Review

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Symptomatic Epileptic Seizures in Patients with Brain Gliomas

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INTRODUCTION Epileptic seizures are an important problem that significantly worsens the quality of patients' life with both newly diagnosed and recurrent brain gliomas.

REVIEW The analysis of domestic and foreign literature showed that low-grade gliomas, this symptom occurs on average in 76%, with high-grade gliomas - in 21% of patients. Despite the maximum allowable tumor resection, it is likely that epileptic seizures persist in 18-64% of patients, and in 5% of patients they first appear in the postoperative period. From 15 to 50% of epileptic seizures in cerebral gliomas are drug-resistant. In patients undergoing chemotherapy, it is better to use new antiepileptic drugs because their cross-effects are minimal.

CONCLUSION There is no generally accepted algorithm for prescribing and discontinuing antiepileptic drugs in patients with symptomatic epileptic seizures with cerebral gliomas. Further research is needed to determine the optimal combination and dosage regimen of antiepileptic drugs, especially during chemotherapy.

Keywords: glioma, epileptic seizures, glioblastoma, convulsive seizures, symptomatic epilepsy, drug-resistant epilepsy, brain tumor

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GABA – gamma-aminobutyric acid
BG – brain glioma
MRI – magnetic resonance imaging
AEDs – antiepileptic drugs
SESSG – symptomatic epileptic seizures secondary to gliomas
ECoG – electrocorticography

INTRODUCTION

Primary brain tumors account for 2% of all neoplasms [1]. Among them, 40–45% are glial tumors [2]. Epileptic seizures are an important problem affecting the quality of life of patients with brain gliomas (BG) [3]. They are often the first symptom of a glial tumor, and in 50% of patients they are the only clinical manifestation of the disease for a long time [4, 5].

PATHOGENESIS OF EPILEPTIC SEIZURES IN BG PATIENTS

Huberfeld G. et al. (2016) suggested that the onset of symptomatic epileptic seizures secondary to gliomas (SESSG) occurs due to the stimulation of *NMDA* and *AMPA* receptors by extracellular glutamate, impaired inhibition of signaling by gamma-aminobutyric acid (GABA), activation of the *mTOR* signaling pathway, epigenetic changes [4].

Gliomas are able to independently produce glutamate, which is a neurotransmitter. Its increased concentration determines the effect of excitotoxicity and the occurrence of epileptic activity. *Blecic S. et al.* (2013) suggested that necrosis of the cell structures of the perifocal zone of the tumor, realized through the glutamate-calcium cascade, increases the level of autoantibodies to *the GluR1* subunit of *AMPA*-glutamate receptors, which precedes the appearance of structural epilepsy in the clinical picture of the disease [6].

Also, with the growth of glial tumors, infiltration of the pretumoral neocortex occurs, accompanied by focal electrolyte disturbances. They include excessive accumulation of extracellular potassium, intracellular chlorine, leading to decreased perfusion of the brain parenchyma, acidosis and failure of adequate cellular metabolism, which is also a pathophysiological cause of epileptic seizures [7, 8]. Not only does the volumetric effect lead to seizures, but epileptic activity also stimulates tumor growth. The growing understanding of the general mechanisms leading to tumor progression and epileptogenesis may in the future allow one medication to treat both conditions, which would significantly reduce the toxic effect on the body and adverse drug reactions [4].

RISK FACTORS FOR GLIOMA-RELATED EPILEPTIC SEIZURES

Most often, low-grade SESSG occur when the pathological process affects the frontal and insular lobes of the brain [9-14]. While studying the risk factors for the occurrence of epileptic seizures in glioblastoma, *Cayuela N. et al*. (2018) found that they are most often present in the clinical picture of the disease when the tumor is localized in the posterior parts of the middle frontal, precentral, postcentral gyri, insular lobe and Heschl's gyrus [15]. *Liang S. et al*. (2016) suggested that the involvement of the frontal and temporal lobes plays a significant role in the SESSG onset [16].

The incidence of epileptic seizures depending on the histological type of glioma is shown in the Figure [9–19].

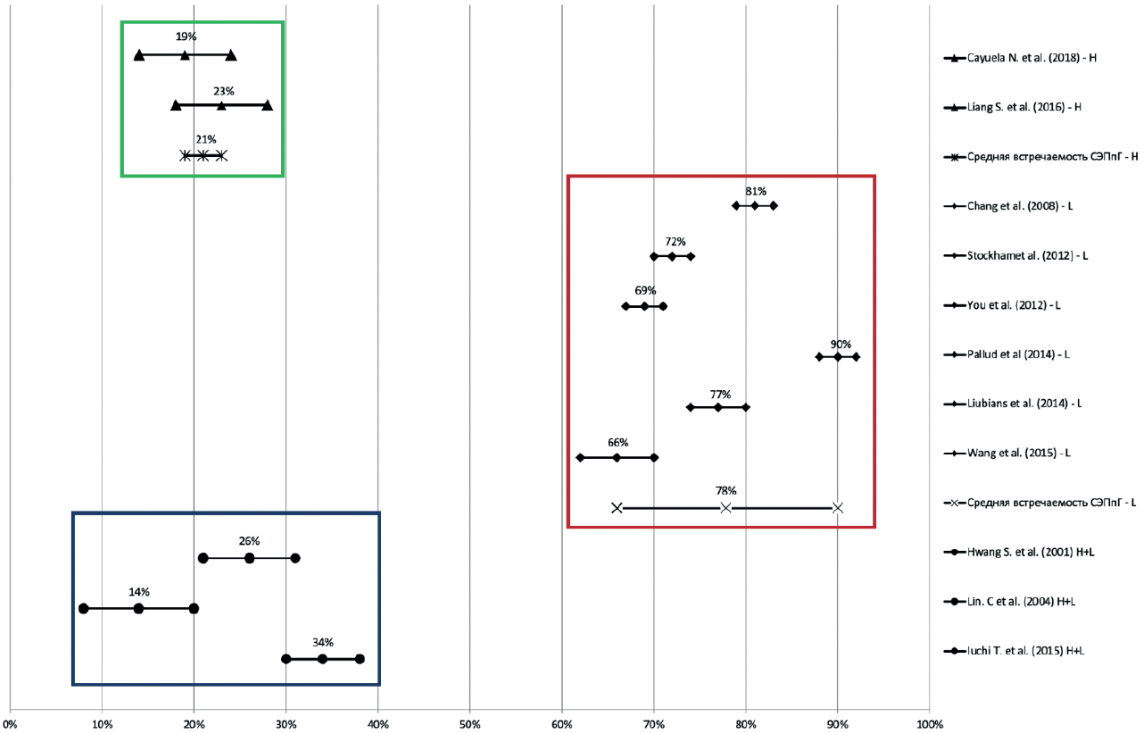

Figure. Dependence of the incidence of symptomatic epileptic seizures in patients with glioma on its degree of malignancy. H — Grade III–IV; L — Grade II; H+L — Grade II–IV

Mukhacheva M.V. et al. (2016) found that epileptic seizures in patients with high-grade gliomas occur with a tumor diameter of 3-4 cm, however *Liang S. et al*. (2016) found no correlation between the incidence of SESSG and tumor size [16, 20]. In case of low-grade gliomas with a tumor of up to 1–2 cm in diameter, epileptic seizures usually appear long before the onset of other symptoms of the disease [20]. *Murzakanova D.A. et al.* (2019) investigated the relationship between the volume of brain neoplasms of various histological structures and epileptic seizures. The majority (86%) of the examined were patients with glial tumors. The authors found that epileptic seizures develop in 54% of cases with a tumor volume of up to 45 cm3, in 44% - with 46–60 cm3, in 35% - with a volume of more than 60 cm3 [21].

Mukhacheva M.V. et al. (2016) found that in patients with glial tumors, secondary generalized seizures are the most common (52%), partial and primary generalized seizures occur much less frequently - in 28% and 20% of patients, respectively [20]. According to *Liang S. et al.* (2016) most of the seizures in patients with high-grade gliomas are secondary generalized - 61%, and only 39% - partial seizures [16].

One of the complications of the BG-related epileptic seizure can be its transition to status epilepticus [22]. According to *Giovannini G. et al.* (2019), *Casazza M. et al.* (2011), from 3 to 12% of status epilepticus have a brain tumor as an initial cause [22, 23]. Patients with high-grade BG face this condition 5.6 times more often than patients with WHO grade II gliomas [23].

According to *Di Bonaventura C. et al.* (2017), *Berendsen S. et al.* (2016), epileptic seizures in the structure of the clinical picture of BG are associated with better survival of patients with highly malignant gliomas [24, 25]. 2 years after the onset of the disease, 59% of patients with a history of seizures were alive compared to 51% of patients without them. The reason may lie in the earlier conduct of neuroimaging studies at the onset of the disease with epileptic seizures [25].

EPILEPTIC SEIZURES IN PATIENTS WITH RELAPSED GLIOMA

Over time in patients with WHO grade II gliomas, the level of differentiation of their cells decreases, which leads to an increase in the malignancy of the neoplasm up to Grade IV [26]. A characteristic feature of glioblastoma is the inevitability of its continued growth after surgery [27]. Epileptic seizures can be one of the signs of glioma recurrence. If before the first surgery, 23–28% of patients with glioblastoma suffer them as a cancer symptom, then during the first year after neoplasm removal, SESSG develop in 42–45% of patients [5, 16]. However *Mukhacheva M.V. et al.* (2016) revealed a different pattern of relapses: in 50% of patients, SESSG were observed before the first surgery, and in 25% - in case of ongoing tumor growth [20]. In a small sample of patients, *Di Bonaventura C. et al.* (2017) found that seizures in case of continued growth of glioblastoma occurred 2.89 months before the appearance of signs of the relapse on magnetic resonance imaging (MRI), being a kind of "red flag" requiring urgent neuroimaging in the postoperative period [25].

EPILEPTIC SEIZURES IN THE POSTOPERATIVE PERIOD

In patients with brain tumors without concomitant SESSG in history, the question of the necessity of prophylactic administration of antiepileptic drugs (AEDs) intraoperatively and in the postoperative period remains controversial [28]. Epileptic seizures that first develop after the first surgical intervention may be due to the consequences of surgical treatment [29]. There are two hypotheses for their occurrence. The first is that, due to the products of hemoglobin breakdown, the resulting peroxide compounds reduce the concentration of GABA, inhibiting the neuronal activity of the cerebral cortex [30]. The second putative mechanism is a change in the potential of the cell membrane due to impaired transmembrane transport of water and ions caused by a decrease in the synthesis of adenosine triphosphate in peritumorous brain tissue [31].

Oushy S. et al. (2018) revealed that SESSG in 5% of patients first occur in the intraoperative and postoperative periods, among which 2% are intraoperative epileptic seizures. A large proportion of *de novo* epileptic seizures is attributed to infiltrative gliomas of WHO grade II to IV [28].

In patients with epileptic seizures that occurred before glioma resection, the incidence of seizures in the perioperative period is somewhat different. Up to 7% of patients undergo intraoperative seizures, 18–64% have seizures in the early postoperative period [32–34]. Even if AEDs are administered in the postoperative period, 9% of patients with BG experience seizures in the first week after surgery [17]. This leads to a longer

hospital stay compared to patients without epileptic seizures in the early postoperative period [35, 36]. More perioperative seizures occur in patients with grade III gliomas than in those with grade IV gliomas [33].

It was found that glioma localization in the temporal lobe is associated with the highest risk of postoperative seizures [33]. But in case of glioblastoma, the connection between epileptic seizures and localization is different: 62% - when it is located in the frontal lobes, 40% - in the temporal lobes and 35% - in the parietal lobes [16].

The volume of tumor resection is associated with the frequency of seizures in the postoperative period. In 80% of patients with total glioblastoma removal, seizures do not occur within a month after surgery, which can be achieved only in 30% of patients with partial resection [16]. Similar results were observed in patients after total resection of grade II gliomas during postoperative seizure outcome assessment 6 months after surgery: they were absent in 71–73% of patients [37, 38].

EPILEPTIC SEIZURES DURING POSTOPERATIVE RADIOTHERAPY

Intracranial radiation therapy for BG increases the risk of epilepsy progression or occurrence, which is associated with cerebral edema due to demyelination, gliosis, and vascular changes that occur after brain irradiation [39]. In 35% of patients with BG, epileptic seizures occur during radiation therapy for the first time, and 67% of them have WHO grade III – IV gliomas [40].

In the long term, early postoperative radiation therapy significantly reduces the incidence of epileptic seizures in BG patients. The European Organization for Research and Treatment of Cancer (EORTC) conducted a large prospective randomized controlled study of 311 patients with low-grade gliomas who received early postoperative radiation therapy, which showed that this treatment algorithm achieves better seizure control [41]. However, there have been no generally accepted guidelines for prophylactic use of AEDs during radiation therapy, and the timing of withdrawal of antiepileptic therapy after its completion has not been determined [25].

THERAPY FOR SYMPTOMATIC EPILEPTIC SEIZURES IN GLIOMA PATIENTS

When prescribing antiepileptic drugs for patients with gliomas, it is necessary to take into account the potential interactions of AEDs with other medications used in the treatment of this pathology [42]. Some first-generation AEDs, including carbamazepan, phenytoin, oxcarbazepine, affect the cytochrome P450 system [42, 43]. A number of anticancer drugs including nitrosourea derivatives work through the same enzyme system [43]. The consequence of this drug interaction is a mutual decrease in the concentration of these substances in the blood, which leads to insufficient effectiveness of the medications [43, 44].

Temozolomide and bevacizumab, used in the treatment of high-grade gliomas, are not metabolized in the liver and do not interact with AEDs, which removes restrictions on the administration of this series of AEDs [43]. Valproic acid has an inhibitory effect on enzymes - monooxygenases of the cytochrome P450 group, which can lead to an increase in the concentration and half-life of other anticonvulsants, but it does not affect the blood concentration of other drugs used in the treatment of gliomas [42, 43, 45].

In order to reduce glioma-related perifocal edema steroid drugs are used, which metabolism is also associated with the cytochrome P450 system. Therefore, under the influence of first-generation AEDs, the effectiveness of dexamethasone may decrease due to its accelerated metabolism [46]. Glucocorticosteroids have a weakening effect on epileptogenesis, since in case of perifocal cerebral edema the space between neurons decreases, which leads to an increase in the excess excitation due to nonsynaptic interaction between cells [47].

For the treatment of glioma-related epilepsy, it is preferable to use AEDs that do not have an inducing effect on enzymes included in the metabolic system of cytochrome P450 - lacosamide, levetiracetam, gabapentin, pregabalin, lamotrigine, topiramate [42, 46].

Zachenhofer I. et al. (2005) conducted a study in which patients with BG in the perioperative period took levetiracetam at a dose of 1000 to 3000 mg per day. This resulted in a lower number of early postoperative seizures than in patients without exposure to the AED. The authors of the study concluded that the prophylactic use of levetiracetam is beneficial for BG patients [44]. Despite the fact that levetiracetam is an effective drug in the treatment of BG-related epileptic seizures, there is a group of patients whose condition does not improve by taking this AED. *Masashi Chonan et al.* performed a research in which 18 patients with

levetiracetam-resistant epileptic seizures took a second drug, perampanel. In 78% of patients, complete control of seizures was achieved with the combination of levetiracetam with 2 mg, and in 22% with 4 mg of perampanel per day [49].

Liang S. et al. (2016) conducted a study, during which for prophylactic purposes glioma patients in the postoperative period took levetiracetam at a dose of 20-30 mg / kg, valproic acid - 20-25 mg / kg, oxarbazepine - 15-20 mg / kg as monotherapy or in combination. The authors concluded that the use of the AEDs for more than 6 months leads to a reduction in seizure frequency compared with the group of patients where anticonvulsant therapy was discontinued in the early postoperative period or was not carried out at all [16].

Ryu J.Y. et al. (2019) suggested that levetiracetam exhibits antitumor effects and, therefore, may affect the life expectancy of glioblastoma patients with methylated *MGMT* promoter undergoing temozolomide chemotherapy [50]. Gap-junctional interaction between glioma cells and surrounding astrocytes is an important channel of intercellular communication, accelerating the growth of glioma. A research by *Ismail F.S. et al.* (2017) demonstrated that *in vitro* exposure to levetiracetam and dexamethasone may decrease these intercellular contacts [48]. Similar assumptions were made for other AEDs, including valproic acid. However, there are studies proving the beneficial effect of this drug [51] and refuting this idea [24].

The most common side effects of epileptic seizure treatment in neurooncology are cognitive impairment and bone marrow toxicity [24]. Intellectual and mnestic disorders can be caused both by the disease itself and AED side effects, with each additional drug leading to a decrease in mental activity [52, 53].

RESISTANT TO PHARMACOLOGICAL THERAPY EPILEPTIC SEIZURES IN GLIOMA PATIENS

From 15 to 50% of Grade II SESSG are not amenable to pharmacologic therapies [12]. The supposed reason of drug resistance in glioma patients is the overexpression of G protein-coupled receptors in cancer cells that block the transport of lipophilic AEDs to the cells of the brain parenchyma which causes multiple drug resistance [44].

The main method of treatment for pharmacoresistant epileptic seizures in BG patients is surgery with removal of the epileptogenic zone [22, 54]. The effectiveness of surgical treatment based on the achievement of a certain degree of seizure control is assessed according to Engel Epilepsy Surgery Outcome Scale developed by Engel J. in 1993 [55].

While removal of low-grade gliomas in 80–90% of cases helps achieve complete control of seizures according to the Engel classification system, in the case of high-grade gliomas this happens extremely rarely [22]. *Yao P. et al.* (2018) on a population of 108 patients evaluated the utility of electrocorticography (ECoG) in determining the volume of low-grade BG resection including the epileptogenic zone. One group consisted of patients in whom the volume of surgical intervention was aimed at total tumor removal without the use of ECoG, and the other group included patients who underwent total resection of glioma with additional removal of the epileptogenic zone, determined by ECoG. In the ECoG group, Engel I class was achieved by 74% of patients, while in the control group, only 39% of patients could get rid of seizures completely [56].

A rare cause of drug-resistant epileptic seizures in patients with BG is the presence of dual brain pathology [57]. In the study of *V.V. Krylov. et al.* (2016) histopathological analysis of tissue resected during surgery for pharmacoresistant epilepsy revealed that 1 out of 59 patients had a combination of focal cortical dysplasia and a brain tumor, and 1 patient suffered from AED resistant seizures due to a low-grade BG [58].

Akgun M.Y. et al. (2019) performed a research with the aim of morphological study of the mesial temporal cortex in 10 patients with low-grade gliomas of temporal localization in the absence of signs of double pathology according to MRI data. In 70% of patients, histological signs of gliosis were revealed, in 20% - focal cortical dysplasia, and only in 10% of patients the temporal cortex did not contain additional pathological tissue [59]. They also compared the effectiveness of epileptic seizure control achieved after total resection of low-grade gliomas located in temporal lobes with the extending of surgery volume due to hippocampectomy, which showed a greater effectiveness of the latter. Engel I class was achieved in 79% of patients after standard and in 87% after extended resection, which indicates a greater prevalence of concomitant pathology in temporal lobe gliomas than it is diagnosed in routine practice [60].

There is currently no algorithm for prescribing and discontinuing of AEDs in the postoperative period of glioma resection. The infiltrative nature of tumor growth is a risk factor for the recurrence of epileptic seizures, however, in case of its total removal, it is possible to achieve complete control over the seizures. The

decision to discontinue AED administration after surgery should be made taking into account the spectrum of their side effects and the restrictive behavior of patients due to the fear of recurrent seizures because of anticonvulsant treatment termination [61].

CONCLUSION

Symptomatic epileptic seizures are a manifestation of cerebral gliomas that significantly impairs the quality of life. In high-grade glioma patients, they appear less frequently than in case of low-grade gliomas, however, they are characterized by a higher incidence of status epilepticus and persistence of epileptic seizures after surgical treatment. Currently, there has been no generally accepted algorithm for the treatment of patients with symptomatic epileptic seizures caused by both newly diagnosed and recurrent gliomas.

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