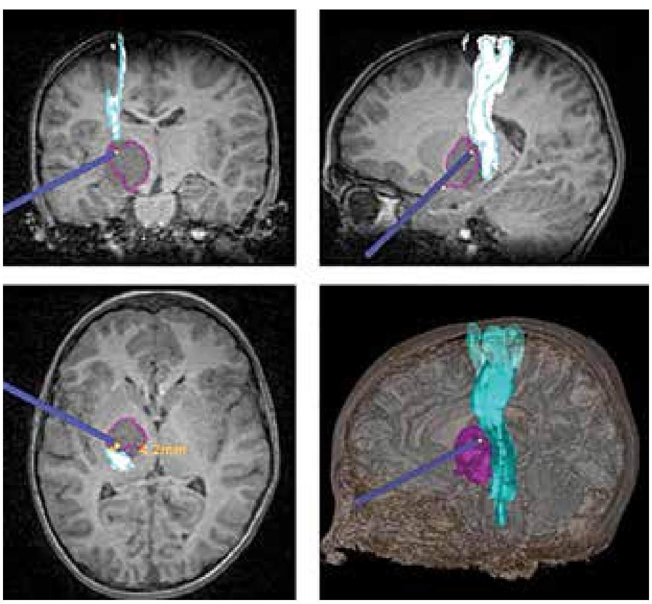

Fig. 8. *After identification of the left corticospinal tract during dynamic monopolar stimulation (3 mA), using the pointer of the neuronavigation station, the distance from the resection edge to the corticospinal tract was determined to 4.2 mm*

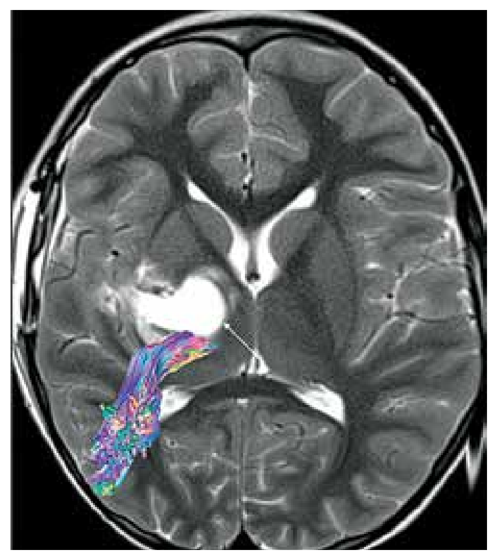

Fig. 10. *Postoperative magnetic resonance imaging in T2 mode (axial plane) shows a resection cavity 45 × 20 × 23 in size, surrounded by a zone of edema (indicated by an arrow)*

partially regressed during rehabilitation) which can indirectly confirm an opinion that resection is unsafe with motor responses at current 1–2 mA [19, 20].

The results of simultaneous use of neuronavigation and tractography demonstrated in clinical observation 1 were compared to the subcortical stimulation data. In our experience, the data on the distance to the arcuate fasciculus differed by 1 mm. Such accuracy of neuronavigation and tractography significantly differs from mean difference evaluated in large case series [26, 27]. However, simultaneous use of tractography and neuronavigation data can be useful in the absence of subcortical stimulation.

In our experience, fMRI at rest allowed to locate the sensitive speech zone at the stage of preoperative planning which was confirmed by cortical stimulation.

The use of metabolic navigation with 5-ALA in clinical observation 2 did not affect the resection volume. Individual parts of the tumor visualized with this method were identified during microscopy in visible light spectrum.

CONCLUSION

Currently, estimation of the incidence of FCA tumors in children is difficult. But the importance of the issue, as well as the difficulties the surgeon faces in every individual case due to the absence of a universal algorithm for treatment of FCA tumors, are undisputable.

Our experience and literature data allow to conclude that successful treatment of FCA tumors requires changes in the traditional neurooncological paradigm. Thus, solely visual intraoperative evaluation of surgical intervention should be complemented by pre- and intraoperative evaluations based on the results of the above-described methods to achieve the optimal balance between oncological utility and functional outcome.

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Authors' contributions
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