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Clinical-Morphological Risk Factors for the Development of Epilepsy in Patients with Glial and Metastatic Brain Tumors

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Objective. To determine the incidence and identify the clinical-morphological risk factors for the development of epileptic seizures in patients with glial and metastatic brain tumors. **Materials and methods.** The study included 225 patients (88.6%) with glial and 29 (11.4%) with metastatic brain tumors. **Results.** Statistically significant differences in the incidence of epileptic seizures depending on age and histological characteristics of tumors, level of malignancy, location, involvement of the cerebral cortex, and displacement of midline structures were found. **Conclusions.** Epilepsy and epileptic seizures developed in 51.11% and 24.14% cases of glial and metastatic brain tumors, respectively. Risk factors for epileptic seizures were younger age (up to 57 years), histological characteristics corresponding to diffuse astrocytoma, anaplastic astrocytoma, oligodendroglioma, and oligoastrocytoma, malignancy grades I–III, lesions to the temporal lobe, and involvement of the cerebral cortex. Factors decreasing the risk of seizures were age over 57 years, histological characteristics corresponding to glioblastoma, metastatic tumors, malignancy grade IV, subcortical location of neoplasm, lesions to the occipital cortex, involvement of the conducting tracts (commissures) in the pathological process, subtentorial tumor location, absence of lesion in the temporal and frontal lobes of the brain, involvement of both hemispheres of the brain in the pathological process, lesions of two or more lobes of the brain, and displacement of midline structures.

Keywords: CNS tumors, glioma, glioblastoma, anaplastic astrocytoma, metastatic tumors, epilepsy, seizure.

The annual incidence of primary malignant tumors of the brain is around 3.7 cases per 100,000 of the population in men and 2.6 per 100,000 for women. Measures are higher in developed countries (men 5.8 and women 4.1 per 100,000). Throughout the world, mortality for primary malignant brain tumors is around 2.8 per 100,000 for men and 2.0 per 100,000 for women [1].

Epileptic seizures are the primary clinical symptom of brain tumors in more than 50% of cases [2]. Neoplasms are diagnosed in fewer than 0.5% of cases of epilepsy in children [3] and 10–15% in adults. Epilepsy develops in more than 95% of cases in neuroglial tumors and fewer than 75% in low-malignancy gliomas [4]. The development of seizures leads to significant degradation of quality of life, cognitive impairments [5], traumas, and social maladaptation. At the same time, it should be noted that results reported by a number of authors indicate that the occurrence of seizures is a prognostically favorable factor in relation to duration of life [6–8]. There is potential for identifying the clinical and instrumental factors reflecting the course of disease [9].

The aim of the present work was to establish the incidence and clinical-morphological risk factors for the development of epileptic seizures in patients with glial and metastatic brain tumors.

Materials and Methods. By design this was a single-center retrospective clinical study of 254 patients receiving hospital care at the Clinic for Neurosurgery and Nervous Diseases at the Military Medical Academy in the period from 2014 to 2017. *Inclusion criteria* were age 18 and above,

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brain tumors whose histological characteristics corresponded to diffuse astrocytomas and oligodendrogliomas, malignant gliomas, and other astrocyte, neuronal, and mixed neuronal-glial, embryonic, and metastatic brain tumors. *Exclusion criteria* were: age under 18 years, brain tumors whose histological characteristics corresponded to lymphomas, cranial nerve tumors, meningiomas, mesenchymal, nonmeningothelial tumors, histiocytomas, and germinogenic tumors, tumors of the sella turcica, history of surgery for brain neoplasms, and absence of histological confirmation of diagnosis.

The study included 225 patients with glial tumors (88.6%) and 29 (11.4%) with metastatic tumors. The distribution of tumors by histological characteristics was as follows: glioblastoma in 92 patients (36.22%), anaplastic astrocytoma in 54 patients (21.26%), diffuse astrocytoma in 49 patients (19.29%), oligodendroglioma in 15 patients (5.9%), oligoastrocytoma in seven patients (2.76%), other tumors present in small numbers (medulloblastoma, subependymal astrocytoma, pilocytic astrocytoma, ganglioglioma) in eight patients (3.15%), and secondary tumors (metastases) in 29 patients (11.42%).

The distribution of secondary brain tumors in terms of primary anatomical location of malignant neoplasms in other organs and tissues was as follows: skin in four patients (nodular melanoma), thyroid in two (papillary carcinoma in one and medullary carcinoma in one), breast in two patients (invasive carcinoma of nonspecific type), lung in 11 patients (adenocarcinoma in 10 and glandular/squamous cell carcinoma in one), sigmoid colon in in one patient (adenocarcinoma), rectum in one patient (adenocarcinoma), and kidney in five patients (light-cell renocellular carcinoma).

The anatomical location of the primary tumor in patients with brain metastases was determined by analysis of clinical data in medical records (existence of primary tumor and metastases, their anatomical locations, time since diagnosis, and histological tumor confirmation), comparison of the histological characteristics of metastases and primary tumors, (by comparison of histological specimens of the primary tumor and brain metastases), and immunohistochemical investigation.

In three cases (10.34% of secondary malignant brain neoplasms), the primary anatomical location of the primary malignant neoplasm could not be established and immunohistochemical studies identified the tumors as epithelial.

The distribution of glial tumors by malignancy was as follows: grade IV in 95 cases (42.22%), grade III in 67 patients (29.78%), grade II in 58 patients (25.78%), and grade I in five patients (2.22%).

All patients underwent MRI scans on a Magnetom Symphony with a magnetic field of 1.5 T. Brain MRI scans used contrast and were in three projections (sagittal, axial, and coronal) using the T1, T2, and FLAIR modes.

Clinical results were analyzed in Statistica for Windows version 10. A set of descriptive indicators were computed for quantitative parameters, i.e., mean, standard deviation, error of the mean, minimum and maximum values, and medians and quartiles. Comparison of the frequency characteristics of qualitative indicators (sex, location, histology) used the nonparametric methods χ^2, χ^2 with the Yates correction (for small groups), and Fisher's test. Comparisons of quantitative indicators (age) in the study groups was with the Mann–Whitney test, median χ^2, and ANOVA module. Age threshold values, which are very important for assessment of the development of seizures, were determined by constructing classification trees.

Results. The commonest clinical signs of brain neoplasms were headache and epileptic seizures, which were seen in 67.32% (n = 171) and 48.03% (n = 122) of cases, respectively. Furthermore, epileptic seizures were the first symptom of disease in 41.73% (n = 106) of cases and the only clinical manifestation in 9.84% (n = 25).

Epileptic seizures occurred with retention of consciousness (vertigo, olfactory, gustatory, visual, motor, sensory, aphatic, "dejà vu," anxiety or fear, and auditory hallucinations) in 40.16% of cases (n = 49), with impaired consciousness (cessation of activity, carpal and oroalimentary automatisms, atonic) in 9.84% (n = 12) and focal seizures with evolution to tonic-clonic seizures in 68.85% (n = 84). Patients were distributed in terms of seizure frequency as follows: single seizures were diagnosed in 42 patients (34.43%), rare (less than one a month) in 44 cases (36.07%), frequent (more than one a month) in 26 cases (21.31%), and very frequent (more than one a week) in 10 patients (8.2%). Single seizures occurred in a quite high proportion of patients. This may be linked with the rapid subsequent diagnosis of neoplasms by structural neuroimaging and the short time to surgery. Published data do not give a precise risk of recurrence of seizures in cases displaying single seizures in brain gliomas, so epilepsy was not diagnosed. Structural epilepsy was diagnosed in all other cases. We will use the term "epileptic seizures" for convenience.

To identify groups at risk of developing epileptic seizures we assessed clinical and morphological factors such as age at disease onset, sex, histological characteristics of tumor, degree of malignancy, location of tumor in the CNS (lobes of the brain), involvement of conducting tracts (commissures) number of brain lobes involved, lateralization of the focus to the corresponding cerebral hemisphere, type of tumor growth (single focus or multifocal lesions), involvement of cerebral cortex, and displacement of midline structures.

The mean age of disease onset was 47.42 ± 16.16 years. Logical structural analysis by construction of classification trees was run to seek age thresholds. Fundamentally important threshold values were obtained for age, i.e., 32 and 57 years, which defined significantly differing age groups depending on seizure frequency (Table 1).

These results show that the frequency of developing epileptic seizures in patients aged over 57 years was significantly ($p < 0.01$, χ^2 test for assessment of linkage tables consisting of three age groups with the frequencies of ep-

TABLE 1. Incidence of Epileptic Seizures in Patients of Different Age Groups

Age group	Presence of epileptic seizures	Absence of epileptic seizures	Total	OR (95% confidence interval)
18–32 years	50.91% (n = 28)	49.09% (n = 27)	55	2.32 (1.15–4.72)
33–57 years	58.47% (n = 69)	41.53% (n = 49)	118	3.15 (1.74–5.73)
Over 57 years	30.86% (n = 25)	69.14% (n = 56)	81	
p	<0.001			

TABLE 2. Incidence of Epileptic Seizures Depending on Location of Tumor in CNS

Tumor location	Presence of epileptic seizures		Significance of difference
	area involved	areas not involved	
Frontal lobe (n = 121)	50.41% (61/121)	45.86% (61/133)	$p > 0.05$
Temporal lobe (n = 111)	54.95% (61/111)	42.66% (61/143)	$p = 0.07$
Parietal lobe (n = 78)	43.59% (34/78)	50.00% (88/176)	$p > 0.05$
Occipital lobe (n = 29)	20.69% (6/29)	51.56% (116/225)	$p < 0.01$
Paracentral lobule (n = 22)	59.09% (13/22)	46.98% (109/232)	$p > 0.05$
Conducting tracts (n = 37)	18.92% (7/37)	53.00% (115/217)	$p < 0.001$
Subtentorial location (n = 14)	0% (0/14)	50.83% (122/240)	$p < 0.001$

ileptic seizures in each) lower, at 30.86%. The odds ratio (OR) for the age group 18–32 years was 2.32, while OR for patients aged 33–57 years was 3.15. Lower risks of developing epileptic seizures were typical of patients with brain neoplasms in the older age group, which is consistent with results from other studies [10]. In developed countries, the incidence of epilepsy is stable in the intermediate age group and increases after age 50 years [11].

The study included 146 men and 108 women. Epileptic seizures developed in 48.03% of cases in men (n = 69) and 49.07% (n = 53) in women. No statistically significant differences were seen.

The incidence of epileptic seizures differed significantly depending on the histological characteristics of tumors ($p < 0.001$). Epileptic seizures developed in 51.11% of patients with glial tumors (n = 115) and 24.14% (n = 7) of those with metastatic tumors. The highest incidence of seizures was seen in patients with diffuse astrocytomas, anaplastic astrocytomas, oligodendrogliomas, and oligoastrocytomas, reaching 69.39% (n = 34), 61.11% (n = 33), 60.00% (n = 9), and 57.14% (n = 4), respectively. The lowest seizure frequencies were seen in glioblastomas and metastatic tumors, in 34.78% (n = 32) and 24.14% (n = 7), respectively. In the group with other tumors, which included patients with small numbers of cases (medulloblastomas, subependymal astrocytomas, pilocytic astrocytomas, gangliogliomas), seizures developed in 37.50% of cases (n = 3).

The incidence of epileptic seizures differed significantly depending on the level of malignancy of brain tumors ($p < 0.001$). Seizure incidence increased with decreases in tumor malignancy, at 33.68% (n = 32) in grade IV, 59.70% (n = 40) in grade III, and 68.97% (n = 40) in grade II. Seizures occurred in 60% of patients with grade I tumors (n = 3). A decrease in seizure incidence in high-malignancy tumors can be explained in terms of rapid growth of formations with disruption of the conducting tracts. Other mechanisms of epileptogenesis can also be proposed.

The incidence of epileptic seizures depending on neoplasm location is shown in Table 2.

Frontal lobe tumors were seen in 121 of 254 cases. Seizures in frontal lobe lesions developed in 61 of 121 patients (50.41%). When the frontal lobe was not involved in the pathological process, seizures developed in 45.86% of cases (61 of 133). These differences were not statistically significant.

In cases with lesions of the temporal lobe, the incidence of developing seizures was 54.95% of cases (61 of 111); when there was no involvement of temporal lobe the incidence was only 42.66% (61 of 143 cases) ($p = 0.07$).

Thus, despite the absence of any statistically significant differences, clinically important information was obtained indicating that the leading symptom was the development of epileptic seizures in more than half of patients with tumors of the temporal lobe and half of those with tumors of the frontal lobe.

Lesions of the occipital lobe were characterized by the development of seizures in only 20.69% of cases (six of 29), which was statistically significantly different ($p < 0.01$)

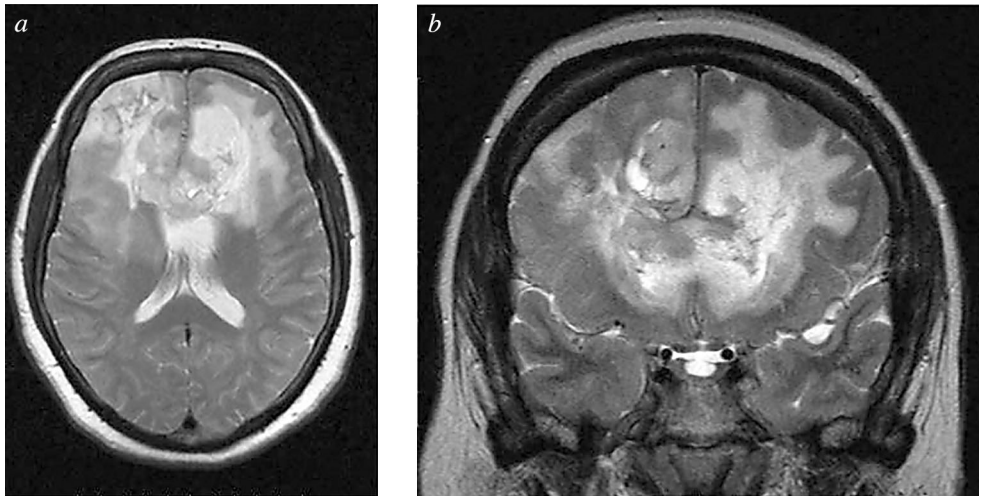

Fig. 1. Patient M, female, age 65 years. Diagnosis: anaplastic oligodendroglioma of right frontal lobe with growth through the corpus callosum to the left frontal lobe. Clinically no epileptic seizures. Pathological MRI signal defined an extensive zone of pathology of irregular shape in the frontal lobes on both sides with extension through the genu of the corpus callosum, with inhomogeneous hyperintensity on T2-WI (*a*, *b*).

from the frequency when the occipital lobe was not involved in the pathological process (development of epileptic seizures in 56.5% of cases (116 of 225 cases).

Statistically significant differences were found when the conducting tracts of the brain (commissures) were involved in the pathological process ($p < 0.001$) and when tumors had a subtentorial location ($p < 0.001$). The probability of developing seizures was lower in both groups.

Thus, the factors decreasing the risk of developing epileptic seizures related to the involvement of the occipital lobe of the brain and conducting tracts (commissures) in the pathological process and the location of tumors in the subtentorial areas. A factor leading to increases in the risk of developing tumors was the location of lesions of the temporal lobe of the brain.

Attention is drawn to the fact that when there was no lesion to the temporal or frontal lobe of the brain, there was a sharp decline in the frequency of developing seizures (27.45%, $n = 14$).

Brain lesion location was used to divide patients into two groups: group 1 included patients with involvement of the cerebral cortex ($n = 160$) and group 2 included those with subcortical neoplasms ($n = 94$). Epileptic seizures occurred in 60.00% of patients ($n = 96$) in group 1 and only 27.66% ($n = 26$) in group 2. This difference was statistically significant ($p < 0.001$).

Patients were divided into three groups depending on neoplasm location. Group 1 included patients with left-sided tumors ($n = 113$), group 2 included those with right-sided tumors ($n = 118$), and group 3 included those with bilateral lesions ($n = 23$). Seizures developed in a total of only 21.74% of cases with involvement of both hemispheres of the brain in the pathological process, compared with 51.33% in patients with left-sided pathology and 50.0% in those with right-sided lesions. Thus, epileptic seizures developed in a higher proportion of patients with single-hemisphere tumors than in those with involvement of both hemispheres ($p < 0.05$).

No statistically significant differences were found in seizure rates between patients with solitary and multifocal brain diseases.

In patients with lesions to one lobe, seizures were seen in 54.84% of cases ($n = 85$), compared with 37.37% ($n = 37$) when two or more lobes of the brain were involved in the pathological process ($p < 0.01$) (Fig. 1).

Seizures developed more frequently when there was no displacement of midline structures – in 58.99% of cases ($n = 82$), compared with 34.78% when displacement was present ($n = 40$). The difference was statistically significant ($p < 0.001$).

Discussion. The most significant etiological factors for epilepsy in all regions of Russia are head injury, stroke, brain tumors, perinatal pathology, and infectious diseases [12]. Our results provide evidence that epilepsy and epileptic seizures are among the leading clinical manifestations of glial and metastatic brain tumors, developing in 51.11% and 24.14% of cases, respectively. Results from other studies also identify a high frequency of seizure development in brain neoplasms [2].

The world literature contains different evaluations of the significance of epileptic seizures. Some authors take the view that the presence of seizures is prognostically favorable factor in relation to patients' survival time [6–8]. A review by Breeman et al. and results reported by Moots et al. [13, 14] showed that among patients with brain tumors, those with seizures were younger, had less malignant neoplasms, and higher Karnofsky scores. Fan et al. [8] conducted a meta-analysis including 11 studies and 2088 patients and came to the conclusion that seizures are an independent prognostic factor giving a more favorable prognosis (sur-

vival time) when developing in patients with diffuse gliomas. However, Rigamonti et al. [15] took the opposite view, that the presence of seizures in patients with glioblastomas has no influence on survival time. At the same time, there is no doubt that the presence of epileptic seizures in patients with brain gliomas has a significant influence on quality of life in these patients [16, 17], which was significantly lower than in healthy people.

Thus, the search for and identification of clinical and morphological factors determining the risk of developing epileptic seizures in patients with brain neoplasms allows risk groups to be defined for dynamic follow-up.

The results of our study indicate that factors influencing the development of epileptic seizures are the patient's age, the histological characteristics, the degree of malignancy, the location and dissemination of the oncological process, and the involvement of the cerebral cortex.

Our data indicate that younger age (<57 years) is an independent risk factor for developing epileptic seizures. This is consistent with results from other studies. Data reported by Kaloshi et al. [10] indicate that epileptic seizures develop in 47% of patients over 60 years of age and in 85% of patients in the younger age group. This age-related tendency in the frequency of epileptic seizures is indicated in work reported by another group, who found that at age over 55 years the probability of developing seizures decreased twofold [18].

The most epileptogenic tumors were neuronal-epithelial tumors: dysembryoblastic neuroepithelial tumors, and gangliogliomas. Kerkhof and Vecht [19] found that the incidence of epilepsy in dysembryoblastic neuroepithelial tumors reached 80–100%, compared with 65–85% in those with low-malignancy gliomas and 30–60% of those with high-malignancy gliomas (glioblastomas). Chaichana et al. [18] noted that anaplastic astrocytomas were characterized by seizures in the pre-operative period ($p = 0.03$). Our study found that the incidence of developing epileptic seizures decreased with reductions in malignancy. We also showed that the highest incidence of seizures was seen in diffuse and anablastic astrocytomas, oligodendrogliomas, and oligoastrocytomas.

Xing Su et al. [20] carried out a meta-analysis of publications on tumors and the risk of developing seizures. This group showed that the development of seizures was more characteristic of frontal than occipital location. Our study also noted that when neoplasms were located in the occipital lobe of the brain and subtentorially, and also when the conducting tracts (commissures) were involved, the incidence of developing epileptic seizures was lower, though the highest incidence was seen when lesions were located in the temporal lobe.

Our data have also been confirmed by other authors [18, 21]. Thus, involvement of the temporal lobe of the brain in the pathological process and supratentorial [21] and cerebral cortex [18] tumor location have been shown to be factors leading to the development of seizures.

Neoplasm size was an important risk factor for the development of epileptic seizures. Greater tumor size was linked with a lower probability of developing epilepsy. Data reported by Chaichana et al. [18] found that at tumor sizes of >3 cm, the probability of developing epilepsy was threefold lower.

Thus, our data indicate that the clinical and morphological factors promoting the occurrence of epileptic seizures in patients with brain neoplasms include younger age (up to 57 years of age), histological characteristics corresponding to diffuse and anaplastic astrocytomas, oligodendrogliomas, or oligoastrocytomas, grade I–III malignancy, lesions to one lobe, one hemisphere, the temporal and frontal lobes, and involvement of the cerebral cortex.

Conclusions. Epilepsy and epileptic seizures are among the leading clinical manifestations of brain neoplasms, developing in 51.11%, and 24.14% of cases in glial and metastatic brain tumors, respectively. Risk factors for the development of epileptic seizures include younger age (up to 57 years), histological characteristics corresponding to diffuse astrocytomas, anaplastic astrocytomas, oligodendrogliomas, and oligoastrocytomas, grade I–III malignancy, lesions of the temporal lobe, and involvement of the cerebral cortex. Factors decreasing the risk of developing seizures were age older than 57 years, histological characteristics corresponding to glioblastomas and metastatic tumors, malignancy grade IV, subcortical location, lesion of occipital lobe, involvement of the conducting tracts (commissures) in the pathological process, subtentorial location of tumor, absence of lesions in the temporal and frontal lobes of the brain, involvement of both hemispheres in the pathological process, lesions to two or more lobes of the brain, and displacement of midline structures.

The authors have no conflicts of interests.

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