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Review article

Brain tumor related-epilepsy

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ABSTRACT

Introduction: Gliomas are commonly associated with the development of epilepsy; in some cases the two conditions share common pathogenic mechanisms and may influence each other. Brain tumor related-epilepsy (BTRE) complicates the clinical management of gliomas and can substantially affect daily life.

State of the art: The incidence of seizures is high in patients with slow growing tumors located in the frontotemporal regions. However, recent studies suggest that epileptogenesis may be more associated with tumor molecular genetic markers than tumor grade or location. Although the exact mechanism of epileptogenesis in glioma is incompletely understood, glutamate-induced excitotoxicity and disruption of intracellular communication have garnered the most attention.

Clinical management: Management of BTRE requires a multidisciplinary approach involving the use of antiepileptic drugs (AEDs), surgery aided by electrocorticography, and adjuvant chemoradiation.

Future directions: Insight into the mechanisms of glioma growth and epileptogenesis is essential to identify new treatment targets and to develop effective treatment for both conditions. Selecting AEDs tailored to act against known tumor molecular markers involved in the epileptogenesis could enhance treatment value and help inform individualized medicine in BRTE.

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1. Introduction

Epileptic seizures often develop in patients with gliomas (40–70%) and approximately 30% are pharmacoresistant even after glioma resection [1,2]. Brain tumor-related epilepsy (BTRE) is characterized by symptomatic seizures due to the presence of a brain tumor, manifesting as focal aware or focal impaired awareness, generalized tonic–clonic, or focal to bilateral tonic–clonic seizures [3–5]. The incidence of seizure is higher in patients with slow growing, low-grade tumors located in the frontal and temporal lobes [2]. However, recent studies suggest that epileptogenesis may be more associated with molecular genetic markers than tumor grade or location [1,3].

Although glioma-related seizures have favorable effects on the overall survival of glioma patients, increased seizure burden and refractory seizures affect quality of life, causes cognitive deterioration, and significant morbidity [2]. To date, there is no standard of care for the management of BTRE. Despite tremendous progress in the field of neuro-oncology,

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the pathogenesis of BTRE is also incompletely understood. Insight into the mechanisms of glioma growth and epileptogenesis will provide the opportunity to develop interventions that target the dysregulated processes [1]. The aim of this review article is to discuss key topics in BTRE including epidemiology, epileptogenesis, and management with focus on adult glial-based tumors.

2. Epidemiology

2.1. *Prevalence*

Globally, cerebral gliomas of all grades account for 28% of all brain tumors and have an incidence of 3–6 per 100 000 per year, with nearly 80 000 new cases of primary CNS tumors in the USA estimated to be diagnosed within the year 2018 [6,7]. BTRE is estimated to occur in 40–70% of patients with glioma and pharmacoresistence occurs in 8–40% [6–10].

2.2. *Risk factors*

Identification of predictors of epileptic seizure in patients with glioma is valuable as epilepsy carries a substantial degree of morbidity and mortality [8,9]. The lifetime risk of epileptic seizures in patients with primary brain tumors varies by age, tumor grade, location, and size [8–16]. The incidence of preoperative seizure is lower in high grade brain tumors such as glioblastoma and primary CNS lymphoma, but higher in some lower grade tumors [8–10,17]. The probability of developing epilepsy ranges from 10% in primary lymphomas to 100% in dysembryoblastic neuroepithelial tumors (DENTs) [8,16,17]. Epilepsy has been reported to occur in up to 90% patient with low-grade gliomas [8,9]. Seizures also occur more commonly in patients with tumors located in cortical regions as opposed to subcortical areas, with a seizure frequency of 56% compared with 15%, respectively [8–11]. A summary of seizure prevalence and prognosis by tumor type is provided in Table 1.

Preoperative seizure incidence is highest in gliomas located in the frontal and temporo-insular regions [8,10,17]. Recent studies, however, suggest that epileptogenesis may have more to do with tumor molecular genetic markers than tumor grade or location [1,13]. Gliomas with an isocitrate dehydrogenase-1 (IDH1) mutation or an over expression of *p*53 overexpression (>40%), have a higher rate of seizures [13]. Similarly, secondary glioblastoma (i.e. those emerging from lower-grade gliomas) carries an increased likelihood of IDH1 mutation and seizures [13]. Other factors influencing preoperative seizure occurrence include premorbid epilepsy, tumor recurrence, and concomitant oncologic therapy [1,12].

Postoperative seizure control follows tumor activity and tumor progression begets seizures while adjuvant chemo-radiotherapy can reduce seizure burden [14]. In low-grade gliomas, favorable prognostic factors for postoperative seizure control are presence of pre-operative generalized seizures, surgery within one year after presentation, gross tumor resection, and successful preoperative control by AEDs [16]. To date, the exact biological and clinical factors that predispose to the development of postoperative seizures in brain tumor patients have not been established [18].

3. Clinical presentation

Seizures are commonly a presenting feature of supratentorial gliomas; however seizures could also emerge late in the disease course or as a result of oncologic treatments [1,2]. Seizure semiology mainly reflects the location of the lesion and would manifest as focal aware, focal impaired aware, generalized tonic–clonic, or focal to bilateral tonic–clonic seizures [2]. In a recent study patients with low-grade glioma: 23.7% had focal motor aware, 6.6% focal with impaired awareness, and 69.7% focal to bilateral tonic–clonic seizures [19]. In contrast, patients with high grade glioma had a later average age of onset with 38% focal motor aware seizures, 40% focal to bilateral tonic–clonic seizures, and 14% mixed focal and generalized onset seizures [19]. Patients can also present with clinical or subclinical status epilepticus (more common with high-grade gliomas) [20,21].

Preoperative seizures have favorable effects on the overall survival of glioma [11,17]. Some patients will continue to have

Table 1 – Seizure prevalence and prognosis in brain tumor-related epilepsy.

	Seizure frequency	Seizure freedom rate with optimal therapy[a]
Glioneuronal tumors		
Dysembryoblastic neuroepithelial tumor	90–100%	70–100%
Ganglioglioma	60–95%	60–90%
Low-grade glioma		
Astrocytoma	50–75%	60–75%
Oligodendroglioma	75–85%	60–85%
Diffuse gliomas[b]	60–80%	50–75%
Anaplastic gliomas[c]	45–60%	40–60%
Glioblastoma multiforme	30–45%	40–50%
Meningioma	30–40	40–80%
Primary CNS lymphoma	10–15%	Variable
Brain metastasis	20–35%	Variable

[a] With gross-total resection and AEDs.
[b] Diffuse astrocytoma, diffuse oligodendroglioma, oligoastrocytomaa, pleomorphic xanthoastrocyoma.
[c] Anaplastic astrocytomas, anaplastic oligodendroglioma, and anaplastic oligoastrocytomas.

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