
Pathogenesis and Management of Brain Tumor-Related Epilepsy

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Abstract: Up to 50% of patients with brain tumors will initially present with seizures, while an additional 10–30% will develop seizures during the course of the disease. Gliomas are the most common primary intracranial tumors and are associated with a number of changes which are involved in the pathogenesis of epilepsy, including blood-brain barrier disruption, molecular changes, edema, and peritumoral environmental changes. Epilepsy is a source of significant morbidity and mortality for patients with gliomas. The two main treatments for patients with glioma-related epilepsy involve antiepileptic drugs as well as surgical resection of the mass and surrounding epileptogenic tissue, if feasible. Given the propensity for neighboring tissue to also be epileptogenic, intraoperative electrocorticography can be of benefit to define the seizure onset and spread areas. Surgical treatment of glioma-associated epilepsy can provide significant relief for affected patients. Unlike non-lesional epilepsy, which is primarily managed medically, glioma-related epilepsy frequently requires surgery because of its medically refractory nature.

Keywords: anti-epileptic drugs; high-grade gliomas; intractable epilepsy; refractory seizures; tumor-associated epilepsy

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INTRODUCTION

Seizures are one of the common presenting symptoms of brain tumors, accounting for up to 50% of initial presentations. One third of patients diagnosed with a brain tumor will develop seizures during the clinical course if they did not initially present with seizures (1–4). Although the incidence of seizures is high among brain tumor patients, the incidence of intracranial tumors as an underlying etiology of epilepsy is relatively low (3, 5). Despite significant advances, management of seizures in patients harboring a brain tumor remains challenging. These difficulties arise from suboptimal response to anticonvulsants, interplay between antiepileptic drugs (AEDs) and chemotherapeutic agents, and possible adverse effects of both medical and surgical treatment. Seizures can tremendously affect patients' quality of life and negatively impacts overall survival (6). The focus of this chapter will be new literature and guidelines related to brain tumor-related epilepsy (BTRE).

EPIDEMIOLOGY AND PATHOGENESIS

The exact pathophysiology of BTRE is not well characterized; however, it is thought to be multifactorial (Figure 1) (7, 8). Tumor burden, type, location, growth rate, microenvironment of the blood-brain barrier, altered neurotransmitter homeostasis, and gap junction alterations are factors that influence

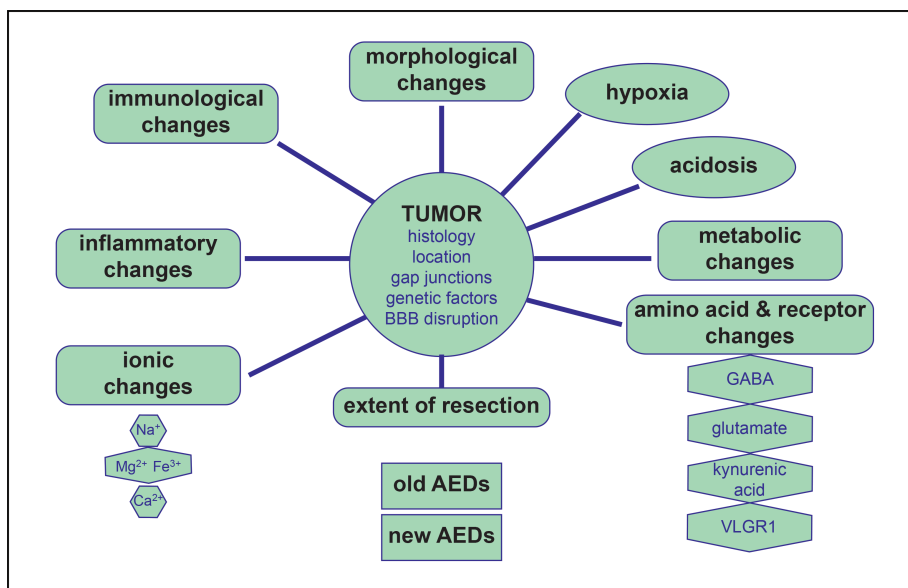


Figure 1. Known mechanisms underlying the pathogenesis of brain tumor-related epilepsy. Modified from Wu et al. (39).

BTRE (7, 8). The likelihood of epilepsy among patients with brain tumors differs depending on the tumor's histopathological subtype. Patients with low-grade gliomas have a greater tendency to suffer from seizures than those with high-grade gliomas. One study found that patients diagnosed with low-grade glioma had a significantly higher rate of seizures compared to patients diagnosed with glioblastoma (85% vs. 49%, respectively) (9). Dysembryoplastic neuroepithelial tumors (DNETs) and gangliogliomas have an extremely high propensity for seizures with an incidence greater than 80% (3, 10). Metastatic lesions tend to have a low incidence of seizures (9, 11, 12). Melanoma, however, has the highest seizure rate among the metastatic lesions because it involves gray matter, frequently has multiple lesions, and has an intrinsic high frequency of hemorrhage (13, 14).

Tumor Location

Tumor location is one of the most important aspects to consider when it comes to tumor epileptogenesis. Cortical tumors involving the frontal, temporal and parietal cortices as well as tumors in the cortical gray matter are associated with greater seizure frequency compared to lesions involving the infratentorial region, suprasellar region, or occipital lobe (Table 1) (1, 10). Seizure type is also associated with anatomical location of tumor. For example, focal awake seizures are associated with lesions involving left inferior and middle frontal gyrus, while focal unaware seizures are associated with the right temporal-insular region (15).

Tumor Growth Rate

Studies show that seizure prevalence and tumor growth rate are inversely proportional (9). Intuitively, slower growing and more indolent gliomas have a longer amount of time to provoke a seizure. Moreover, epileptogenesis requires complex re-organization and vascularization of tumor cells which often does not happen with rapidly growing tumors (7). Moreover, slow growing neoplasms tend to possess innate epileptogenic properties (7).

The pathogenesis of epilepsy differs among the various types of tumors. Tumors such as DNETs have high incidence of seizure because they tend to cause

TABLE 1

Seizures by tumor location in 65 patients with gliomas. Adapted from Lote et al. 1995 (9)

Tumor Location	Seizure at Onset	Recurrent Seizures	Late Onset Seizures	Status Epilepticus
Frontal	10/19	8/10	2/9	0/19
Temporal	3/11	3/3	2/8	1/11
Parietal	10/24	7/10	3/14	5/24
Occipital	0/2	—	2/2	1/2
Multifocal/Bilateral	6/9	3/6	1/3	3/9

cortical disruption due to disruption of the underlying cortical and subcortical structures (3, 10). The mechanisms behind the higher seizure frequency of other low-grade lesions is likely secondary to mechanical and vascular changes which slowly develop overtime (10). In contrast, high-grade gliomas and other rapidly dividing tumors tend to cause seizures because of irritation from necrosis or products of hemorrhage, such as hemosiderin (10, 16–21).

Neurotransmitters and Gap Junctions

Various animal and human tissue studies have identified glutamate, γ -aminobutyric acid (GABA), and adenosine kinase (ADK) as possible contributory factors for epileptogenesis in patients with brain tumors (22–24). Glioma studies in animals illustrated that seizure activity originated due to elevated glutamate production causing hyperexcitability around the peritumoral area (22). Studies comparing patients with lesion-associated medically refractory epilepsy and patients with similar lesions but no clinical epilepsy demonstrated that approximately 73% of tissue obtained from patients with lesional refractory epilepsy shows disruption of GABA and N-methyl-D-aspartate (NMDA) receptors (19). Dysregulation of ADK among the peritumoral tissue has also been hypothesized to induce seizure activity among patients with brain tumors. One study comparing normal brain tissue with excised epileptogenic foci of patients with epilepsy showed higher expression ADK in tissue of epilepsy patients (23). Disruption of the blood-brain barrier can also cause dysregulation of neurotransmitters such as glutamate and GABA and can contribute to BTRE (25). A recent study noted that proteolytic enzymes released by tumor cells disrupt perineuronal nets resulting in decreased GABAergic inhibition and overall excitation/inhibition imbalance (26).

One of the main functions of gap junctions in the brain is intercellular communication. Connexin 43 (CX43) is an important transmembrane protein and functional element of gap junction; its expression was found to be high in glial cells, such as astrocytes (27). Peritumoral cells in low-grade gliomas also express CX43 to a greater extent than the peritumoral cells of high-grade gliomas, which could be a reason why patients with low-grade gliomas have seizures more frequently than patients with malignant gliomas (28–31). Unsurprisingly, drugs that target gap junctions may have an anticonvulsant effect (30, 31).

Molecular Genetics and Peritumoral Environmental Changes

The genetic implications of BTRE are poorly understood. Genes such as *LGII* (a tumor-suppressor gene) and phosphatase and tensin homolog (PTEN) have been associated with gliomas and epilepsy; however, their exact role in epileptogenesis is not well characterized (32–35). The microenvironment and neurotransmission between peritumoral tissue and normal brain tissue is vastly different (36). Gliomas cause disruption of the blood-brain barrier in surrounding tissue by changing the endothelial permeability which can lead to vasogenic edema, inflammatory changes, poor perfusion, and changes in hemostasis (37). All these microenvironmental changes in peritumoral tissue can lead to sodium and calcium imbalance in the neuronal cells eventually causing hyperexcitability and seizures (19, 20, 38, 39).

CLINICAL PRESENTATION

It is well documented that BTRE causes significant burden in quality of life, mental status, cognition, and morbidity (40–43). The clinical manifestation of seizures related to brain tumors are usually focal or generalized with motor onset. Focal seizures are mostly location-dependent and correspond to specific function. For example, involvement of the precentral gyrus will typically manifest as focal motor seizures involving the contralateral extremities. Visual changes, altered mental status, behavioral changes, or altered sensorium could also be clinical symptoms associated with tumor-related seizures. Patients can also experience postictal Todd's paralysis, severe agitation with psychosis, and status epilepticus (SE) (44). The rate of SE in patients with brain tumors is variable; however, approximately 7% of all SE cases can be attributed to brain tumors (45). Patients who suffer from SE and brain tumors have higher 30-day mortality when compared patients with SE who do not have brain tumors (46). As mentioned above, patients with low-grade gliomas are more likely to have seizures compared to patients with high-grade gliomas (9). Additionally, patients with low-grade gliomas are more likely to have secondary generalized seizures. Focal aware seizures are more common among patients with high-grade gliomas (47).

MEDICAL MANAGEMENT OF BTRE

Epilepsy can be defined as at least two unprovoked seizures occurring more than 24 hours apart or one unprovoked seizure with at least 60% probability of another one occurring over the next 10 years. With this definition, any patient with a brain tumor who has one seizure will automatically have epilepsy (48). As a result, it is imperative to treat these patients with AEDs to prevent seizures and their complications.

The American Association of Neurology (AAN), the Congress of Neurological Surgeons (CNS), and the American Society of Therapeutic Radiology and Oncology (ASTRO) all recommend withholding AEDs in brain tumor patients who have not had a seizure. In an instance where an AED has been started, it is recommended to withdraw after the first week of surgery (4). BTRE patients, however, need AEDs to prevent further seizures. AEDs such as levetiracetam, lamotrigine, lacosamide, topiramate, and pregabalin are recommended as they have favorable side effect profiles (49, 50). In a retrospective study comparing seizure control rates and adverse effects of levetiracetam and valproic acid (VPA), both AEDs show similar seizure control rates. VPA had a statistically significant higher rate of adverse drug effect when compared to levetiracetam (51). Another study demonstrated that patients with BTRE and high-grade gliomas tended to require multiple AEDs for seizure prophylaxis (47). VPA or a combination of VPA and levetiracetam had more success in controlling seizures than other agents (47).

Drug–drug interactions present some additional challenges in patients with BTRE who are taking multiple medications, including one or more AEDs with or without chemotherapy. AEDs that are metabolized in the liver have the most interactions with other drugs. Phenobarbital, carbamazepine, oxcarbazepine, and phenytoin are classically known for their enzyme inducing abilities, allowing faster

metabolism of chemotherapy drugs such as methotrexate, steroids, paclitaxel and so on, potentially compromising the efficacy of oncological treatment (52).

Monotherapy is preferred when it comes to BTRE as it is safer for the patient and compliance is less of an issue. Nonetheless, patients having seizures refractory to AED monotherapy will require additional agents. This is more common among patients with BTRE. In a study of 99 patients with BTRE, more than half did not respond to one AED. Among the non-responders, VPA and levetiracetam was the most effective combination to prevent further seizures (47). Studies have demonstrated that more than 50% of patients continue to have seizures despite the maximal medical management (1, 53). Seizures refractory to two AEDs will likely not be controlled with additional medications (54).

Surgical Treatment

Surgery is essential for diagnosis and treatment of brain tumors. In patients with BTRE, surgery is required for tissue diagnosis, reduction of tumor burden and mass effect, as well as seizure management. One study demonstrated that two-thirds of the epileptogenic focus of patients with BTRE is located within or adjacent to the tumor (55). Thus, surgical intervention can often be curative for patients with BTRE (56). In patients with BTRE who failed medical management with two first line AEDs, surgery can be beneficial for seizure control (4, 54, 57). In one series of 207 patients, 82% of patients with BTRE were seizure-free following tumor resection (56). This study also demonstrated that patients with one seizure focus tended to have better outcomes than patients with multiple seizure foci (56). A meta-analysis involving 773 patients with BTRE who underwent surgical resection showed approximately 71% were seizure-free after surgery (57, 58). The authors also demonstrated that patients who underwent gross total resection of the tumor had higher seizure freedom rates (58). As previously described, DNETs and ganglioglioma have higher frequency of seizures at presentation and they can be especially resistant to anticonvulsants. Thus, these patients often require surgical treatment (40, 55).

Surgical planning for medically refractory epilepsy starts with obtaining a regular scalp EEG to localize the seizure focus; however, these non-invasive studies are generally not adequate for precise seizure localization. Intracranial EEG with subdural grids, strip electrodes, and depth electrodes can be extremely helpful to accurately localize seizure focus and provide better outcome for patients with BTRE (59, 60). Electrocorticography (ECoG) and stereoencephalography (SEEG) are techniques utilized to further help localize the seizure focus when scalp EEG is inconclusive or unclear.

Different surgical treatment options as well as advanced imaging modalities are available for patients with BTRE. Intraoperative cortical brain mapping with electrocorticography, radiosurgery, and laser interstitial thermal therapy are additional surgical techniques that can be effectively utilized in BTRE. EEG mapping is also another modality that can be beneficial for identifying the epileptogenic focus. Epileptogenic foci can be identified within or overlying the tumor, the peritumoral tissue, and even distant areas away from the tumor (Figure 2) (61, 62). The extent of tumor resected directly correlates with seizure freedom; however, patients may benefit from subtotal resection if the epileptic focus was identified before the resection, especially if the tumor is in eloquent areas of the brain (62).

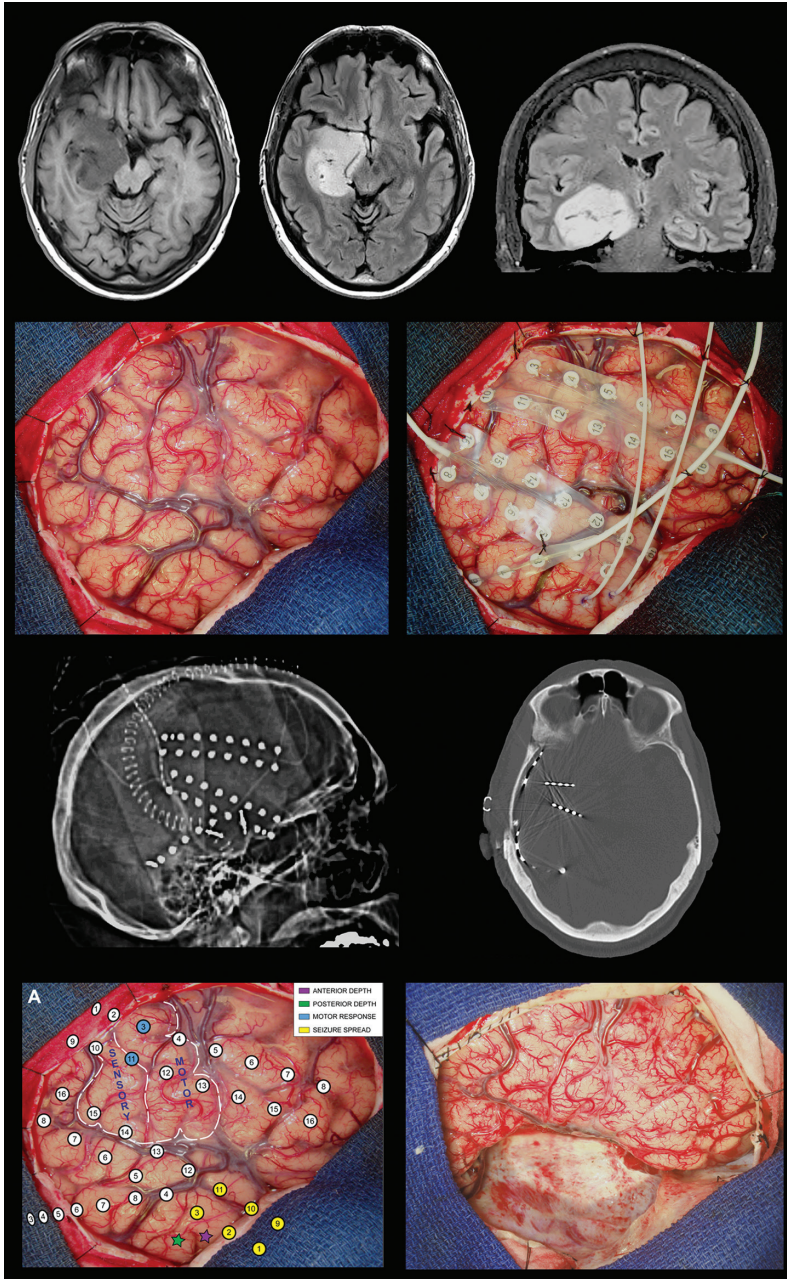


Figure 2. Surgical management of brain tumor-related epilepsy. This patient presented with recurrent seizures and a non-enhancing mass in the right medial temporal region (*top row*). Intraoperative photographs during intracranial electrode implantation (*second row*). Postsurgical CT scan showing placement of subdural grid electrodes and depth electrodes (*third row*). Intraoperative photographs showing intracranial electrode arrays with cortical mapping results and following resection of the tumor and epileptogenic tissue (*bottom row*).

It is essential to identify patients where the tumor is not the primary epileptogenic focus, as they may benefit from a combined approach encompassing both tumor resection and epilepsy surgery (61).

Gross total resection can provide seizure freedom as high as up to 87% compared to 55% seizure freedom with subtotal resection (63). Seizures in BTRE patients are best treated surgically irrespective of AEDs (40). It is also particularly important to note that surgery has its own risks. Proper discussion and informed consent with patient and family (if applicable) regarding risks, benefits, and alternatives to surgery is essential. Intractable epilepsy associated with brain tumors can significantly impact a patient's life. Studies suggest that early surgical resection is beneficial for disease control and improvement in quality of life (4, 56, 63, 64). Equivalent results were noted when compared to extent of surgical resection and seizure freedom (58, 63, 65–67).

CONCLUSION

Among patients with brain tumors, seizures are one of the common presenting symptoms (10). Many studies have shown that tumors have intrinsic effects on surrounding normal brain tissue, causing it to become epileptogenic. As we discussed, pathogenesis of BTRE involves multiple factors such as tumor size, location, types of tumor, growth rate, peritumoral environmental changes, and much more which is still to be discovered. There is no evidence for AEDs as prophylaxis for brain tumor patients without seizures. However, in patients with BTRE, first- and second-generation AEDs are both beneficial medical treatment options. A carefully planned surgery can help patients with BTRE achieve complete seizure freedom and cytoreduction. With advances in EEG mapping technology and targeted therapies against tumors, a comprehensive multidisciplinary management approach should be undertaken and can help improve quality of life as well as long-term oncologic and seizure outcomes in patients suffering from brain tumor associated epilepsy.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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