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ВЕРИФИКАЦИЯ ГАНГЛИОГЛИОМЫ АССОЦИИРОВАННОЙ С НЕЙРОНАЛЬНОЙ ГЕТЕРОТОПИЕЙ У ВЗРОСЛОГО ПАЦИЕНТА БЕЗ ЭПИЛЕПСИИ С ПРИМЕНЕНИЕМ МУЛЬТИМОДАЛЬНОГО ПОДХОДА К ВИЗУАЛИЗАЦИИ

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Известно, что ганглиоглиомы являются редкими, и в основном, медленно растущими доброкачественными первичными опухолями центральной нервной системы, чаще всего встречающимися у детей и молодых людей. Это наиболее распространенные опухоли, ассоциированные с эпилепсией, часто локализующиеся в височной доле. Хирургия часто кажется лучшим подходом к контролю приступов у таких пациентов. В данной статье рассматривается редкий случай ганглиоглиомы локализованной в височной доле, ассоциированной с нейрональной гетеротопией белого вещества у молодого пациента, но без эпилепсии. Длительное динамическое наблюдение, включающее углубленное клиническое, электроэнцефалографическое, радиологическое и послеоперационное гистологическое исследование, документально подтвердили наличие неопластического процесса без приступов в течение десяти лет. Хирургическое вмешательство основывалось на результатах комплексного радиологического исследования, продемонстрировавшего наличие неоплазмы в структуре патологического субстрата неясной этиологии.
Ключевые слова: ганглиоглиома, эпилепсия, нейровизуализация

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MULTIMODAL NEUROIMAGING VERIFICATION OFGANGLIOGLIOMAASSOCIATED WITH NEURONAL HETEROTOPY IN AN ADULT PATIENT WITHOUT EPILEPSY

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Gangliogliomas are known to be rare and mainly slow-growing benign primary central nervous system tumors, most frequently occurring in children and young adults. They are the most common epilepsy-associated tumors, which frequent location is the temporal lobe. Surgery often seems to be the best approach in controlling seizures in such patients. This paper deals with a rare case of ganglioglioma in a young adult patient with a temporal lobe tumor associated with neuronal heterotopy of white matter, but without epilepsy. Long-term dynamic observation including in-depth clinical, electroencephalographic, radiologic, and post-surgical histologic examination confirmed the documented neoplastic process without any manifestation of seizures over ten years. Surgical intervention was based on the results of a multimodal radiological examination, which demonstrated the presence of neoplasm in the structure of the pathological substrate of unclear etiology.
Key words: ganglioglioma, epilepsy, neuroimaging

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Introduction. Ganglioglioma and dysembryoplastic neuroepithelial tumors (DNT) are considered to be the most frequent cases for epilepsy surgeries in children and yang adults [1, p 606]. Epileptic seizures are usually the principal and, in some cases, the only clinical manifestation of these tumors. Of the 1.680 tumors associated with epilepsy collected in the German Neuropathology Reference Center for Epilepsy surgery, gangliogliomas together with DNT make up about 70% and are by a large margin the leaders in the united group under the abbreviation LEAT — "Long-term Epilepsy Associated Tumors" [2, p. 3]. Due to their huge epileptogenic potential some years ago these tumors were suggested to be called "epileptomas" or "epilepsomas" [3, p. 734; 4, p 5]. But this terminology has not received official recognition. Neuronal heterotopy of white matter (NHWM) is often associated with neuronal-glial tumors. The importance of heterotopic neurons in the formation of epilepsy has been still under debate [5, p. 593; 6, p. 181–182]. Ganglioglioma may lack typical neuroradiological signs of a tumor, and in some cases of an atypical picture, verification of the neoplastic process requires an in-depth comprehensive examination, long-term follow-up and presents certain difficulties [7, p. 96]. If there are such properties, the importance of timely identification of these neoplasms increases due to the fact that, having a benign character, they are nevertheless slowly growing tumors and can in some cases transform into more malignant forms [2. p. 8]. This paper is devoted to the discussion of the detection of ganglioglioma in combination with neuronal heterotopy of white matter with atypical clinical and radiological picture in a young adult patient.

Case report. The patient is a 26-years-old man with a diagnosis of generalized form of myasthenia gravis involving the cranio-bulbar muscles in a state of incomplete remission. The patient has been suffering from myasthenia since the age of 14. Having had a serious stressful reality situation, he at first noticed changes in the voice timbre; some time later the weakness of the proximal extremities muscles developed with dropping eyelids and bulbar dysfunction. Myasthenia gravis was diagnosed at the age of 15, and the patient was prescribed pyridostigmine bromide (*Kalymin*). The medicine has still being taken. During a comprehensive examination of the patient, magnetic resonance imaging (MRI) of the brain was performed, which revealed a lesion in the right temporal lobe unclear etiology. To clarify the changes, a CT-scan of the brain was performed with the following conclusion: the identified lesion in the right temporal lobe may be both post-contusive in nature, and represent the consequence of small hemorrhages in the structure of the arteriovenous malformation (Fig. 1).

When the patient reaches the age of 26 years a dynamic series of brain MRI scans were performed. The previously described pathological signal area was found in the right temporal lobe without signs of significant dynamics compared to the previous study (Fig. 2). According to routine 1.5 T MRI, the stable size of the lesion, together with the cortical / subcortical localization, the presence of a transmantle extension towards the lateral ventricle, a regionally thickened cortical plate, and local bluring of gray-white differentiation suggested the presence of focal cortical dysplasia (FCD) type II. In order to exclude a neoplastic process, a multimodal radiological examination was carried out. MRI 3.0 T was performed with modification of the epileptic scanning protocol for individual characteristics of the patient with additional tractography (DTI), MR perfusion with arterial spin label (ASL) and contrast enhancement. There was no perifocal reaction, mass effect and contrast enhancement. DTI showed deformation of neural pathways with no signs of infiltration or loss of integrity. However, ASL demonstrated local and regional hyperperfusion characteristic of grade III–IV glial tumors according to the WHO classification. The proposed PET-CT scan with 11C-methionine showed the accumulation of a radiopharmaceutical characteristic of grade I–II glioma in the structure of the lesion and confirmed the neoplasm (Fig. 2). Considering the high epileptogenicity of the localization of the pathological substrate, a 4-hour video EEG monitoring with daytime sleep was performed to exclude hidden epileptiform signs. However, no epileptic activity was found in the stages of wakefulness and sleep (Fig. 3).

The lesion was surgically removed. Postoperative MRI confirmed the total resection of the pathological substrate and adjacent tissue. Histological examination identified the ganglioglioma WHO grade I (Fig. 4).

On the pre-surgical MRI, the state of the cortical plate within the structure of the pathological substrate demonstrates a perifocal disturbance of gray-white matter differentiation and an area of dysgyria with an unevenly thickened cortical plate (Fig. 2 *a, b*). Upon re-examination of all available tissue blocks, tumor tissue together with neocortex and underlying white matter were more closely observed. Neoplastic tissue had a typical histological structure of ganglioglioma represented by two types of cellular elements. The neuronal component consisted of large ganglion cells and dysmorphic neurons surrounded by tumoral glial cells.

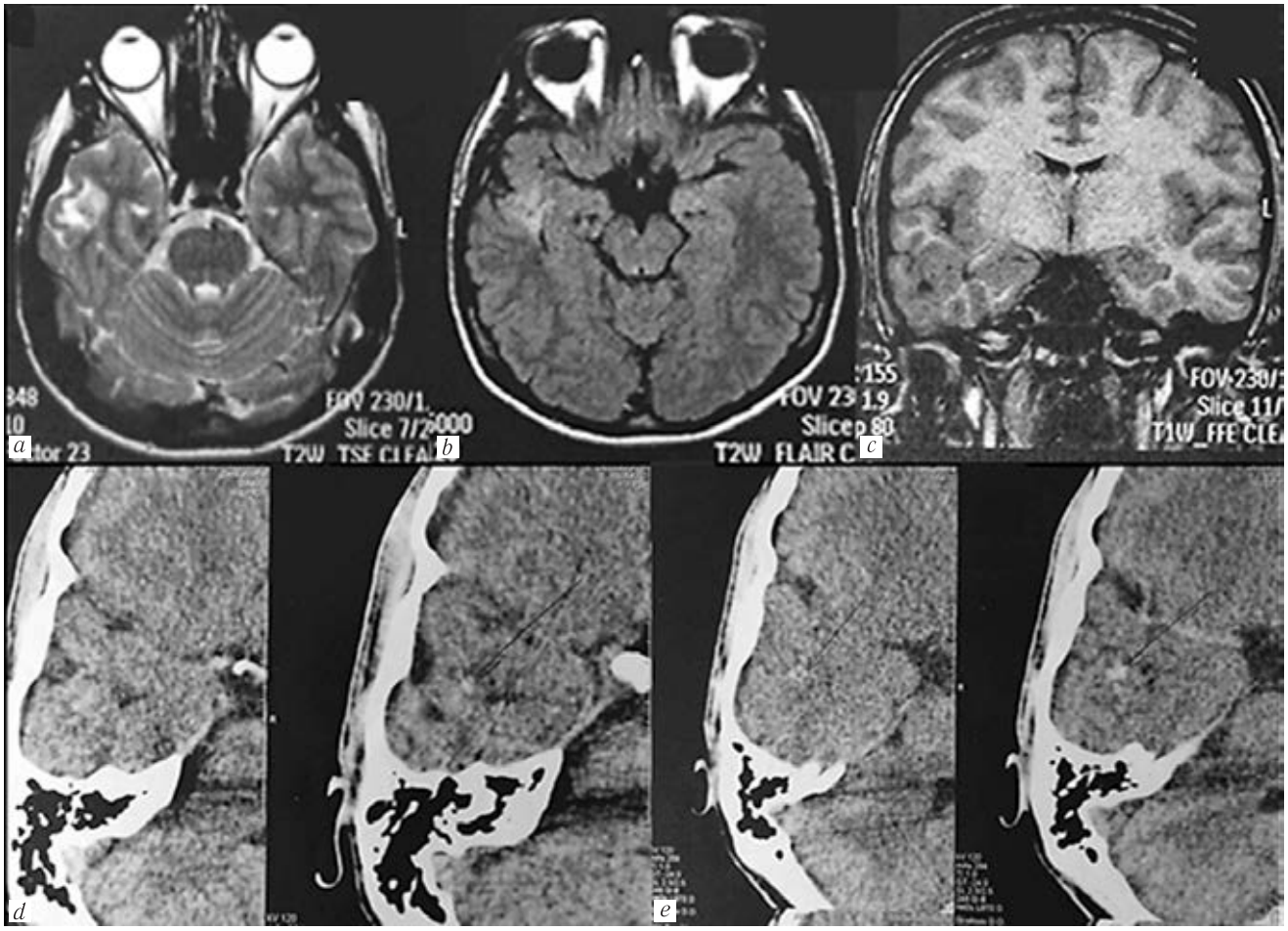

Рис. 1. Пациент С. 15 лет. Результаты МРТ и КТ головного мозга. 1,5 Т МРТ показала участок патологического сигнала в правой височной доле в T2, FLAIR (*a, b*) и T1 (*c*). Участок демонстрирует трансмантийный признак, распространяющийся от височного рога гомолатерального бокового желудочка к корковой пластинке, без масс-эффекта и перифокального отека. Контрастное усиление не проводилось. На КТ выявлены очаги повышенной плотности до 59 единиц Хаунсфилда размерами 5,0×4,7 мм, 3,0×2,0 мм и 2,0×1,0 мм в базальных отделах правой височной доли, типичной для кальцинатов (*d, e*). Контрастное усиление также не проводилось

Fig. 1. Patient 15 years old Results of MRI and CT scan of the brain. 1,5 T MRI showed a pathological signal in the right temporal lobe inT2, FLAIR (*a, b*) and T1 (*c*). Transmantle signs preading from the temporal horn of the same side lateral ventricle to the cortical plate, without mass effect and perifocal edema. Contrast enhancement was not performed. CT-scan showed foci of increased density up to 59 Hounsfield units in size 5,0×4,7 mm, 3,0×2,0 mm, and 2,0×1,0 mm in the basal parts of the right temporal lobe typical for calcifications (*d, e*). Contrast enhancement was not performed

Mitotic activity of the tumor could not be determined, necrosis or signs of vascular proliferation were not detected. In some areas, the tumor location was very close to the cortex, but the cortex's hexalaminar structure was preserved. Cortical areas without tumor connection presented without architectural disturbance. However, in the underlying white matter pronounced neuronal heterotopy was observed. Cytological abnormalities (i.e., balloon cells and dysmorphic neurons) characteristic of FCD IIb were not found as stainings for neurofilament and vimentin were both negative. Diagnosis: Ganglioglioma, WHO grade I, with heterotopic neurons in white matter (Fig. 5).

The postoperative follow-up lasted three years. There were no fixed episodes of loss of consciousness, seizures or changes in neurological status. We have continued to observe the patient with dynamic studies of MRI and video-EEG monitoring. Any evidence for the presence of a residual tissue fragment, recurrence of the tumor, or epileptic activity has not been observed.

Discussion. This paper discusses the case of the young adult patient with ganglioglioma in combination with neuronal heterotopy of white matter with a reliably established absence of epilepsy. These tumors are considered to be biologically stable without tendency to progression, and usually require surgery in the case of incurable epilepsy. The average age of patients at the onset of epilepsy is approximately 12,8 years [2, p. 3; 8, p. 42]. As mentioned above, gangliogliomas not always demonstrate typical neuroradiological signs to be characteristic for tumors. That is the reason why differential diagnosis of these tumors, and even in some cases verification of neoplastic process requires a long follow-up and is associated with certain difficulties [7, p. 96; 9, p. 1446]. In our case, the ganglioglioma looked like a

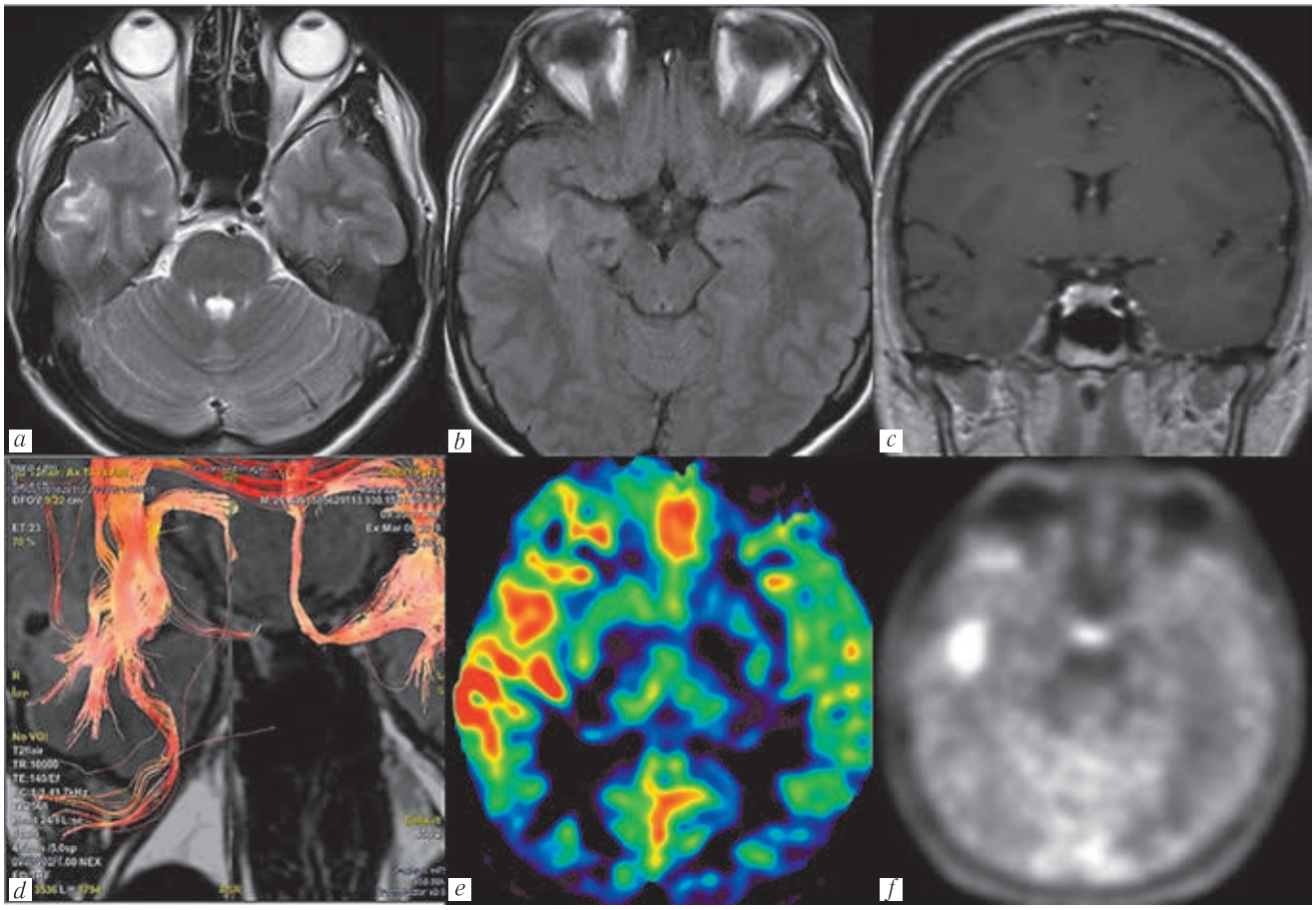

Рис. 2. Мультимодальная предоперационная оценка, включающая рутинную МРТ 1,5 Т и 3,0 Т по протоколу эпилептического сканирования, ПЭТ КТ. 1,5 Т МРТ выявила корково-подкорковый субстрат с признаками регионарного нарушения корковой организации, треугольной конфигурации, наличием мелких кист в структуре и трансмантийного признака хорошо видного в режиме FLAIR. Отсутствие перифокальной реакции, масс-эффекта или контрастного усиления, трансформацию размеров и конфигурации в течение восьми лет (*a, b, c*). 3,0 Т МРТ на трактографии (DTI) показала деформацию проводящих путей без признаков инфильтрации или нарушения целостности (*d*). Бесконтрастная МР – перфузия (ASL) продемонстрировала локальную и региональную гиперперфузию (*e*). ПЭТ КТ показала накопление радиофармпрепарата (^{11}С-метионин) в структуре патологического субстрата (*f*)

Fig. 2. Multimodal pre-surgical evaluation including 1.5 T and 3.0 T MRI using epilepsy protocol, PET CT.1.5 TMRI showed a cortical-subcortical substrate with signs of regional disturbance of the cortical organization, triangular configuration, small cysts in the structure, and a transmantle sign in the FLAIR mode. No perifocal reaction, mass effect or contrast enhancement; transformation in size and configuration were observed for eight years (*a, b, c*). 3.0 T MRI DTI showed deformation of neuronal pathways without signs of infiltration or integrity loss (*d*). ASL demonstrated local and regional hyperperfusion (*e*). PET CT showed accumulation of radiopharmaceutical drug (^{11}C-methionine) in the structure of the pathological substrate (*f*)

dynamically stable contrast-negative pathological focus, transmantle spreading from the temporal horn of the right lateral ventricle to the cortical plate of the inferior and middle temporal gyrus, simulating the radiological picture of FCD. However, the results of ASL and PET CT demonstrated a neoplastic process, and its values were characteristic of more malignant growth than grade I which allowed for surgery. This was later refuted by histological examination showing a ganglioglioma WHO grade I. In addition to the histological signs of ganglioglioma, heterotopic neurons in the underlying white matter were observed with a relatively preserved structure of neocortex. Moreover, fragments of tumor infiltrating (or, in other words, tumor satellite clusters) the peritumoral neocortex were revealed. Few reports are known to confirm that some gangliogliomas are not manifested by epileptic seizures in patients of different ages. The information given in a published article is considered the most interesting. They said that in twelve patients from twenty-four ones the gangliogliomas were localized in the temporal lobe, 5 of them had no epileptic seizures at the time of performing surgery. Two patients with the temporal tumor and without epilepsy underwent the surgery at the age of 23 and 32 correspondingly. At the same time the authors note that postoperative electroencephalographic examination was performed only for patients with epileptic seizures in medical history, but whether it was routine EEG or video EEG monitoring of daytime or nighttime sleep is not reported in the paper. It does not allow to exclude the presence of epileptic activity in patients without seizures at the time of surgery. Moreover, just

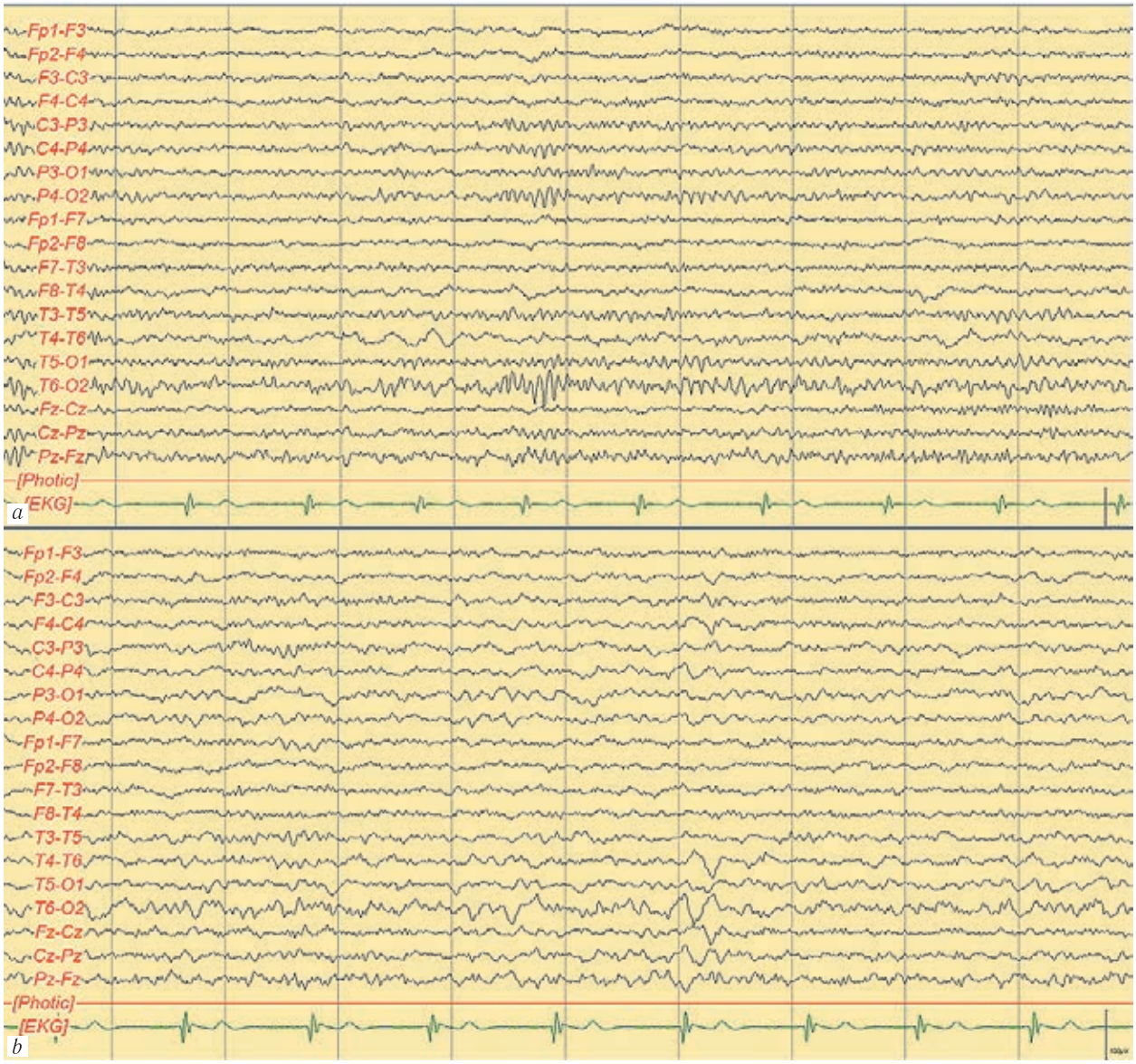

Рис. 3. Результаты видео-ЭЭГ мониторинга. Амплитудная асимметрия альфа-ритма ЭЭГ в бодрствовании D>S. Регионарное неравномерное замедление в тета- и дельта-диапазонах в правой височной доле (*a*). На кривых ЭЭГ в состоянии сна, наблюдается нарастание выраженности регионарного замедления в правой височной доле. Однако при ЭЭГ-мониторинге сна признаков эпилептиформных разрядов не обнаружено (*b*).

Fig. 3. Results of video-EEG monitoring. Wake EEG amplitude asymmetry of alpha rhythm D>S. Regional irregular slowing in theta- and delta-diapason from the right temporal lobe (*a*). Sleep EEG at sleep state is seen the increasing the expression of the regional slowing from the right temporal lobe. However, there were no signs of epileptiform discharges during sleep EEG-monitoring (*b*)

in a few medical histories of patients undergone epileptic surgery there is the reference of the relation the tumor to neocortex and its resection. There are no data about the degree of the cortex affection in patients with temporal lobe tumors but without epilepsy neither in the results nor in the discussion of the research [10, p. 408–410]. It also should be noted that the majority of non-epileptogenic gangliogliomas in a number of publications were located in the deep matter of the cerebral hemispheres or infratentorially [10, p. 408; 11, p. 4]. In a previous paper devoted to the radiological examination of these tumors, we had described three non-epileptogenic supratentorial gangliogliomas, including the patient in question, and only in this particular case the tumor was intimately adhered to the cortex infiltrating it with tumor satellites. In one case the anaplastic ganglioglioma WHOIII grade was localized in the lateral ventricle; the patient was operated immediately after tumor detection due to its aggressive growth and progressing clinical symptoms. In another patient, the tumor was localized in the deep white matter of the frontal lobe, had significant (large) proportions, a cystic-solid structure and patterns of contrast enhancement. A desmoplastic infantile ganglioglioma was revealed in histological examination. The origin of tumor-related epilepsy seemed to be multifactorial. There is a believe that several factors are believed to be predisposing for the development of epilepsy in patients

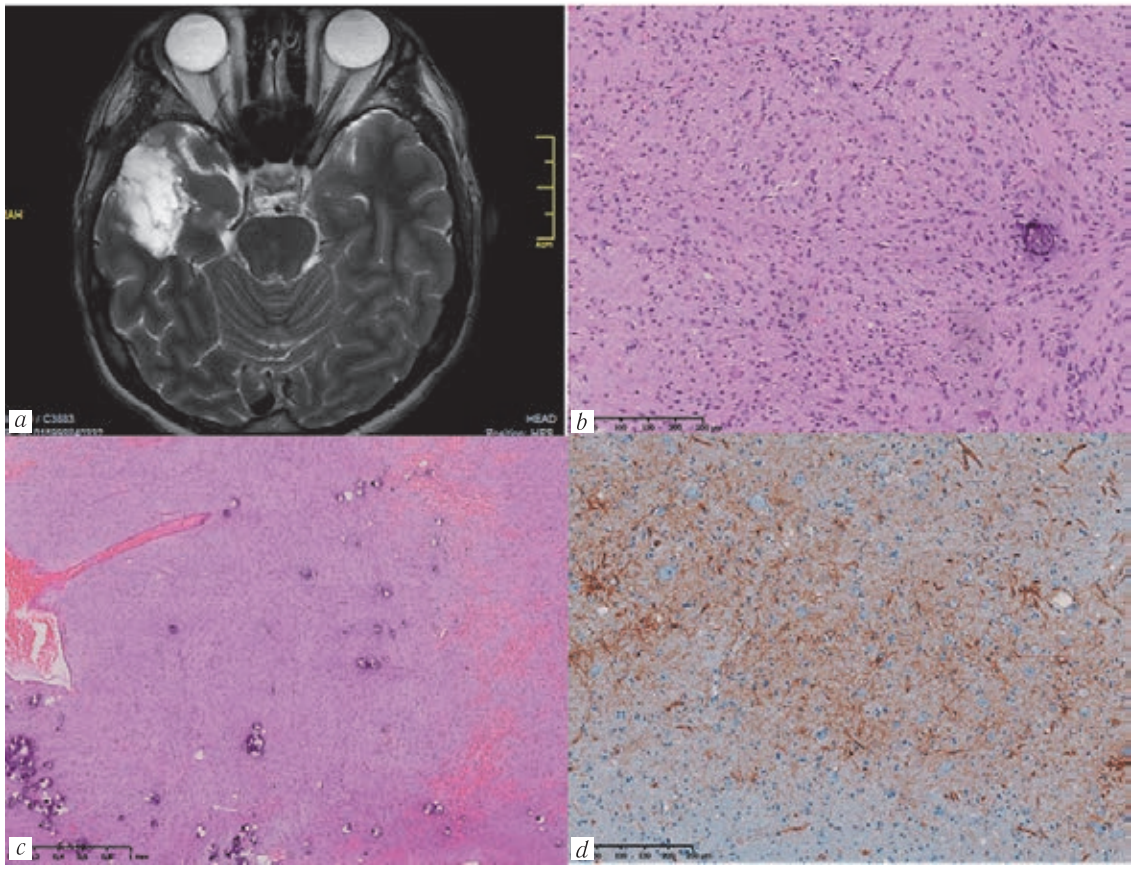

Рис. 4. Результаты послеоперационной МРТ и гистологического исследования. МРТ показала тотальную резекцию патологического корково/подкоркового субстрата вместе с перифокальной кортикальной пластинкой и трансмантийным признаком (*a*). Окраска гематоксилином и эозином показала опухолевую ткань с микрокальцинатами, состоящую из двух типов клеток - нейрональных и глиальных (*b, c*). В опухолевой ткани отмечена фокальная экспрессия CD34, характерная для ганглиоглиомы, иммунная окраска (*d*)

Fig. 4. Results of postoperative MRI and histological examination. MRI showed total resection of the pathological cortical / subcortical substrate together with perifocal cortical plate and the transmantle sign (*a*). Hematoxylin and eosin stain showed tumor tissue with microcalcifications, consisting of two types of cells — neuronal and glial (*b, c*). Focal expression of CD34 to be characteristic for ganglioglioma was noted in the tumor tissue, immune stain (*d*)

with intracerebral tumors, such as histological type, age, tumor location, and genetic and peritumoral changes in the brain [12, p. 421]. Changes in peritumoral tissue can dramatically alter neuronal and glial homeostasis and microenvironment in favor of a proepileptogenic condition [2, p. 7]. Moreover, two main hypotheses — tumor-centric and epileptocentric — were proposed, but they are relevant for gliomas of low malignancy on which experimental researches have been conducted [13, p. 30–31]. However, currently the problem of how and why the tumor is involved in the development of epileptogenesis is still unclarified. Gangliogliomas predominate quantitatively in the LEAT group. They are often combined with focal cortical dysplasia (FCD IIIb ILAE 2011), and heterotopy of white matter neurons or small satellite tumors (tumor satellite clusters) penetrating into the neighboring or distant neocortex [2, p 7]. The question of whether the combination or any of these signs individually contributes to an increase in the epileptogenic potential of gangliogliomas currently remains unanswered and requires clarification and further studies. But the absence of epilepsy in an adult patient with such a potentially epileptogenic structural base as a combination of ganglioglioma, neuronal heterotopia of peritumoral white matter, infiltration of the peritumoral cortex by tumor cells, and its localization in the neocortex, requires a more detailed study of possible mechanisms that inhibit epileptogenesis or responsible for it. Another interesting observation is worthy of notice and discussion. Quite often, heterotopic neurons are detected in the neocortex in the 1st layer of the cortex and white matter, which is designated by the term microdisgenesis. This is what that was found in patient C., during morphological examination. ILAE Commission in 2011 presented a new classification of FCD, where the group FCD III to be by definition a combination of a violation of the architectonics of the cortex (cortical lamination abnormalities, which, in turn, is classified as FCD type I) was identified; and in the presence of any additional structural pathology is divided into the following subtypes: the combination of neocortex structural disorders with hippocampal sclerosis is subtype IIIa, with tumor presence is subtype

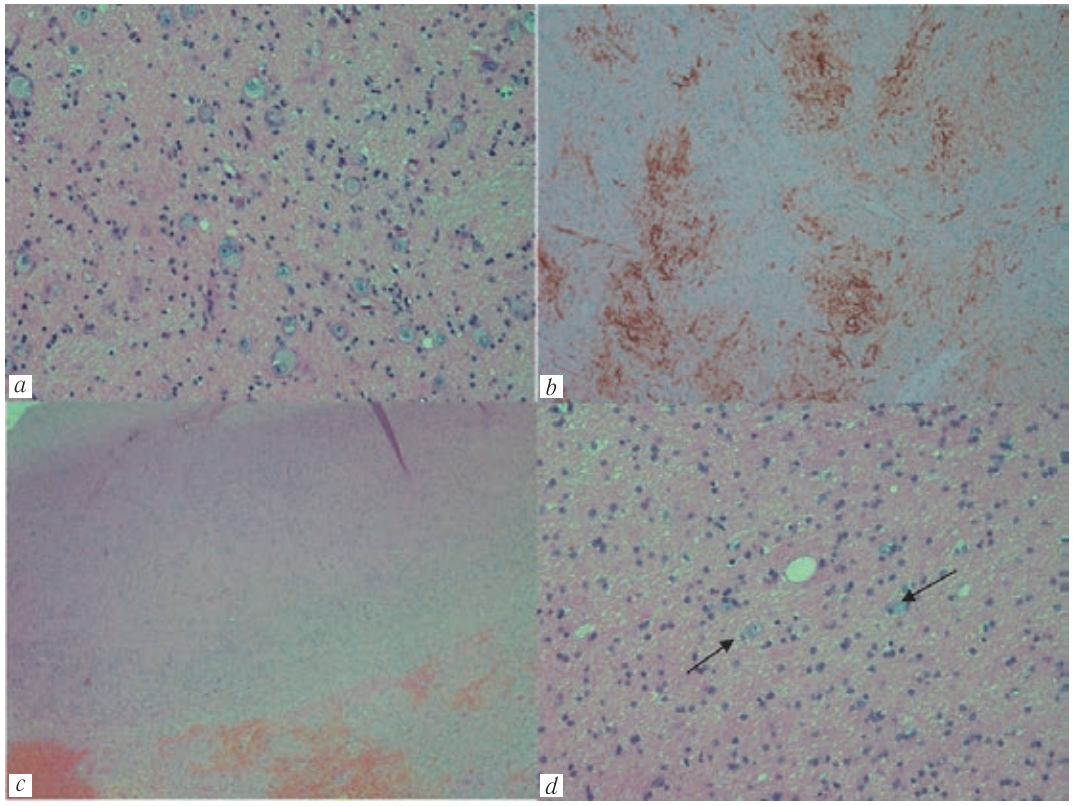

Рис. 5. Результаты пересмотра гистологических препаратов. Гистологическая картина соответствовала ганглиоглиоме, состоящей из крупных ганглиозных клеток с глиальной частью; H&E, ×200 (*a*). В опухолевой ткани отмечена очаговая экспрессия CD34, характерная для ганглиоглиомы; иммунная окраска, ×100 (*b*). Опухоль (нижняя часть) частично прилегала очень близко к неокортексу, но гистоархитектоника коры не была нарушена; H&E, ×40 (*c*). В остальных участках образца, где не было связи с опухолью, структура коры не изменена. Гетеротопические нейроны (стрелки) определялись субкортикально в белом веществе. H&E, ×200 (*d*)

Fig. 5. Results of revision of histological preparations. Histological picture corresponded to the ganglioglioma consisting of large ganglion cells along with glial portion; H&E, ×200 (*a*). Focal expression of CD34 to be characteristic for ganglioglioma was noted in the tumor tissue; immune stain, ×100 (*b*). The tumor (lower part) partially lied very close to the neocortex, but the histoarchitectonics of the cortex was not disrupted; H&E, ×40 (*c*). In other parts of the sample, where there was no association with the tumor, the structure of the cortex was not changed. Heterotopic neurons (arrows) were visualized subcortical in white matter. H&E, ×200 (*d*)

IIIb, with vascular malformation is subtype IIIc, with a variety of pathology that occurred at young age (trauma, ischemia, encephalitis) is classified as subtype IIId [14, p. 160]. Microdisgenesis, the role of which in epileptogenesis has not yet been fully understood, is attributed to the so-called small malformations of the cerebral cortex. Nevertheless, after the classification having been introduced, in some publications authors describing them as being revealed close to the main lesion classify such combinations as FCD type III. For example, in the S. Itamura et al. (2019), in two of the three cases presented, the histological analysis indicates the preservation of the normal cortex structure, and the changes appear only in an excessive number of neurons and glial cell sin the white matter with intact cortical architecture and absence of aberrant cells (neuronal heterotopia) [15, p. 3]. Nevertheless, the authors believe that structural changes only in the underlying white matter with normal cortical architectonics can be regarded as a version of FCDIII. In another paper, the authors explicitly say that on revealing the microdisgenesis with hippocampal sclerosis the diagnosis is defined as type CD IIIa [16, p. 111]. Based on this, a proposal for a similar diagnostic approach may be suggested for discussion: with the existence of a tumor, the presence of a normal neocortex and neuronal heterotopy in the underlying white matter in the adjacent zone, whether it is possible to regard such a phenomena as a FCD IIIb version?

The model of a multimodal neuroimaging algorithm for verifying the tumor process on subcortical/cortical pathological substrates of unclear etiology requires additional analyzes on a larger number of patients and seems relevant.

There are reports in the literature that gangliogliomas can be hyperperfusional despite the low grade of the tumor, which is not typical for gliomas grade I–II and DNT [17. p 398]. The mandatory inclusion of MR-perfusion (ASL/DSC) in the study protocol when a pathological substrate of unclear etiology is detected can significantly help in the verification of neoplasm already at this stage. This theory requires further research.

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Kislyakov Alexey N.— conducted histological verification of the primary morphological material and provided again upon request. He was engaged in the preparation of paraffin blocks and glasses for sending for independent rechecking to Institute of Neuropathology University Hospital Erlangen, Germany. Took part in writing part of the article devoted to the verification of histological diagnosis and discussion;

Kholin Alexey A.— conducted a neurological examination of the patient, analysis of preoperative video EEG video monitoring for the absence of epilepsy at the time of surgery. Took part in the writing of a part of the article devoted to clinical symptoms and discussion;

Gazdieva Khava S.— conducted a neurological examination of the patient before and after surgery. Took part in the writing of a part of the article devoted to clinical symptoms and discussion;

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Zavadenko Nikolay N.— has coordinated the examination of the patient using modern methods, interdisciplinary interaction of specialists taking part in the study described in the article. Participated in the writing of the introduction and discussion;

Kobow Katja — participated in the interdisciplinary morphological diagnosis being one of the members of international researchers group, translated and adapted the text of the manuscript during it preparation for publication.

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