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Review article

Brain tumor related-epilepsy

Eric D. Goldstein, Anteneh M. Feyissa *

Department of Neurology, Mayo Clinic, Jacksonville, FL, United States

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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 BTRE.

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1. Introduction

Epileptic seizures often develop in patients with gliomas (40–70%) and approximately 30% are pharmaco-resistant 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,

* Corresponding author at: Department of Neurology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, 32224 FL, United States.

E-mail address: Feyissa.Anteneh@mayo.edu (A.M. Feyissa).

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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 pharmacoresistance 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 p53 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 chemoradiotherapy 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, oligoastrocytoma, pleomorphic xanthoastrocytoma.

^c Anaplastic astrocytomas, anaplastic oligodendroglioma, and anaplastic oligoastrocytomas.

seizures after glioma resection, whereas some only start to experience seizures following surgery [17]. As a sign, seizures may accompany localizing and non-localizing symptoms including focal motor or sensory symptoms, irritability, altered mental status, and dizziness. Seizures and their sequelae could mimic tumor progression and prompt unwarranted interventions. Seizure could also masquerade signs of increased intracranial pressure, such as diplopia, nausea, headache and decreased visual acuity. A recurrence or worsening of seizures following first-line antitumor therapy typically heralds progression of tumor [14,16].

4. Pathophysiology

The pathogenesis of BTRE remains poorly understood but appears to be multifactorial [1–5]. Local inflammation, hypoxic-ischemic injury, metabolic changes and disruption of blood-brain barrier (BBB) have been suggested to promote epileptogenesis [22]. Disturbances at the cellular level including alterations in synaptic and neuronal function and connectivity and excitotoxicity and alterations in the expression of specific genes and proteins relevant to intracellular communication is one proposed mechanism that has recently gained traction [1,22] (Fig. 1). The mechanism of preoperative seizures is likely

different from those of postoperative seizures [18,21,23]. In the latter, surgical and effects of chemoradiotherapy are thought to contribute to epileptogenesis.

4.1. Local direct effect

Historically, mechanistic theories to explain glioma-related seizures have included architectural distortion of surrounding cortex, vascular compression, cerebral ischemia, or lesional hemorrhage [22,23]. The peritumoral microenvironment may contribute to epileptogenicity via a multitude of avenues. Increased vascular permeability from disruption of the BBB may occur through tumoral down-regulation of transmembrane junctional proteins such as claudin-1, occludin, vascular endothelial growth factor (VEGF), and transforming growth factor- β (TGF- β) [24]. The ensuing increased peritumoral edema could lead to alterations in the tumor microenvironment, which may promote epileptic activity through the activation of glutamatergic transmission [24]. The tumor itself may also directly promote epileptogenesis by out-stripping of its vascular supply, leading to hypoxia, tissue necrosis, aberrant extracellular ionic concentrations, and acidosis which could result in alterations in neuronal metabolism, worsening of peritumoral edema, and release of inflammatory mediators that foster epileptogenesis [22–24]

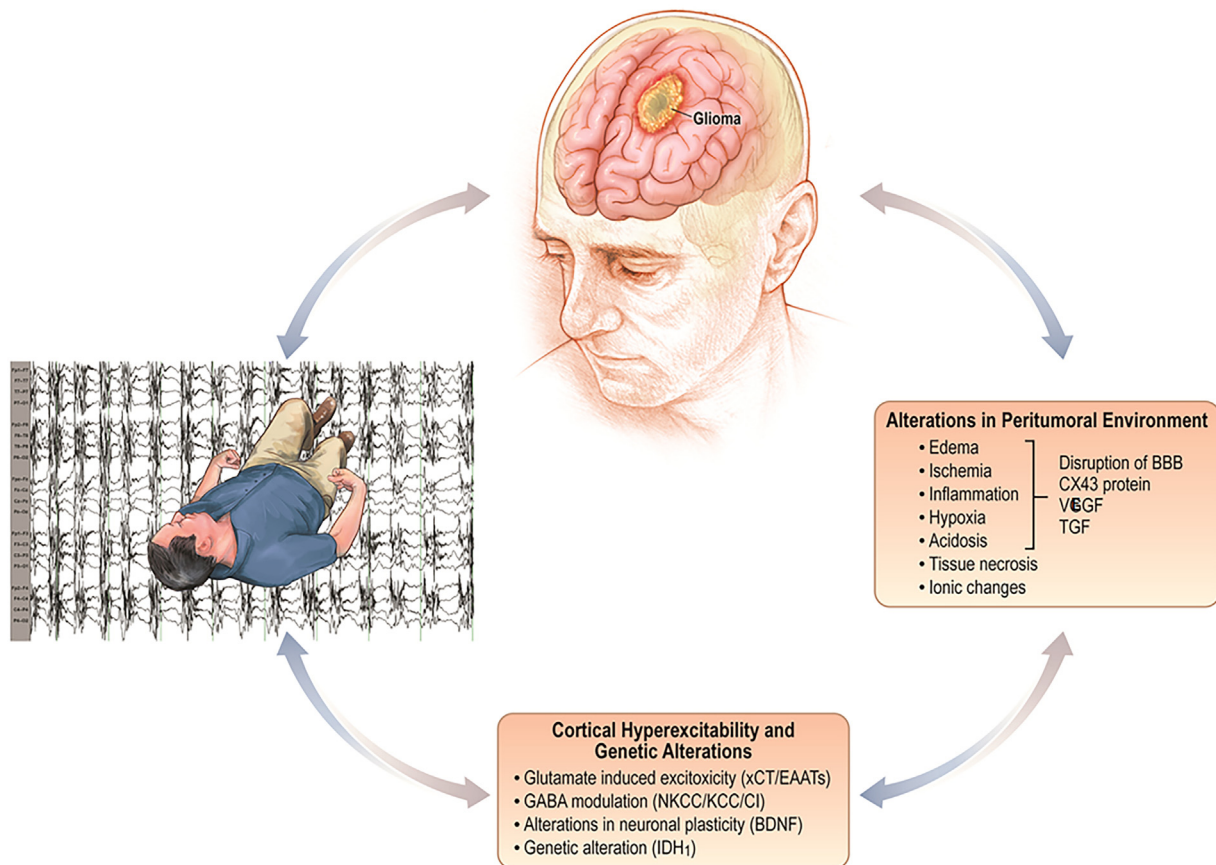


Fig. 1 – Proposed mechanisms of epileptogenesis in BTRE. BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; Cl, chloride; CX43, connexin 43; xCT, cysteine-glutamate antiporter; EAAT, excitatory amino acid transporter; IDH1, isocitrate dehydrogenase 1; KCC, potassium chloride cotransporter; NKCC, Na⁺–K⁺–Cl[–] transporter; TGF, transforming growth factor beta 1; VEGF, vascular endothelial growth factor.

4.2. Cortical hyperexcitability

4.2.1. Glutamatergic modulation

Glutamate appears to have a pivotal role in BTRE, with elevated concentrations found within the peritumoral microenvironment corresponding to a higher risk for seizure development and recurrence [25–29]. Extracellular glutamate concentrations are regulated in part by the cysteine-glutamate antiporter (xCT) and the excitatory amino acid transporter reuptake system (EAAT1 and EAAT2) [1,29–31]. Within glioma tissue, xCT has been found to be upregulated, and is thought to render a survival advantage by minimizing oxidative damage through elevated glutathione levels in the relatively hypoxic peritumoral microenvironment [27–31]. EAAT2 and glutamine synthetase have also been found to be downregulated, and further increase the extracellular glutamate concentration [25–31]. The excess glutamate could result in excitotoxic damage promoting epileptogenesis [28,29].

Gathering evidence suggests that tumor growth stimulates seizures and that seizures encourage tumor growth suggesting the two conditions share common pathogenic mechanisms and influence each other [33–35]. A close link exists between seizures and glioma growth in that elevated extracellular glutamate levels promote over-activation of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors in both conditions [33,34]. The aberrant activation of NMDA and AMPA receptors could promote tumor progression through influence on the mGluR, mitogen-activated protein signal related kinase (MAPK), phosphoinositide 3-kinase (PI3K/AKT) and the mammalian target of rapamycin (mTOR) pathways [33,35]. Activation of the PI3K and mTOR pathways leads to the expression of the synaptic protein neuroligin-3 (NLGN3), which promotes glial precursor cell differentiation and glioma growth [33]. Recently Venkatesh and colleagues have elegantly demonstrated that excitatory neuronal activity promotes high grade proliferation and growth in vivo by using optogenetic control of cortical neuronal activity in a patient-derived pediatric glioblastoma xenograft model [33]. However, further studies are needed to reconcile this phenomenon with the rate of seizures by glioma grade (higher with slow growing glioma), location, genetic markers, and ongoing therapies.

4.2.2. γ -Aminobutyric acid (GABA) modulation

GABA receptors are anionic ligand-gated channels, permeable most readily to chloride anions mainly promoting neuronal inhibition [36]. Important in the modulation of chloride homeostasis is the potassium chloride cotransporter (KCC2) which transports chloride anions into the extracellular space [36–39]. Elevated extracellular glutamate concentrations are known to downregulate KCC2 leading to elevated intracellular chloride concentrations causing hyperpolarization of GABAergic neurons and leading to reduced network inhibition [38]. Although GABA levels were higher in peritumoral tissue than in the tumor core, GABAergic synaptic density on nearby pyramidal cells was reduced. This leads to a cumulative reduction in inhibitory postsynaptic potential, which could foster epileptogenesis [37,38]. The dysregulation of intracellular chloride and GABAergic activity has also been suggested to promote glioma cell mitosis and migration,

further supportive of a shared mechanism between seizures and glioma growth [40].

4.2.3. Changes in neuroplasticity

Gliomas could enhance axonal branching and synaptic formation, creating hyperexcitability and predisposition for seizures [41,42]. This could potentially result in the alterations of the neuronal network creating a conducive environment for seizure propagation. One proposed mechanism is through elevated peritumoral concentrations of matrix metalloproteinase 9 (MMP-9), promoting the conversion of pro-brain derived neurotrophic factor (BDNF) to mature-BDNF [41,42]. This results in increased activation of tropomyosin receptor kinase B, which likely promotes axonal branching and results in hyperexcitable circuits [40,42]. These two processes are further augmented by chronic activation of NMDA receptors in the setting of elevated extracellular glutamate. These pathways, together with abnormal neuronal morphology and pathologic synaptic plasticity, may further promote epileptogenesis [41].

4.3. Genetic alterations

Several molecular biological factors including IDH1, p53, O⁶-methylguanine DNA methyltransferase (MGMT), MMP-9, BDNF, and adenosine kinase (ADK) have been recognized in the epileptogenesis of brain tumors [42–46]. Patients with IDH enzyme 1 and 2, specifically codons R132 and R172, have been reported to have an increased likelihood of developing seizures [13,47]. The non-mutated (wild type) enzyme catalyzes the conversion of isocitrate to α -ketoglutarate while in its mutated form, it reduces α -ketoglutarate to D-2-hydroxyglutarate (D2HG) [48,49]. The overproduction of D2HG may act similarly as glutamate on NMDA receptor fostering epileptogenesis [47]. Additionally, loss of heterozygosity on chromosome 19q, <40% p53 overexpression, and the lack of Ki-67 have been suggested to be associated with improved seizure frequency and control [42–46]. On the other hand, astrocytomas with a higher expression of adenosine kinase (ADK) have been shown to have lower physiologic extracellular concentrations of the inhibitory neurotransmitter adenosine and increased aquaporin-4 channel expression, which are thought to reduce seizure threshold [45,46].

5. EEG in BTRE

5.1. Scalp EEG

EEG changes observed in gliomas result mainly from disturbances in bordering brain parenchyma, as tumoral tissue is electrically silent [50]. Findings from scalp EEG may include normal, focal or generalized slow activity, focal attenuation of background activity, interictal epileptiform discharges (IEDs), and ictal discharges [52]. For patients with glioma, the presence of IEDs within the tumor site as well as seizure semiology may suffice for establishing an anatomic connection between the tumor and the origin of the seizure [51]. Hence, very few centers order long-term video EEG monitoring (LTM) in patients with glioma. However, LTM can be useful for various reasons including distinguishing epileptic from

nonepileptic events, identifying subclinical seizures as the cause of an unexplained change in cognitive state, and in the management of status epilepticus [20,21,51]. The detection of subclinical seizures in patients with glioma could be indicative of progression or recurrence of the disease [23,24].

5.2. Intraoperative electrocorticography

Patients with BTRE rarely undergo extraoperative intracranial monitoring with subdural grid and strip electrodes. Instead, some patients undergo intraoperative electrocorticography (ECoG), typically during awake craniotomy [52–55]. The primary role of ECoG during brain tumor surgery is to confirm the absence of after-discharges during electrical cortical stimulation [52]. Craniotomies tailored to limit cortical exposure, even without localization of language sites, could permit most gliomas to be aggressively resected with minimal postoperative deficit [54–58]. Often, the epileptogenic cortex is not perfectly circumscribed and ECoG could help determine

with high specificity the epileptogenic focus location and ictal spread pathways, aiding in either presurgical planning or intraoperative guidance for optimization of the resection [56]. High-frequency oscillations seen during EcoG have recently been shown to determine epileptogenicity of gliomas and help tailor surgical resection [57]. Along the same lines, several groups have reported favorable seizure outcomes using ECoG-guided tailored resection [54–56]. Lastly, ECoG can help recognize electrographic or subtle clinical seizures that may not otherwise be recognized intraoperatively [57,58]. Figs. 2–4 highlight illustrative cases where ECoG was used in the management of patients with BTRE.

6. Management of BTRE

Conclusive evidence based guidelines for the management of BTRE is not currently available [59–61]. The overall management of BTRE requires an interdisciplinary approach with

Table 2 – Commonly used antiepileptic drugs in brain tumor-related epilepsy.

	Mechanism of action	Dosage (maintenance)	Drug–drug interactions	Pros	Cons and major AEs
Levetiracetam (LVT)	Modify presynaptic protein SVA2	750–1500 mg BID	None	<ul style="list-style-type: none"> • Safety and tolerability • Potential concomitant antineoplastic efficacy • Large data on efficacy available 	<ul style="list-style-type: none"> • Worsening NPAA in frontal lobe gliomas • Requires dose adjustment in renal failure and dialysis
Valproic acid (VPA)	Multiple mechanisms	250–1000 mg BID	Mild enzyme inhibition (LTG)	<ul style="list-style-type: none"> • Potential anti-tumor effect • Large data on efficacy available 	<ul style="list-style-type: none"> • Thrombocytopenia • Unsafe in a reproductive aged women
Lacosamide	Slow inactivation of voltage gated sodium channels	100–200 mg BID	Not clinically significant	<ul style="list-style-type: none"> • Efficacious regardless of tumor activity • Synergism with LVT use • Favorable pharmacokinetic profile 	<ul style="list-style-type: none"> • Diplopia and dizziness especially when combined with LTG • Caution in patients with AV block
Perampanel	AMPA receptor antagonist	8–10 mg daily	Mild enzyme inhibition	<ul style="list-style-type: none"> • Once daily dosing • Potential anti-tumor effect 	<ul style="list-style-type: none"> • Homicidal ideation and threats; psychosis; delirium
Lamotrigine (LTG)	Fast inactivation of voltage gated sodium channels	100–200 mg BID	Minimal except with concomitant VPA use	<ul style="list-style-type: none"> • Good tolerability and efficacy • Low drug interactions • Synergism with VPA or ZNS use 	<ul style="list-style-type: none"> • No IV formulation • Allergic skin reactions • Slow up-titration • No IV formulation
Zonisamide (ZNS)	Multiple mechanisms	100–300 mg daily	Minimal	<ul style="list-style-type: none"> • Class A evidence on efficacy 	<ul style="list-style-type: none"> • No IV formulation • Weight loss, negative impact on cognition
Oxcarbazepine	Fast inactivation of voltage gated sodium channels	150–600 mg BID	<ul style="list-style-type: none"> • Mild enzyme inhibition • Pharmacokinetic interactions 	<ul style="list-style-type: none"> • Potential concomitant antineoplastic effect 	<ul style="list-style-type: none"> • Hyponatremia (2–5%) • No IV formulation
Topiramate	Multiple mechanisms	100–200 mg BID	<ul style="list-style-type: none"> • Mild enzyme inhibition • Pharmacokinetic interactions 	<ul style="list-style-type: none"> • Potential concomitant antineoplastic effect 	<ul style="list-style-type: none"> • No IV formulation • Weight loss, negative impact on cognition
Enzyme inducing antiepileptics (EAIADs)	Fast inactivation of voltage gated sodium channels	Variable	<ul style="list-style-type: none"> • Strong CYP 450 enzyme inducers 	<ul style="list-style-type: none"> • Class A evidence for efficacy (phenytoin and carbamazepine) 	<ul style="list-style-type: none"> • Osteoporosis, Diplopia, and Ataxia • Lower efficacy of antineoplastic agents

AE; adverse events; BID; twice daily; CYP450; cytochrome; IV, intravenous; NPAA, neuropsychiatric adverse events.

considerations for antiepileptic drugs (AEDs), concomitant chemotherapeutics and radiotherapy, as well as surgical intervention [61].

6.1. AEDs

AEDs are often the first line therapy in BTRE [60]. The introduction of an AED should be made upon the first clinical seizure, as prophylactic or perioperative AEDs are not recommended regardless of tumor type [62–65]. Those presenting with a first-time seizure and a glioma warrant AED initiation, as there is increased likelihood of future seizures [65]. The final choice of AED in BTRE is typically based on several individual patient characteristics including age, sex, weight, seizure type, comorbidities or co-therapies that increase the risk of drug interaction [61,65]. There is a general agreement to avoid enzyme inducing AEDs (EIAEDs) (e.g. phenytoin, carbamazepine, phenobarbital) in spite of their

good anticonvulsant efficacy, as they can alter the pharmacokinetics of anti-neoplastic agents [60]. Monotherapy is preferred first-line, though polytherapy may be required in most [64]. The duration of therapy for patients with BTRE is not guideline based but is likely dependent upon tumor histopathologic and molecular findings [64]. For example, low-grade gliomas that are amenable to resection will not likely need chronic AED therapy and AED wean after 2 years of seizure freedom post-operatively could be considered [63,64]. In contrast, those with high-grade gliomas have a shortened life expectancy and tend to be resistant to surgical and medical therapy, therefore, these patients are likely to remain on AED therapy indefinitely [61,65].

6.1.1. Commonly used AEDs

There is no evidence that specific AEDs are more effective than others in BTRE [66–68]. However, levetiracetam is the most commonly used given its clinical efficacy, low rate of

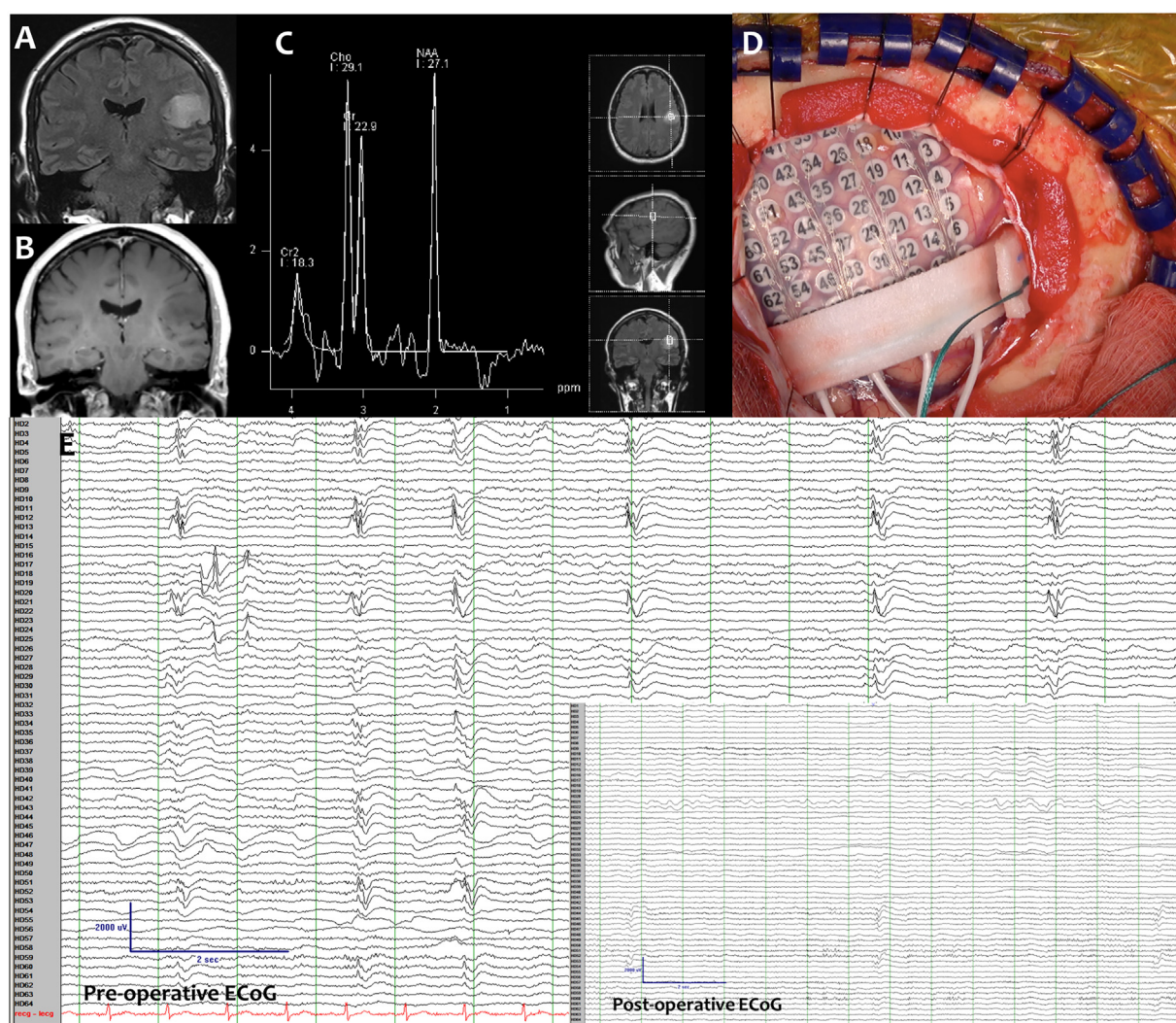


Fig. 2 – A 57 year old with focal aware sensory seizures with/without aphasia. (A) Coronal FLAIR and (B) post-contrast T1 MRI revealing a non-enhancing left parietal operculum glioma. (C) MR-spectroscopy showing elevated choline peak suggestive of a neoplasm. (D) Intraoperative photo showing a high density 8 × 8 grid overlying the tumor. Intraoperative electrocorticography prior to tumor resection showing frequent periodic epileptogenic discharges involving the peritumoral area (E) with resolution of peritumoral frequent periodic epileptogenic discharges post-resection (post-operative ECoG, E).

medication interactions, availability of parenteral dosing, and safety profile [67]. Levetiracetam is considered as an attractive option, both as monotherapy and in combination [69]. Numerous studies administering levetiracetam either as monotherapy or add-on therapy have reported seizure freedom ranging from 60 to 100% [69,70]. The use of levetiracetam in combination with a range of AEDs including Valproic acid and lacosamide may produce enhanced antiepileptic activity (pharmacodynamic synergism) [70]. Nevertheless, neuropsychiatric adverse event (NPAEs) monitoring is crucial with levetiracetam use particularly in those with frontal gliomas, since these patients are at higher risk of NPAEs. NPAEs in this setting could lead to suboptimal compliance and poor seizure control [71].

The rationale for the use of valproic acid monotherapy is supported by a large experience and efficacy profile in BTRE showing seizure freedom in 30–78% patients with low-grade glioma or GBMs [72]. However, VPA may cause thrombocytopenia (particularly in combination with chemotherapy), increased appetite, and tremor. Unlike levetiracetam, valproic acid

requires close monitoring of serum levels [70]. If seizure control is insufficient with monotherapy of levetiracetam or valproic acid, polytherapy with both drugs combined is preferred over sequential trials of AED monotherapy [67]. When seizures are resistant to first line therapy, we suggest adding a second AED with a differing/unique mechanism of action (rational polypharmacy) than just replacing the existing agent. Subsequent AEDs that represent justifiable choices include lacosamide, lamotrigine, zonisamide, parampanel, or oxcarbazepine. Despite these options, however, the occurrence of pharmacoresistance is seen in 8–40% of patients with BTRE [64,73–75]. A summary of the commonly used AEDs is provided in Table 2.

6.1.2. Anti-tumoral properties of AEDs

The use of levetiracetam and valproic acid in patients with GBMs has recently drawn attention because of their potential beneficial antitumor activity leading to increased survival [69,70]. Levetiracetam may have anti-tumoral effect by increasing the efficacy of temozolomide (TMZ) through epigenetic silencing of the enzyme MGMT [69]. VPA is also

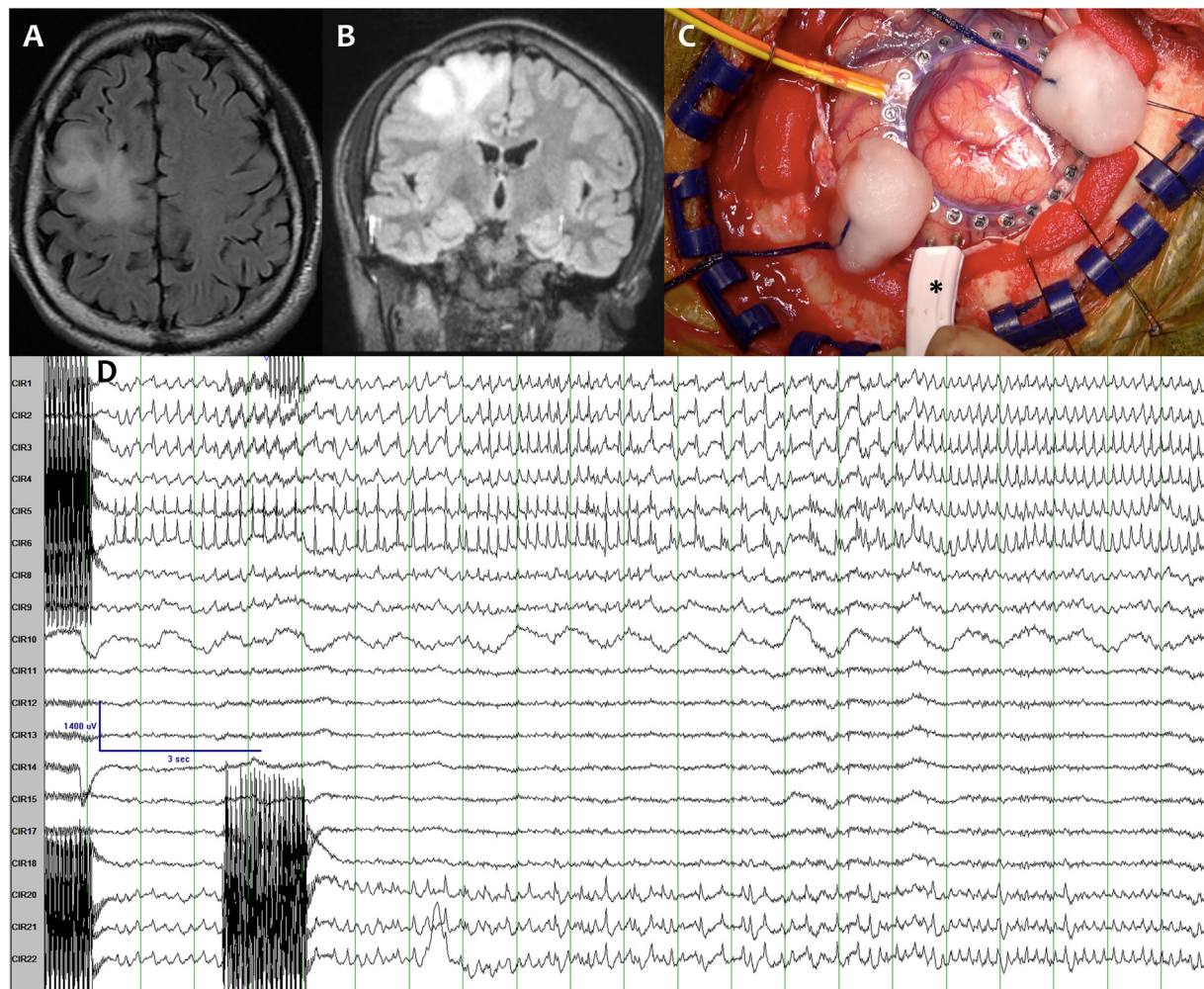


Fig. 3 – A 22 year old with generalized tonic-clonic seizures. (A) Axial T1 and (B) coronal FLAIR MRI showing a mass in the subcortex and right superior and middle frontal gyri. (C) Cortical mapping using an Ojemann stimulator (*) while recording using a 22-contact circular grid. (D) Intraoperative electrocorticography showing stimulation artifact and a stimulation induced electrographic focal seizure during cortical mapping. Cold irrigation aborted the seizure while further stimulations identified the motor cortex (not shown).

suggested to have anti-tumoral effect and may provide a survival advantage for patients undergoing concomitant treatment with TMZ through histone deacetylase enzyme inhibition, enhancement of cellular redox reactions in combination with chemotherapy and reduced clearance of TMZ through P450 interactions [72,76,77]. Those AEDs with anti-glutamatergic mechanisms (such as perampanel and talampanel) have also been shown to have antitumoral effect [32,78]. Lastly, in vitro and animal models have suggested anti-tumor effects with topiramate and phenytoin [60,63–65].

6.1.3. Prophylactic AED use

Most neurosurgeons will introduce AED monotherapy following tumor resection in patients without a history of seizures as a primary preventative strategy [62]. The American Academy of Neurology (AAN) and multiple studies have recommended against prolonged prophylactic or perioperative AEDs regardless of tumor type due to lack of proven benefit [62,79,80]. However, we suggest the consideration of prophylactic AEDs in patients without history of seizures in the presence of additional risk factors related to the tumor genetic marker (e.g. IDH1 mutant) and location (e.g. temporal lobe) of the

tumor and occurrence of IEDs on EEG. Given our growing understanding of the relationship between tumor genetic markers and epileptogenicity as well as the prospect of individualized medicine, it is tempting to speculate that in the near future we may be able to identify those with the highest risk of developing seizures (for example IDH1 mutant temporal lobe GBM) and initiate prophylactic AED therapy early. Perhaps, the early initiation of AEDs with antitumorigenic properties (e.g. perampanel) in these patients could not only prevent seizures but may also potentially suppress of glioma growth.

6.2. Surgical treatment

Brain tumor surgery aims not only to improve survival through reduction of tumor burden, but also by achieving seizure freedom [81,82]. For patients with BTRE, gross-total tumor resection, including the peritumoral epileptogenic foci provides the greatest chance of seizure freedom and reduced AED requirement [81–84]. Patients undergoing tumor resection need to have a preoperative functional magnetic resonance imaging (MRI) and intraoperative ECoG for preservation of

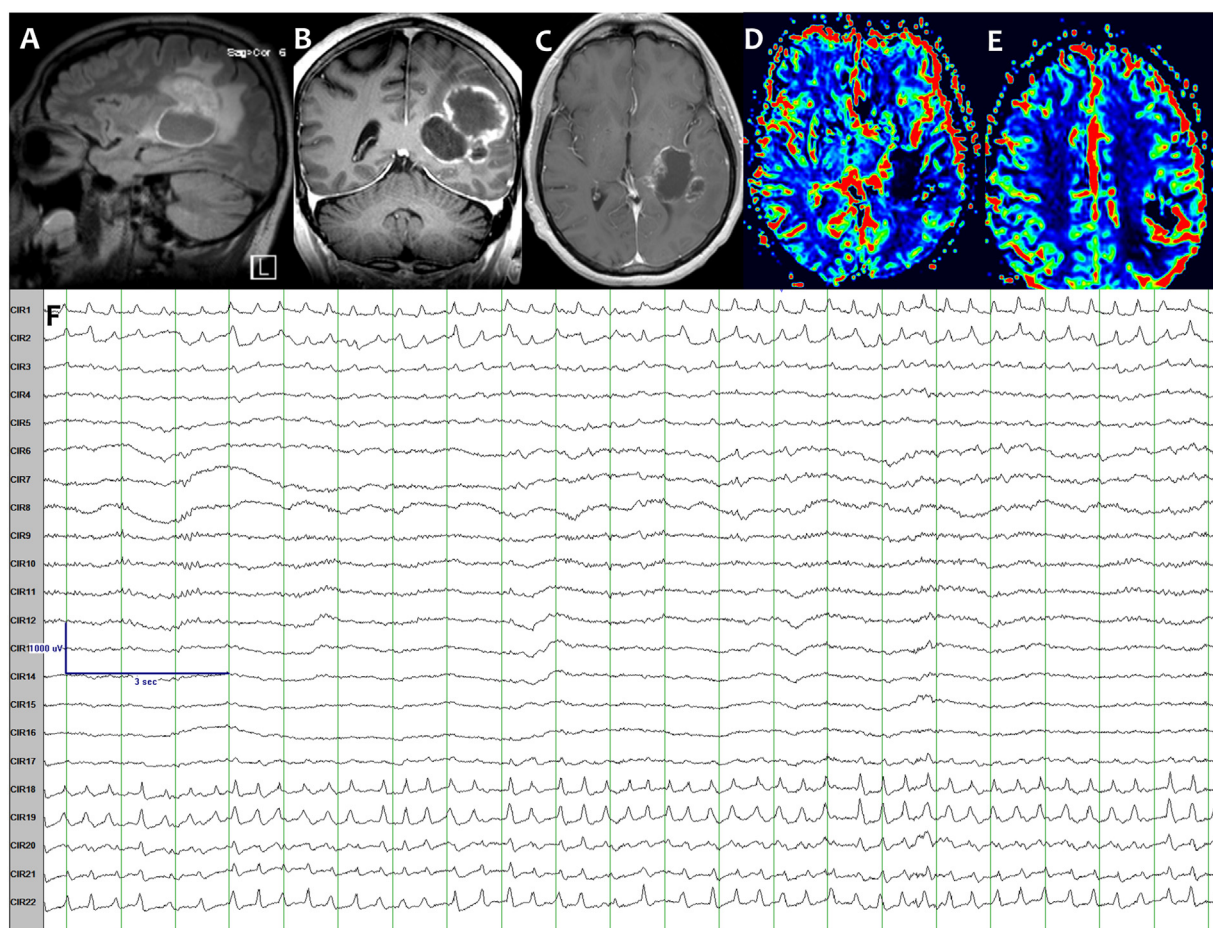


Fig. 4 – A 62 year old with glioma without history of seizure undergoing intraoperative cortical mapping. (A). Sagittal FLAIR, (B) post-contrast T1 coronal and (C) post-contrast T1 axial MRI showing a ring-enhancing mass of the left parietal and temporal lobes. Note increased cerebral blood volume corresponding to contrast enhancement along the inferomedial (D) and postero-superior (E) margins. Intraoperative electrocorticography prior to cortical stimulation mapping using a 22-contact circular grid revealed a focal subclinical seizure discharge (F) which was aborted by a 4 mA cortical stimulation using an Ojemann stimulator (not shown).

eloquent structures and minimizing postoperative deficits [82]. Gross total resection reportedly resulted in seizure freedom rates ranging from 65 to 77% [81,83,84]. High grade gliomas typically require tumor resection followed by radiation therapy with concomitant and adjuvant chemotherapy with seizure freedom rates ranging from 40 to 77% [84]. Evidence is supportive of total surgical resection for low grade gliomas within the insula if seizures become intractable [85]. Complete resection, lack of pre-operative seizures, seizures other than focal seizures, tumor recurrence and previous seizure response to pharmacotherapy has been associated with improved postoperative seizure control [84,86]. Less favorable postoperative seizure freedom outcomes were found in patients with short disease duration, total resection, parietal lobe based tumors, and preoperative focal to bilateral seizures [18]. Brain MRI may also serve as a prognosticative tool for postoperative seizure risk. Nodularity and/or blurring of tumor borders and mass effect on T2 weighted fluid attenuated inversion recovery (FLAIR) or contrast-enhanced T1 weighted brain MRI sequence may reflect tumor growth and increased seizure propensity [87,88]. We have provided illustrative cases to highlight various imaging findings in BTRE in Figs. 2–4.

6.3. Chemotherapy and radiotherapy

Radiotherapy contributes to better seizure control with reported seizure freedom ranging from 38 to 75% at 12 months in one study [89,90]. The reduction in seizure burden appears to worsen with time to treatment, with focal radiotherapy being performed early in the therapeutic course being more beneficial [89,90]. Treatment with TMZ or procarbazine-lomustine-vincristine also provided a reduction in seizure frequency, varying between 48% and 100% [90].

6.4. Immunotherapy

Immunotherapy of gliomas holds great promise but largely lacks evidence of efficacy from clinical trials [91]. A wide variety of immunotherapeutic agents have been introduced for the treatment of primary brain tumors. Bevacizumab, a humanized monoclonal antibody against VEGF which is FDA approved for recurrent GBM [92], may speculatively reduce peritumoral vasogenic edema and reduction of peri-tumor microenvironment epileptogenicity. Additionally, a peptide vaccination against IDH1 mutations being developed could hypothetically help reduce seizure burden in BTRE.

7. Conclusions

Epileptic seizures are common (40–70%) in patients with brain tumors, with seizure control being an important part of overall clinical management and preservation of quality of life. Although the exact mechanism of epileptogenesis in glioma is incompletely understood, glutamate-induced excitotoxicity and disruption of intracellular communication have garnered the most attention. The diagnosis of BTRE benefits from routine and prolonged video EEG monitoring. The latter is particularly useful in distinguishing epileptic from nonepileptic events, identifying subclinical seizures as the cause of an unexplained

change in cognitive state, and in the management of status epilepticus. Management of BTRE requires a multidisciplinary approach involving the use of antiepileptic drugs (AEDs), surgery aided by electrocorticography, and adjuvant chemoradiation. Although there are not conclusive guidelines for AED use in BTRE, the use of agents with favorable pharmacokinetic (e.g. levetiracetam) and antitumoral properties (e.g. vaproic acid) as well as avoidance of EIAEDs (inspite of their good anticonvulsant efficacy) is recommended. With the ever-growing understanding of BTRE pathogenesis, novel treatment strategies are being examined. However, further studies are needed to help elucidate the shared mechanisms of glioma growth and epileptogenesis in order to identify new treatment targets and develop effective treatment for both conditions.

Conflict of interest

None declared.

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