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Epilepsy-Associated Glioneuronal Tumors

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Objectives. To summarize data on the radiological and histological diagnosis of benign tumors associated with epilepsy and to provide recommendations for the surgical treatment of epilepsy in these tumors. **Materials and methods**. Articles from PubMed and our own clinical data were used. **Results**. Benign glioneuronal tumors are the second most common cause of structural drug-resistant epilepsy in adults after hippocampal sclerosis. Extremely slow growth, location in the cerebral cortex, the presence of neuronal tissue in the tumor stroma, and concomitant epilepsy are common features of these neoplasms. The difficulty of treating glioneuronal tumors lies in the combination of epileptological and neurooncological aspects. The epileptogenic zone may extend beyond the tumor, so isolated resection may not be enough to stop seizures. **Conclusions**. From a neurooncological point of view, glioneuronal tumors are neoplasms with a very low proliferative potential, but careful differential diagnosis against more aggressive glial tumors is required; this can be extremely difficult but can be achieved using histological and immunohistochemical approaches.

Keywords: epilepsy, surgery, tumor, ganglioglioma, dysembryoplastic neuroepithelial tumor.

Almost any tumor involving the cerebral cortex can cause epileptic seizures, regardless of its histological nature and degree of malignancy [1]. At the same time, in the context of epileptology, special attention is paid to benign glioneuronal tumors not causing significant neurological deficit but associated predominantly with epilepsy. In the literature, these tumors are classified as a separate group called long-term epilepsy-associated tumors (LEAT) or are known by the less official term epileptoma [1–6]. Tumors of this group are characterized by the presence of differentiated neuronal tissue within their structure. Most have grade I malignancy (M) on the WHO classification, and gangliogliomas and dysembryoplastic neuroepithelial tumors (DNET) are more common than others in this group [4, 6, 7]. The distinguishing features of these tumors include an early age of onset of seizures, which are the only manifestation of disease, an extremely low growth rate, and localization in the cerebral cortex (more often the medial part of the temporal lobe). Due to the fact that these tumors have an exceptionally favorable prognosis, with high survival rates and a minimal likelihood of progression, epileptological indications are in the foreground when deciding whether to perform surgery. In the case of glioneuronal tumors of medial temporal localization, achievement of freedom from seizures may require extensive resection to the extent of temporal lobectomy. Video-EEG monitoring and MRI using the epilepsy protocol are necessary steps in determining the location and volume of the epileptogenic zone. In addition, the patient's neuropsychological status (especially assessment of memory function on resection of the dominant hippocampus), the duration of epilepsy, the presence of drug resistance, and the proximity of the tumor to a functionally significant area are also important factors in determining the indications for surgery and the volume of resection. These factors define the importance of using a multidisciplinary approach in the treatment of patients with these tumors.

In 2021, the WHO published the 5th edition of the Classification of Tumors of the Central Nervous System, where increased attention was paid to advances in molecu-

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lar genetic diagnosis and low-grade epilepsy-associated glioneuronal tumors remained in subheadings within the heading *Gliomas, glioneuronal tumors and neuronal tumors*, i.e., *glioneuronal and neuronal tumors* (ganglioglioma, DNET, papillary glioneuronal tumor, multinodular vacuolating neuronal tumor), *diffuse gliomas of low malignancy of childhood* (diffuse astrocytoma, angiocentric glioma, and a new type of tumor – polymorphic neuroepithelial tumor of the young, with low malignancy), and *circumscribed astrocytic gliomas* (pilocytic astrocytoma, pleomorphic xanthoastrocytoma) [8, 9]. Isomorphic diffuse glioma is also identified among epilepsy-associated tumors, but has not been included in the official WHO classification [6, 10].

Radiological Diagnosis of Glioneuronal Tumors. In most cases, epileptogenic glioneuronal tumors are located in the medial parts of the temporal lobe, are small in size, and represent a clearly circumscribed area of altered MR signal in the projection of the uncus, amygdala, and hippocampus, without signs of perifocal edema. A characteristic feature of these tumors, and especially of DNET, is their "bubbly" structure, made up of small cysts; contrast may accumulate and calcifications may be present [11]. Glioneuronal tumors of non-mediotemporal location are generally small in size, present in the cerebral cortex, clearly demarcated, and without signs of perifocal edema; a deformity of the inner plate of the skull bone is often found over the tumor, indicating the age of the pathological process.

Regardless of whether epilepsy is controlled by drugs or not, it is fundamentally important to rule out astrocytoma of WHO M II–III, as the neurooncological indications for surgery are more important when this is present. The main warning sign of a non-malignant tumor is a short (less than 1 year) history of illness in combination with other factors: late age of onset of symptoms, the presence of perifocal edema on MRI, and accumulation of contrast medium by the tumor. Despite the fact that glioneuronal tumors may have a number of distinctive features on MRI, the diagnosis should take account of the clinical presentation, which is characterized by the onset of seizures in adolescence (mean age 16 years) and long-term (mean 12 years) epilepsy [4, 5]. PET with methionine may provide some help with the diagnosis of glioneuronal tumors. Of all glioneuronal tumors, only DNEO may not accumulate methionine or have a moderate index of accumulation. On the other hand, the index of accumulation in gangliogliomas can vary in the same way as with WHO M II–IV astrocytomas – from moderate to elevated. In this regard, only the absence of methionine accumulation can strongly indicate the presence of DNET. A moderate index of accumulation can be seen in DNET, ganglioglioma, and WHO M II astrocytoma [12, 13].

In relation to the duration of epilepsy, it should be borne in mind that the patient may not interpret olfactory or abdominal auras as seizures, which is important to clarify in history-taking. The reasons for the long interval between the onset of seizures and surgery for glioneuronal tumors can be linked both with insufficient awareness among the medical community and patients themselves about the opportunities for surgical treatment of epilepsy and with the late diagnosis of focal epileptic seizures (clinical case 1).

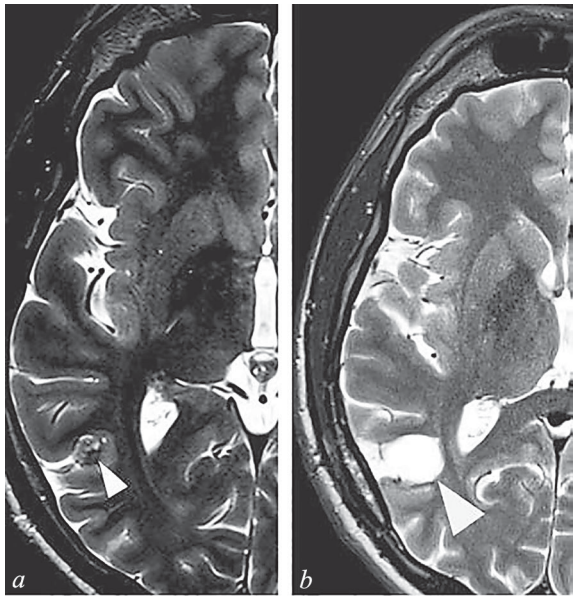

Fig. 1. Axial MRI scan. *a*) T2-weighted high-resolution image (preoperative); *b*) T2-weighted image (postoperative).

Clinical Case 1. A 31-year-old man had been followed from age 13 years with a diagnosis of "cryptogenic epilepsy." Drug history: valproic acid formulations, carbamazepine, topiramate, clonazepam, benzonal. Routine 15-minute recordings showed epileptiform activity predominantly in the right hemisphere of the brain. Brain MRI (1.5 T): no signs of focal pathology. These data formed the basis for a detailed pre-surgical examination with video-EEG monitoring and high-resolution MRI.

Video-EEG monitoring revealed epileptic seizures that began with freezing, followed by oral automatisms, turning of the head to the right, clonus in the left half of the face, and version of the head to the left. During the interictal period, epileptiform activity predominated in the right frontotemporal region with propagation to the posterior temporal region. Seizure onset was characterized by a diffuse flattening of the EEG on the right; a focal ictal pattern was recorded in the frontopolar leads on the right. Thus, the symptoms during seizures, along with ictal and interictal epileptiform activity, indicated involvement of a large area of the right frontotemporal region. High-resolution MRI (Fig. 1, *a*) revealed a small-volume mass in the right lower parietal lobe (arrows) and the decision was taken to perform focal resection of this mass. The postoperative MRI picture is shown in Fig. 1, *b*. After surgery, seizures stopped completely (follow-up two years). Histological conclusion: ganglioglioma, positive expression of GFAP, synaptophysin, neurofilaments and CD34; Ki-67 labeling index <5%.

The apparent disagreement between the location of the tumor and the clinical and electroencephalographic picture is explained by associative anatomical connections between the inferior parietal lobe and the fronto-opercular area, mediated mainly by the superior longitudinal and arcuate fascicles (Fig. 2) [14–17]. This explains the rapid propagation of epileptic activity to a large surface of the frontal cortex, which is typical of parietal epilepsy, where the scalp EEG rarely localizes epileptiform activity in the parietal region [18].

Histological and Molecular Profile of Glioneuronal Tumors. With the advent of new immunohistochemical and genetic methods for studying tumor tissue, it has become apparent that several types of glioneuronal tumors diagnosed using basic hematoxylin and eosin staining hide a whole spectrum of tumors, in some cases bearing mixed molecular and histological characteristics [19–21]. This gives rise to discrepancies in tumor diagnostic criteria between different laboratories; for example, the frequency of detection of DNET and gangliogliomas varies from 7% to 70%, not to mention the fact that some publications discriminate several histological and radiological types of a single dysembryoplastic neuroepithelial tumor [4, 21]. The main task in histological diagnosis is that of determining the potential of the tumor for further growth and malignancy. In this regard, overdiagnosis of WHO M II gliomas (diffuse astrocytomas or oligodendrogliomas) may lead to the prescription of adjuvant treatment which has no affect on the prognosis. On the other hand, diagnosis of a tumor as WHO M I, with its higher malignant potential, carries obvious risks for the patient. The proliferative potential of glioneuronal tumors is very low: it is believed that the probability of recurrence of DNET is about 1%, with a slightly higher risk in ganglioglioma – about 5%. However, it is not clear whether these rare cases are the result of inadequate differential diagnosis of WHO M II astrocytoma and glioneuronal tumors [20, 22]. To solve these problems, the search for the optimal classification of glioneuronal tumors, taking into account the molecular and genetic profiles of these neoplasms, is currently under way [19–21]. Apart from gangliogliomas and DNET, the category of epileptogenic glioneuronal tumors also includes such recently identified types as angiocentric glioma [23] and isomorphic astrocytoma [10]. Some authors hold that supratentorial piloid astrocytomas (WHO M I) and pleomorphic xanthoastrocytomas (WHO M II) may also meet the criteria for this group [20].

Ganglioglioma. Ganglioglioma is one of the most common epileptogenic glioneuronal tumors. In its structure, this tumor contains nodes or compact aggregates of dysplastic neurons with enlarged deformed bodies and large nuclei within (Fig. 3, *a*). Immunohistochemically, these neurons show the presence of synaptophysin, neuronal nuclear antigen (NeuN), and microtubule-associated protein (MAP2). Aggregates of CD34-positive cells are found near neurons in more than 80% of cases. There is proliferation of astroglia and oligodendroglia, along with calcification, and lymphoid infiltrates are often detected (Fig. 3, *b*) [24]. Gangliogliomas are WHO M I, which determines the long-term survival of patients and a low probability of recurrence. In the histological diagnosis of tumors associated with long-term epilepsy, it is important to focus on the search for areas containing ganglion cells. It is equally important to recognize infiltrative diffuse astrocytoma, which can overgrow areas of the neocortex and deform neurons, such that differential diagnosis of astrocytoma and ganglioglioma using standard hematoxylin and eosin staining can be very difficult, especially when the amount of pathological material available is small or severely fragmented. Staining for NeuN is essential in these cases, as this can reveal areas of displaced neocortex, sometimes with a preserved laminar structure, in diffuse glioma. A small (5%) proportion of gangliogliomas have high mitotic activity with a high (>10%) Ki-67 index and are classified as anaplastic with WHO M III [6]. The probability of transformation of ganglioglioma WHO M I into anaplastic varies from 0.6% to 2.6% [24]. Among the risk factors for the progression of gangliogliomas are age over 40 years, extratemporal location of tumor, signs of atypia, and incomplete resection [25]. A useful role in the differential diagnosis with diffuse astrocytomas can be played by analysis for a mutant variant of isocitrate dehydrogenase 1 (IDH1) [26]. Detection of this marker may predict a more aggressive variant of the tumor, and some authors believe that recurrent gangliogliomas are in fact misclassified standard IDH1-positive WHO M II gliomas [27].

Dysembryoplastic Neuroepithelial Tumor. DNET, in terms of histological structure and growth rate, most closely resemble hamartomas: neuroepithelial cells of the oligodendroglial and astrocyte series are present and there is almost always an early onset of epileptic seizures [11]. These tumors have a nodular structure and are located in the cerebral cortex. Moreover, they most often occur in the dentate gyrus, amygdala, temporal neocortex, and periventricular region, which can be explained by the presence of pluripotent stem cells, from which they grow, in these areas in the postnatal period. A characteristic feature of DNET consists of so-called glioneuronal elements (GNE), which are found in 79% of cases and consist of a specific pattern of growth of oligodendroglial cells oriented in microcolumns, often around vessels; also areas of myxoid matrix including occasional neurons are also noted (Fig. 3, *c*) [11]. Depending on the histological structure of DNET, tumors can be simple forms, when the bulk of the tumor is represented by a glioneuronal element, or complex, when, there are both GNE and nodes of astrocytic and oligodendroglial tissue, as well as areas of focal cortical dysplasia [28]. Nonspecific forms are diagnosed when a tumor that is clinically and radiologically similar to DNET does not contain GNE and is made up of nodes of glial tissue, as in complex forms. These histological types have their own characteristic signs on MRI and can serve as a guideline for determining the extent of resection. In particular, in nonspecific

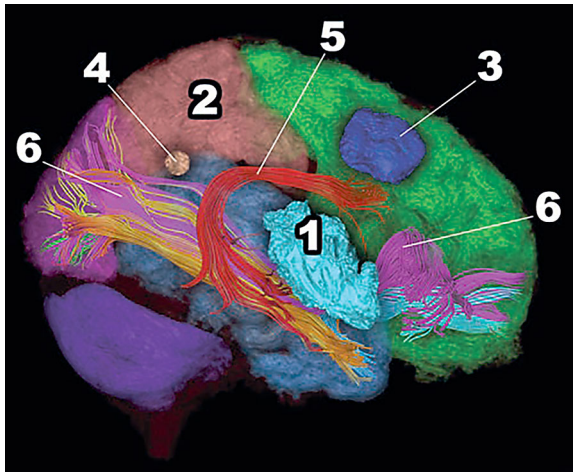

Fig. 2. 3D reconstruction based on MRI data. Numbers indicate the brain areas responsible for producing symptoms during seizures in the patient: *1*) insula (turquoise) and frontotemporal operculum – oroalimentary automatisms; *2*) parietal lobe – version of the head (parietal gaze center); *3*) frontal gaze center – version of the head and eyes; *4*) tumor; *5*) arcuate fasciculus; *6*) superior longitudinal fasciculus.

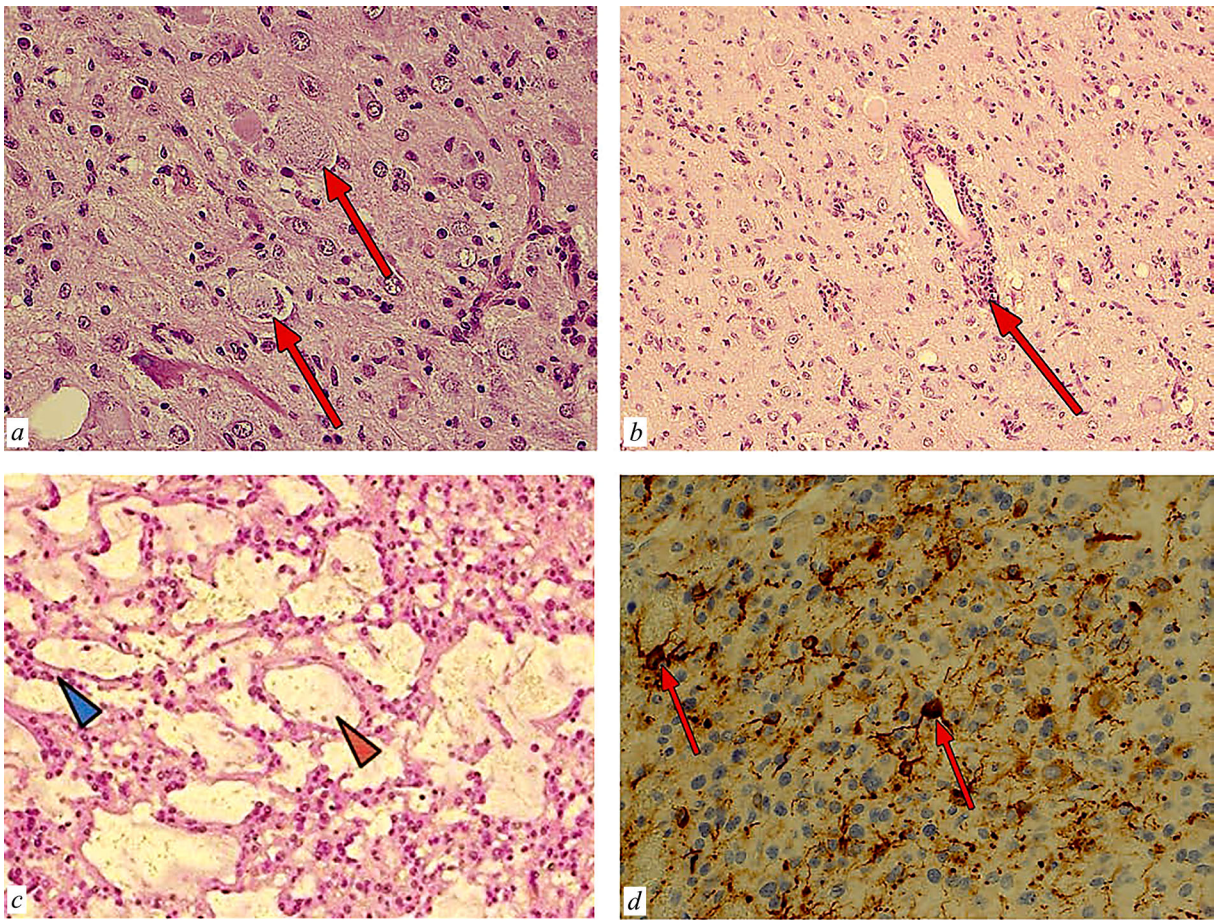

Fig. 3. Histological features of gangliogliomas (*a–b*, stained with hematoxylin and eosin) and DNET (*c–d*, magnification ×200). *a*) Ganglioglioma at high magnification (×400) – large ganglion cells are visible (arrows); *b*) the same at low magnification – perivascular lymphoid infiltration is visible (arrow); *c*) simple DNET with cells (blue arrow) in the mucoid matrix (red arrow), stained with hematoxylin and eosin; *d*) positive MAP2 expression in floating neurons (arrows).

forms of medial temporal DNET, it is advisable to remove the hippocampus if there is no clear boundary between the tumor and normal medulla and there are areas of focal cortical dysplasia (FCD) in the adjacent cortex [29]. Difficulties

TABLE 1. Differential Diagnosis of Glioneuronal Tumors Based on Their Molecular Profile and Histological Features

Tumor type	CD34	MAP2	IDH1	Features of MAP2 expression	Histological features
Simple DNET	More often –	–/+	–	Only in floating neurons	GNE present
Complex DNET	–/+	–/+	–	Variable level of MAP2 expression in glial component	GNE and glial nodes
Diffuse DNET	More often +	More often +	–		May have very similar histological characteristics when stained with hematoxylin and eosin, when there is a small amount of material, or when there is no clear border between cortex and white matter due to fragmented removal
Ganglioglioma	+	–	–		
Oligodendroglioma	–	+	+	Diffuse MAP2 expression	
Pilocytic astrocytoma	–	+	–	MAP2 expression in the glial component	
Diffuse astrocytoma	–	+	+		
Pleomorphic xanthoastrocytoma	+	+	–		Large astroglial cells with excessive eosinophilic cytoplasm and multilobar nuclei. Glial cells with lipid inclusions
Angiocentric glioma	+	+	–		Growth of astrocytic cells around vessels

in histological diagnosis also arise in nonspecific forms, which may be similar to ganglioglioma, as well as diffuse or piloid astrocytoma, especially when a layer of glial tissue overgrows areas of the cerebral cortex, giving the impression of a glioneuronal tumor [30]. In these cases, immunohistochemical diagnosis plays a key role, in particular, examination of tumor tissue for CD34 and MAP2 markers [19, 31]. CD34 is detected during neurogenesis and is not expressed in the normal adult brain. MAP2, a type 2 microtubule-associated protein which regulates cytoskeletal functions, is actively expressed in neuroglial stem cells during brain formation. Normally, in the postnatal period, this marker is detected in neurons in the cerebral cortex and is absent from both astroglia and oligodendroglia. Nonspecific variants of DNET are positive for both MAP2 and CD34, in contrast to gangliogliomas which do not express MAP2 (Fig. 3, *d*). It is particularly important to exclude diffuse astrocytoma or WHO M II oligodendroglioma, and in this respect, analysis for the *IDH1* gene mutation, which is not detected in DNET but is characteristic of standard gliomas, is of diagnostic value [20]. It should be noted at this point that stereotaxic biopsy of these tumors is not advisable, as there is a risk of missing specific histological patterns due to insufficient yields of pathological material. DNET has WHO M I, and malignant transformation is extremely rare, occurring in less than 1% of cases. Tumor malignancy has been described in cases of extratemporal partially resected tumors, which justifies periodic follow-up MRI in these patients [11]. Histological and immunohistochemical features of glioneuronal tumors are systematized in Table 1.

Resection Volume of Glioneuronal Tumors of the Temporal Lobe. As noted above, the main objective of surgery for glioneuronal tumors is to free the patient of epileptic seizures. For tumors with temporal locations, the volume of tissue resection required to stop seizures may extend beyond the zone of altered MRI signal [32]. Thus, the scope of surgery can range from temporal lobectomy (case 2) to removal only of tumor-affected brain tissue (case 3). When a glioneuronal tumor is located outside the amygdalohippocampal complex, the question arises of the need to remove the amygdala and hippocampus, which are prone to independent epileptogenesis in temporal lobe epilepsy but often retain their functionality [33]. The scalp EEG does reliably determine whether or not the hippocampus is a source of epileptiform activity, as this is detected only when it propagates to a significant volume of the temporal lobe, and clinical manifestations of temporal seizures occur when epileptiform activity propagates to the symptom-generating parts of the brain adjacent to the Sylvian fissure. Thus, the EEG picture and the semiology of a seizure may be no different at the onset of a seizure in the hippocampus or in anatomically related areas of the temporal region, i.e., the amygdala, the pole of the temporal lobe, and the fusiform gyrus. It follows from this that EEG data and seizure semiotics alone cannot give an unambiguous indication of the required volume of resection [34–36]. Published data indicate that amygdalohippocampectomy in tumors of medial temporal localization gives the maximum chance of eliminating seizures [32, 37].

Clinical Case 2. The patient, 29 years old, female, suffered from epileptic seizures from age 19 years; seizures began with a feeling of fear, with loss of consciousness and freezing and the addition of oroalimentary and gestural automatisms. Carbamazepine and Depakine were ineffective. The EEG showed interictal epileptiform activity in the left frontotemporal region. FLAIR MRI showed hyperintense signals in the region of the left hippocampus (Fig. 4, *a*) and the pole of the left temporal lobe (Fig. 4, *b*). Attention is drawn to the extensive involvement of the medial structures – to the point of the transition of the parahippocampal gyrus into the lingual gyrus (indicated by the white line in Fig. 4, *a*). T2 (Fig. 4, *c*) and FLAIR (Fig. 4, *d*) images showed a cystic cavity in the region of the posterior hippocampus (black arrow with a white border). Of note is the absence of normal hippocampal structure on the left side as compared with the

right (Fig. 4, *e*). Amygdalohippocampectomy with removal of the parahippocampal gyrus and pole of the temporal lobe was performed (Fig. 4, *e*, *f*). The posterior border of the resection is at the level of the posterior edge of the quadrigeminal plate (Fig. 4, *f*). There were no seizures after the operation (follow-up period 1.5 years). Histological conclusion: hippocampus containing glial tumor, tumor cells expressing GFAP, synaptophysin, MAP2, and CD34, with low Ki-67; the data are more consistent with ganglioglioma. The cortex show derangement of radial architectonics with signs of neuronal heterotopy in the white matter. Conclusion: the morphological picture and immunophenotype correspond to the combined form of focal cortical dysplasia (FCD) IIIb.

On the other hand, temporal lobectomy on a routine basis is not justified, as many patients recover from epilepsy with less extensive resections [32, 33]. The volume of resection should be determined individually for each case, taking into account measures of the patient's verbal memory, quality of life, hemisphere dominance in speech function, preservation of hippocampal structure on MRI, the time of onset of epilepsy, and its duration. The risk of decreased verbal memory is greater in patients with damage to the dominant temporal lobe, normal neuropsychological status, and short duration of epilepsy [38]. In these cases, removal of the tumor alone is justified where there is no invasion into the amygdala and hippocampus.

Clinical Case 3. A 42-year-old female patient suffered from epileptic seizures in the form of freezing and oroalimentary automatisms for four years while taking therapeutic doses of topiramate and levetiracetam. The EEG showed interictal epileptiform activity in the right frontotemporal region. MRI showed a small tumor consisting of small cysts in the right middle temporal gyrus (Fig. 5, *a*) with deformities of the internal cortical plate (arrows). Given the absence of damage to the medial part of the temporal lobe and the limited nature of the tumor, resection of the tumor alone was performed (Fig. 5, *b*). There were no seizures after surgery (follow-up one year). Histological conclusion: DNET.

In diffuse variants of glioneuronal tumors with hippocampal invasion, amygdalohippocampectomy and removal of the temporal neocortex are justified (case 2); in this situation, the final diagnosis can be formulated as type IIIb FCD, where disorganization of the structure of the cerebral cortex is identified along with the tumor [39]. Removal of the non-dominant (usually right) hippocampus is not associated with any significant decrease in verbal memory or quality of life, so resection in the non-dominant temporal lobe can be more extensive in diffuse forms of glioneuronal tumors, where areas of FCD with individual tumor cells occur in the peritumor tissue [11, 32]. Given all these points, the decision on surgery and its scope should take place within the framework of a joint discussion between the neurosurgeon, epileptologist, radiologist and neuropsychologist.

Conclusions. One of the characteristics of glioneuronal tumors is a high level of histological heterogeneity: astroglial and oligodendroglial tumor components are interspersed with normal neurons, areas of lymphocytic infiltration, and calcifications; tumor growth patterns are also variable and may be nodular, papillary, or rosette-shaped. The variability of the morphology of these tumors causes significant divergence in histological diagnoses between different laboratories, often in the direction of overestimating the degree of malignancy. In the light of recent studies demonstrating the benefits of radiochemotherapy in gliomas of WHO M II [40–42], appropriate diagnosis of glioneuronal tumors is necessary to avoid prescribing unnecessary adjuvant treatment for these tumors. Evaluation of the molecular genetic profiles of tumors with assessment of the expression of CD34, MAP2, and the IDH1 mutant variant is necessary to exclude more aggressive variants of gliomas.

The authors declare no conflict of interest.

REFERENCES

1. M. Thom, I. Blümcke, and E. Aronica, "Long-term epilepsy-associated tumors," *Brain Pathol.*, **22**, No. 3, 350–379 (2012), https://doi.org/10.1111/j.1750-3639.2012.00582.x.
2. C. Luyken, I. Blümcke, R. Fimmers, et al., "The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects," *Epilepsia*, **44**, No. 6, 822–830 (2003), https://doi.org/10.1046/j.1528-1157.2003.56102.x.
3. J. S. Duncan and J. De Tisi, "MRI in the diagnosis and management of epileptomas," *Epilepsia*, **54**, Suppl. 9, 40–43 (2013), https://doi.org/10.1111/epi.12442.
4. I. Blumcke, E. Aronica, H. Urbach, et al., "A neuropathology-based approach to epilepsy surgery in brain tumors and proposal for a new terminology use for long-term epilepsy-associated brain tumors," *Acta Neuropathol.*, **128**, No. 1, 39–54 (2014), https://doi.org/10.1007/s00401-014-1288-9.
5. B. S. Kasper and E. M. Kasper, "New classification of epilepsy-related neoplasms: The clinical perspective," *Epilepsy Behav.*, **67**, 91–97 (2017), https://doi.org/10.1016/j.yebeh.2016.12.020.
6. V. S. Khalilov, A. A. Kholin, A. N. Kislyakov, et al., "Neuroradiological and pathomorphological features of epilepsy associated brain tumors," *Luch. Diagn. Ter.*, **12**, No. 2, 7–21 (2021, https://doi.org/10.22328/2079-5343-2021-12-2-7-21.
7. I. Blümcke, E. Aronica, A. Becker, et al., "Low-grade epilepsy-associated neuroepithelial tumours-the 2016 WHO classification," *Nat. Rev. Neurol.*, **12**, No. 12, 732–740 (2016), https://doi.org/10.1038/nrneurol.2016.173.
8. D. N. Louis, A. Perry, P. Wesseling, et al., "The 2021 WHO Classification of Tumors of the Central Nervous System: a summary," *Neuro. Oncol.*, **23**, No. 8, 1231–1251 (2021), https://doi.org/10.1093/neuonc/noab106.
9. E. J. Rushing, "WHO classification of tumors of the nervous system: preview of the upcoming 5th edition," *Memo – Mag. Europ. Med. Oncol.*, **14**, No. 2, 188–191 (2021), https://doi.org/10.1007/s12254-021-00680-x.
10. A. K. Wefers, D. Stichel, D. Schrimpf, et al., "Isomorphic diffuse glioma is a morphologically and molecularly distinct tumour entity with recurrent gene fusions of MYBL1 or MYB and a benign disease course," *Acta Neuropathol.*, **139**, No. 1, 193–209 (2020), https://doi.org/10.1007/s00401-019-02078-w.
11. S. Luzzi, A. Elia, M. Del Maestro, et al., "Dysembryoplastic neuroepithelial tumors: What you need to know," *World Neurosurg.*, **127**, 255–265 (2019), https://doi.org/10.1016/j.wneu.2019.04.056.

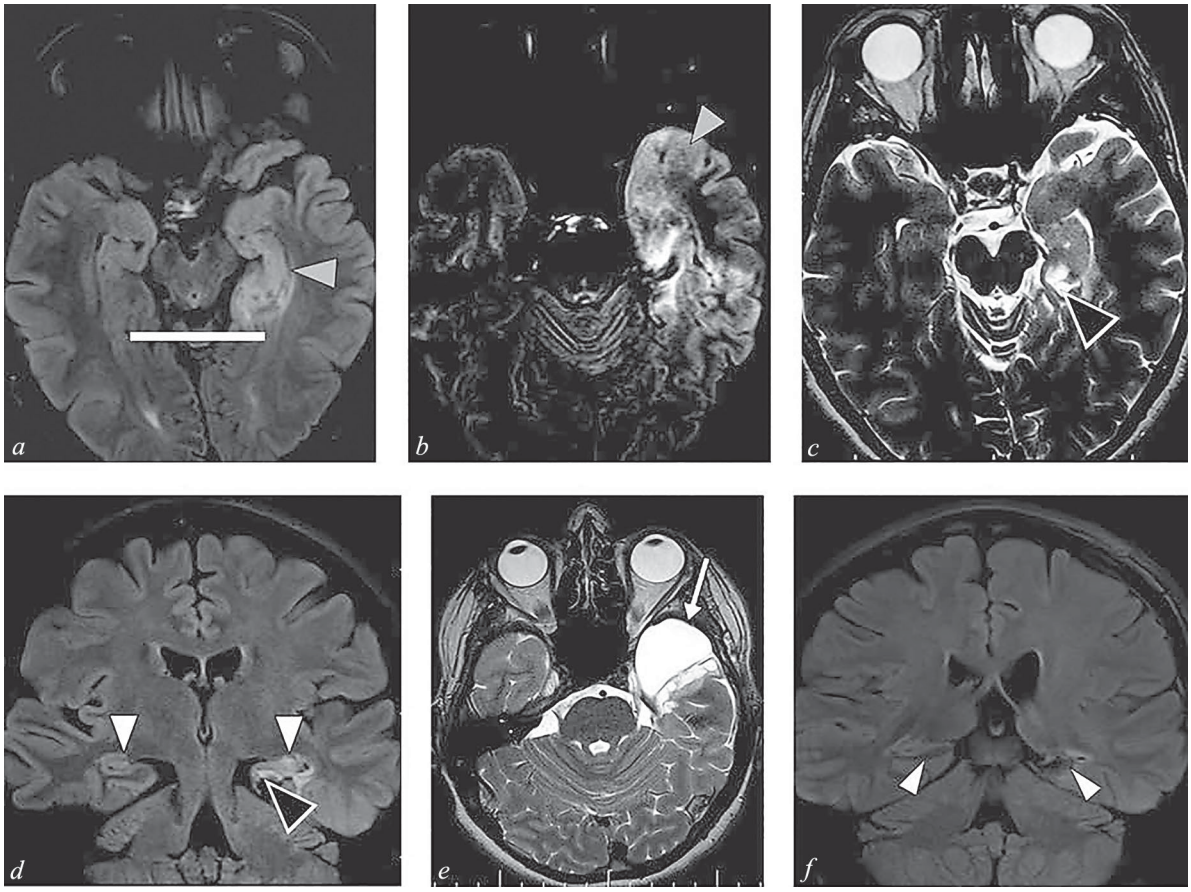

Fig. 4. MRI, clinical case 2. See text for details.

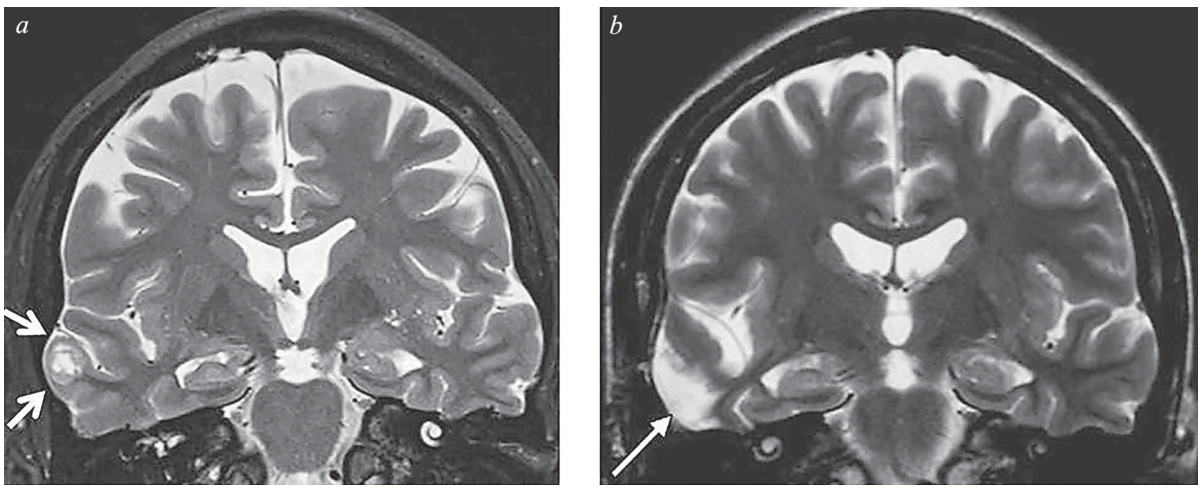

Fig. 5. MRI, clinical case 3. *a*) T2 coronal section, preoperative; *b*) T2 coronal section, postoperative.

12. A. Cistaro, D. Albano, P. Alongi, et al., "The Role of PET in supratentorial and infratentorial pediatric brain tumors," *Curr. Oncol.*, **28**, No. 4, 2481–2495 (2021), https://doi.org/10.3390/curroncol28040226.
13. S. Rheims, S. Rubi, S. Bouvard, et al., "Accuracy of distinguishing between dysembryoplastic neuroepithelial tumors and other epileptogenic brain neoplasms with [^{11}C]methionine PET," *Neuro. Oncol.*, **16**, No. 10, 1417–1426 (2014), https://doi.org/10.1093/neuonc/nou022.
14. F. Bernard, I. Zemmoura, A. Ter Minassian, et al., "Anatomical variability of the arcuate fasciculus: a systematical review," *Surg. Radiol. Anat.*, **41**, No. 8, 889–900 (2019), https://doi.org/10.1007/s00276-019-02244-5.
15. D. Koshiyama, M. Fukunaga, N. Okada, et al., "Association between the superior longitudinal fasciculus and perceptual organization and working memory: A diffusion tensor imaging study," *Neurosci. Lett.*, **738**, No. 8, 135349 (2020), https://doi.org/10.1016/j.neulet.2020.135349.

16. R. Nakajima, M. Kinoshita, H. Shinohara, et al., "The superior longitudinal fascicle: reconsidering the fronto-parietal neural network based on anatomy and function," *Brain Imag. Behav.*, **14**, No. 6, 2817–2830 (2020), https://doi.org/10.1007/s11682-019-00187-4.
17. A. Sasagawa, R. Enatsu, T. Kuribara, et al., "Cortical regions and networks of hyperkinetic seizures: Electrocorticography and diffusion tensor imaging study," *Epilepsy Behav.*, **125**, 108405 (2021), https://doi.org/10.1016/j.yebeh.2021.108405.
18. A. J. Ristić, A. V. Alexopoulos, N. So, et al., "Parietal lobe epilepsy: the great imitator among focal epilepsies," *Epileptic Disord.*, **14**, No. 1, 22–31 (2012), https://doi.org/10.1684/epd.2012.0484.
19. I. Blümcke, R. Coras, A. K. Wefers, et al., "Review: Challenges in the histopathological classification of ganglioglioma and DNT: microscopic agreement studies and a preliminary genotype-phenotype analysis," *Neuropathol. Appl. Neurobiol.*, **45**, No. 2, 95–107 (2019), https://doi.org/10.1111/nan.12522.
20. R. J. Slegers and I. Blumcke, "Low-grade developmental and epilepsy associated brain tumors: A critical update 2020," *Acta Neuropathol. Comm.*, **8**, No. 1, 1–11 (2020), https://doi.org/10.1186/s40478-020-00904-x.
21. K. Kobow, S. Baulac, A. von Deimling, et al., "Molecular diagnostics in drug-resistant focal epilepsy define new disease entities," *Brain Pathol.*, **31**, No. 4, 1–9 (2021), https://doi.org/10.1111/bpa.12963.
22. M. Simon and A. Grote, "Glioneuronal and other epilepsy-associated tumours," in: *Oxford Textbook of Neurological Surgery*, Oxford University Press (2019), pp. 129–140, https://doi.org/10.1093/med/9780198746706.001.0001.
23. Q. Wang, Y. Xiong, J. Chen, et al., "Cystic angiocentric glioma: a clinical case and literature review," *Childs Nerv. Syst.*, **37**, No. 8, 2701–2705 (2021), https://doi.org/10.1007/s00381-020-04882-2.
24. C. Dorfer, "Ganglioglioma," in: *Oncology of CNS Tumors*, Springer (2019), pp. 493–502, https://doi.org/10.1007/978-3-030-04152-6.
25. C. Horbinski, J. Kofler, G. Yeaney, et al., "Isocitrate dehydrogenase 1 analysis differentiates gangliogliomas from infiltrative gliomas," *Brain Pathol.*, **21**, No. 5, 564–574 (2011), https://doi.org/10.1111/j.1750-3639.2011.00480.x.
26. M. Pekmezci, J. E. Villanueva-Meyer, B. Goode, et al., "The genetic landscape of ganglioglioma," *Acta Neuropathol. Comm.*, **6**, No. 1, 47 (2018), https://doi.org/10.1186/s40478-018-0551-z.
27. J. Yoon, M. Cusimano, and D. G. Munoz, "Pilocytic astrocytoma vs. ganglioglioma: Progression, misdiagnosis, and implications in BRAF testing," *J. Clin. Neurosci.*, **66**, 231–234 (2019), https://doi.org/10.1016/j.jocn.2019.05.002.
28. J. H. Phi and S.-K. Kim, "clinical pearls and advances in molecular researches of epilepsy-associated tumors," *J. Korean Neurosurg. Soc.*, **62**, No. 3, 313–320 (2019), https://doi.org/10.3340/jkns.2019.0033.
29. Y. Yao, D. Zhang, Y. Qi, et al., "Surgical resection of dysembryoplatic neuroepithelioma tumor associated with epilepsy based on imaging classification," *Neurol. Res.*, **12**, No. 5, 1–7 (2022), https://doi.org/10.1080/01616412.2021.2024730.
30. M. Yibirin, D. De Oliveira, I. Suarez, et al., "A case of dysembryoplastic neuroepithelial tumor in an adolescent male," *Cureus*, **13**, No. 3, e13917 (2021), https://doi.org/10.7759/cureus.13917.
31. M. Chougule, "Neuronal and mixed neuronal-glial tumors," in: *Neuropathology of Brain Tumors with Radiologic Correlates*, Springer (2020), pp. 139–166, https://doi.org/10.1007/978-981-15-7126-8_9.
32. Z. Zheng, H. Jiang, H. Wu, et al., "Epilepsy surgery for low-grade epilepsy-associated neuroepithelial tumor of temporal lobe: a single-institution experience of 61 patients," *Neurol. Sci.*, **43**, No. 5, 3333–3341 (2022), https://doi.org/10.1007/s10072-021-05703-3.
33. V. L. Vogt, J. A. Witt, D. Delev, et al., "Cognitive features and surgical outcome of patients with long-term epilepsy-associated tumors (LEATs) within the temporal lobe," *Epilepsy Behav.*, **88**, 25–32 (2018), https://doi.org/10.1016/j.yebeh.2018.08.028.
34. L. Maillard, J. P. Vignal, M. Gavaret, et al., "Semiologic and electrophysiologic correlations in temporal lobe seizure subtypes," *Epilepsia*, **45**, No. 12, 1590–1599 (2004), https://doi.org/10.1111/j.0013-9580.2004.09704.x.
35. B. Yang, J. Mo, C. Zhang, et al., "Clinical features of automatisms and correlation with the seizure onset zones: A cluster analysis of 74 surgically-treated cases," *Seizure*, **94**, No. 119, 82–89 (2022), https://doi.org/10.1016/j.seizure.2021.11.015.
36. B. Abarrategui, R. Mai, I. Sartori, et al., "Temporal lobe epilepsy: A never-ending story," *Epilepsy Behav.*, **34**, No. 7, 122 (2021), https://doi.org/10.1016/j.yebeh.2021.108122.
37. M. Giulioni, G. Rubboli, G. Marucci, et al., "Seizure outcome of epilepsy surgery in focal epilepsies associated with temporomesial glioneuronal tumors: Lesionectomy compared with tailored resection – Clinical article," *J. Neurosurg.*, **111**, No. 6, 1275–1282 (2009), https://doi.org/10.3171/2009.3.JNS081350.
38. S. Ljunggren, L. Andersson-Roswall, H. Imberg, et al., "Predicting verbal memory decline following temporal lobe resection for epilepsy," *Acta Neurol. Scand.*, **140**, No. 5, 312–319 (2019), https://doi.org/10.1111/ane.13146.
39. I. Blümcke, M. Thom, E. Aronica, et al., "The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission," *Epilepsia*, **52**, No. 1, 158–174 (2011), https://doi.org/10.1111/j.1528-1167.2010.02777.x.
40. R. J. Keogh, R. Aslam, M. A. Hennessy, et al., "One year of procarbazine lomustine and vincristine is poorly tolerated in low grade glioma: a real world experience in a national neuro-oncology centre," *BMC Cancer*, **21**, No. 1, 1–8 (2021), https://doi.org/10.1186/s12885-021-07809-5.
41. T. J. C. Wang and M. P. Mehta, "Low-Grade Glioma Radiotherapy Treatment and Trials," *Neurosurg. Clin. N. Am.*, **30**, No. 1, 111–118 (2019), https://doi.org/10.1016/j.nec.2018.08.008.
42. J. Wang, L. Yan, P. Ai, et al., "Observation versus radiotherapy with or without temozolomide in postoperative WHO grade II high-risk low-grade glioma: a retrospective cohort study," *Neurosurg. Rev.*, **44**, No. 3, 1447–1455 (2021), https://doi.org/10.1007/s10143-020-01326-y.