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Authors

Chen, Dillon Y
Chen, Clark C
Crawford, John R
et al.

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TOPIC REVIEW

Tumor-related epilepsy: epidemiology, pathogenesis and management

Dillon Y. Chen[2,3] · Clark C. Chen[1] · John R. Crawford[2,3] · Sonya G. Wang[1]

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Abstract

Introduction Seizure is a common comorbidity in patients with brain tumor. It may be the presenting symptom or develop after the tumor diagnosis. The underlying pathophysiology of brain tumor-related epilepsy remains poorly understood.

Methods A comprehensive literature review of Pubmed English articles from 1980–2017 was performed to summarize current knowledge and treatment options of brain tumor-related epilepsy.

Results Multiple factors have been found to contribute to tumor-related epilepsy, including tumor type, speed of tumor growth, location, and tumor burden. The underlying pathogenesis of epilepsy is not clear but perturbations in the peri-tumoral regions, both structural and cellular communications, have been implicated.

Conclusions Surgical and medical treatments of tumor-related epilepsy remain challenging as additional factors such as the extent of surgical resection, interactions with tumor-related oncological treatments and anti-epileptic medication related side effects need to be considered.

Keywords Epilepsy · Brain tumor · Tumor-associated epilepsy · Anti-epileptics · Pathophysiology

Introduction

Epilepsy refers to disorders characterized by recurrent seizures. The World Health Organization estimates that 50 million people worldwide have epilepsy. 25–60% of brain tumor patients develop epilepsy either as the initial symptom or after the brain tumor diagnosis. Indeed, seizures can be the presenting symptoms of a brain tumor in 15–30% of cases [1, 2].

Brain tumor patients with epilepsy incur higher risks of seizure-related morbidities, mortality, as well as experience lower quality of life. For instance, the most common reason for hospital readmission after craniotomy for malignant supratentorial tumors is new onset seizures [3]. Moreover, the adverse consequence of epilepsy is magnified in this patient population. Mortality attributed to status epilepticus, persistent, or recurrent seizure(s) within a 5-min interval, is nearly three times higher in brain tumor patients relative to epilepsy patients without a brain tumor [4]. Although seizures are common in this population, care must be taken to ensure that the movements seen are not decerebrate posturing, which may be seen with posterior fossa tumors and/or other types of brain injury that require emergent neurosurgical intervention [5].

Despite the critical importance of tumor-related epilepsy, the underlying pathophysiology remains poorly understood. Here we perform a comprehensive literature review, summarize the state-of-knowledge on brain tumor-related epilepsy, and discuss treatment options.

Methods

The Pubmed online database was searched from January 1st, 1980 through December 31, 2017 using language filter for English articles and the following query: “epilepsy”, “tumor”, and “pathogenesis OR mechanism”, the number of articles found was 6083. Changing “tumor” to “brain tumor” yielded 3249 articles. Additional query terms such as

✉ Sonya G. Wang
sgwang@umn.edu

[1] Department of Neurology, University of Minnesota, Moos Tower 515 Delaware St SE, Suite 13-250, MMC 295 MAYO, Minneapolis, MN 55455, USA

[2] Department of Neuroscience, University of California, San Diego, USA

[3] Rady Children’s Hospital San Diego, San Diego, USA

"epidemiology", "surgery", "treatment" or "anti-epileptic" were applied for individual sections. Addition of "epidemiology" yielded 298 articles; addition of "surgery" yielded 1421 articles; addition of "treatment" yielded 2023 articles and addition of "anti-epileptic" yielded 513 articles. Additional search terms including "levetiracetam", "valproic acid", "topiramate", "oxcarbazepine", "phenytoin", "zonisamide" were used for the anti-epileptic drugs section. In all, approximately 520 abstracts were screened, and of those, about 190 were further reviewed. Seventy-three articles were cited in this review.

This is a topic review of the current literature. As such, no research involving human or animal subjects was conducted and no informed consent was indicated.

Epidemiology and pathophysiology

While it is estimated that about 4% of brain tumor patients suffer from epilepsy [6], the risk of epilepsy varies significantly depending on the tumor type and characteristics. For example, slow-growing tumors and tumors in the World Health Organization (WHO) grade I–II (low-grade gliomas) are thought to be more epileptogenic than the more rapidly growing high-grade gliomas (WHO III–IV) [7]. Historically, brain tumors are graded based on their histological appearance, but the most recent WHO classification published in 2016 grades gliomas not only based on histology but also on molecular parameters, such as mutations in isocitrate dehydrogenase 1 and 2 (*IDH1* and IDH2), alpha-thalassemia-mental retardation syndrome X-linked (*ATRX*), *TP53, H3 K27M*, co-deletion in 1p/19q, *BRAF* alterations and fusion of *RELA* gene and *c11orf95* [8]. Besides WHO classification, several other tumor and peri-tumoral features have been examined for their association with epilepsy, as discussed below.

Tumor growth rate

There is an inverse relationship between seizure prevalence and tumor growth rate and associated malignancy [9]. Contributing factors to this inverse-relationship may include: (1) a longer life expectancy of patients with low-grade tumors may contribute to the increase in seizure incidence, (2) fast growing tumors do not allow the time needed for the tumor cells to re-organize, vascularize and develop mechanisms necessary for epileptogenesis, and (3) slow-growing tumor cells may have intrinsic epileptogenic properties.

Tumor location

In addition to growth rate, tumor location has also been shown to play a significant role in brain tumor-related epileptogenesis. Tumors involving the frontal, temporal and parietal cortex are more epileptogenic, and tumors located in the cortical gray matter, especially those within the eloquent areas, have a higher seizure frequency [2, 10].

Specific associations between distinct types of seizure and tumor locations have also been defined. Wang et al. [11], as well as others [12–14] showed that, in patients with low-grade glioma, lesions involving different brain areas are associated with different seizure characteristics (Fig. 1).

Tumor burden

The size and number of tumor lesions are often positively correlated with the risk of developing epilepsy. For instance, in tuberous sclerosis (TS), patients with higher numbers of brain lesions seen on MRI were more likely to have severe developmental delay and poorly controlled epilepsy [15]. Larger cortical tubers are also associated with more severe epilepsy [16]. However, this association is not perfect. TS patients with a large cortical tumor burden do not necessarily develop epilepsy [17].

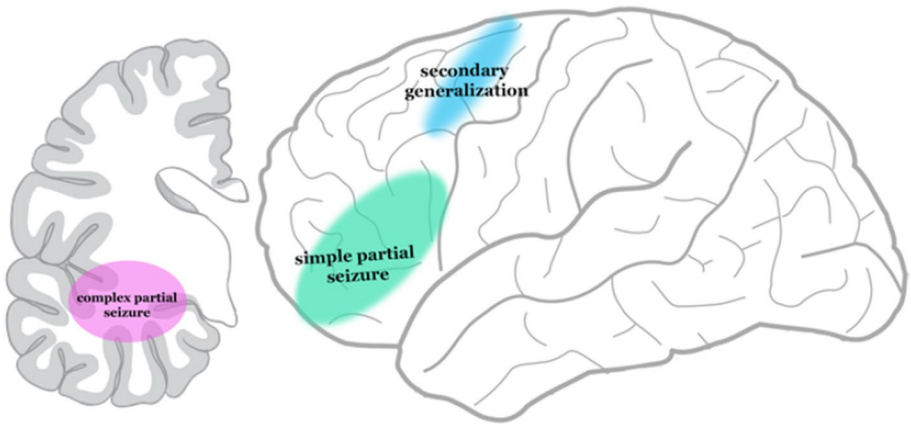

Fig. 1 Low-grade glioma location is associated with seizure risk. Lesions that involved the posterior portion of the left inferior and middle frontal gyrus are associated with increased risk of simple partial seizures (green); lesions involved the right temporal-insular region are associated with increased risk of complex partial seizure (pink); and lesions that involved the left premotor area are associated with seizures that generalize (blue)

Altered neurotransmitter homeostasis in the peri-tumoral region may contribute to tumor-related epileptogenesis

There is evidence that alteration of neurotransmitter homeostasis in the peri-tumoral brain contributes to its epileptogenesis. Specifically, glutamate and GABA transmissions in the peri-tumoral tissue have been closely examined due to their role in excitatory and inhibitory neurotransmissions, respectively [18, 19]. Alterations in glutamate neurotransmission have been well implicated in the epileptogenesis in patients with brain tumors, especially in highly epileptogenic gliomas. In fact, increased glutamate levels have been found in tumor and peri-tumor samples of epilepsy patients with high-grade glioma, in animals with xenografted high-grade gliomas [20, 21], and in patients with tumor-related epilepsy when compared to tumor patients without epilepsy [22]. Yuen et al. reported that, the increased glutamate levels seen in patients with tumor-related epilepsy is due to an increased expression of cysteine/glutamate transporter system in the peri-tumoral tissue [22]. This transporter system exchanges intracellular glutamate for extracellular cysteine resulting in increased extracellular glutamate levels. Furthermore, the *IDH1* mutation, which is associated with increased epileptogenicity in patients with low-grade gliomas [23], results in increased production of D-2-hydroxyglutarate, which acts as a glutamate receptor agonist [24]. Together, these studies suggest intra- and extra-tumoral glutamate play a significant role in tumor-related epileptogenesis.

Another neurotransmitter that has been studied in tumor-related epileptogenesis is γ-aminobutyric acid (GABA). GABA receptors are ligand-gated Cl^- ion channels whose response to GABA ligand is primarily established by the activity of the K^+Cl^- co-transporter (KCC2) and Na^+, K^+ $2Cl^-$ co-transporter (NKCC). In contrast to glutamate, GABA is generally inhibitory, although depolarizing GABA has been described in epileptic human tissues [25]. The inhibitory property of GABA is dependent upon the KCC2 transporter, which extrudes Cl^- from the cell to maintain GABA reversal potential. Comparing to non-epileptic areas surrounding a low-grade glioma, epileptic peri-tumoral regions have fewer GABA containing neurons [26]. Cortical slices from high-grade glioma implanted mouse model that exhibit robust epileptic activity show: a significant reduction in inhibitory neurotransmission, loss of parvalbumin-positive GABAergic interneurons, and significantly lower KCC2 membrane expression [27]. Furthermore, there is a significant reduction in the phosphorylation of KCC2 at the ser940 site, a process mediated by glutamate, seen in the peri-tumor tissues in the glioma mouse model; dephosphorylation of KCC2 at ser940 leads to its down-regulation [28]. Together, these studies suggest that a decrease in inhibitory neurotransmission, perhaps accentuated by glutamate neurotransmission, in the peri-tumoral tissue may underlie tumor-related epileptogenicity.

Management of tumor-related epilepsy

Surgery is the primary modality through which definitive diagnosis can be made for brain tumor patients. Surgery aims to achieve two primary goals in the management of brain tumor patients with epilepsy: (1) achieving definitive tissue diagnosis with or without cyto-reduction, and (2) seizure management. For cyto-reduction, the surgery is typically designed to remove regions of MR findings that proxy significant tumor burden, such as contrast enhancement or FLAIR-signal abnormalities. The most extreme version of maximizing cyto-reduction involves the concept of "supra-total" resection, where resection is carried out to regions of defined eloquence, irrespective of MR appearance of the resected region. Preliminary case series support efficacy for "supra-total" resection in select patients [29–31]. The merit of applying "supra-total" resection to all brain tumor patients remains an area of controversy.

Pertaining to seizure management, the available literature suggests that up to two-thirds of tumor related seizure foci resides within the tumor mass [32]. In these situations, the likelihood of seizure control will be a function of the extent of resection. The published study generally supports this premise [19, 32, 33]. In general, seizure freedom following lesion/tumor resection varies between 65–85% [33]. On the other hand, approximately one-third of brain tumor related epilepsy involves seizure foci that are not located in the tumor mass. For these patients, the extent of tumor resection is unlikely to correlate with seizure control. Efforts to carefully define the seizure foci and carefully determine the optimal strategy of treatment will be critical for this patient population. The clinical challenge is that it is difficult to a priori determine whether the seizure foci are located within the tumor mass based on imaging findings alone. In this context, we believe the approach to seizure in a brain tumor patient requires complex consideration and careful discussion of the matter in a multi-disciplinary board.

An area of active research involves whether prophylactic removal of the hippocampus in brain tumor patients confer clinical benefit in terms of epilepsy risk reduction. For instance, a study by Ghareeb and Duffau showed that hippocampectomy in patients with low-grade glioma with no clear hippocampal involvement resulted in improved incidence of seizure freedom and quality of life [34]. A systematic literature review analysis by Englot et al. reported that additional resection of hippocampus and/or adjacent cortex provided further benefit over gross-total resection alone in terms of achieving seizure freedom [35]. Approaches to optimize seizure freedom and seizure reduction may be different

between tumor types. Table 1 summarizes seizure freedom rates and seizure reduction/freedom predictors for patients with various tumor types [36]. More studies are needed to clarify the benefit of additional tailored resection.

There has been a renaissance in technologies available for surgical treatment of epilepsy and tumor. They include: intra-operative functional mapping [57], laser ablation [58], and radiosurgery [59]. These technologies have added a layer of complexity in the management of tumor-related epilepsy. Laser interstitial thermal therapy (LITT), which is a minimally invasive option, delivers nonionizing radiation to stereotactically targeted tissue to thermal-ablate the lesions. Recent development of MRI-guided laser interstitial thermal therapy allows for monitoring of tissue ablation in real-time. Curry et al. provided the first proof-of-principle clinical experience suggesting efficacy for stereotactic laser ablation (SLA) in the treatment of medically intractable epilepsy [60]. Although the long-term outcomes are still being established, the available clinical experience (with limited follow-up) suggests efficacy of SLA in the management of tumor-related epilepsy [61].

Given the described complexities, we believe that cytoreduction and seizure control are distinct and complex issues that warrant dedicated considerations in the treatment of brain tumor patients with epilepsy. In this context, we would advocate for the involvement of a multi-disciplinary team, including epileptologists, oncologists, surgeons, neuro-radiologists, neuropsychologist, and pathologists, in treatment decision making. In our opinion, only in doing so can we optimize and personalizing the treatment strategies to the particular needs of each individual patient.

Antiepileptic drugs (AEDs)

In patients with brain tumors without seizures, the American Association of Neurology (AAN) practice guideline published in 2000 recommends against starting prophylactic AEDs routinely in patients with newly diagnosed brain tumor patients, and to withdraw these drugs in the first week after surgery (if an AED had been started) [62]. Similar guidelines have been issued by the Congress of Neurological Surgeons (CNS) and the American Society of Therapeutic Radiology and Oncology (ASTRO). A recent comprehensive review by Wali et al. had reached the same conclusion [63].

AEDs are indicated for brain tumor patients who develop at least one seizure. In general, AEDs can be divided into two main groups: first-generation drugs (e.g. phenytoin, carbamazepine, valproic acid, ethosuximide, benzodiazepines and barbiturates) and second-generation drugs (e.g. levetiracetam, felbamate, gabapentin, lamotrigine, pregabalin, tiagabin, zonisamide, oxcarbazepine, vigabatrin, lacosamide and topiramate). Most AEDs exert their effects by modulating voltage-gated sodium, calcium, or potassium channels and/or by acting on GABA receptors, though felbamate and topiramate modulate excitatory transmission. Given that the tumor-related epilepsy is thought to be a result of tumor as the focal brain lesion, symptomatic management of tumor-related epilepsy is similar to that of focal-onset epilepsy. According to a consensus paper by the International League Against Epilepsy (ILAE), a number of drugs are effective for focal-onset epilepsy in adults [64]. Class I evidence supports the use of levetiracteam, carbamazepine, phenytoin, and zonisamide. Class II includes valproic acid. Class III supports the use of gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate and vigabatrin. However, limited studies are available on the efficacy of the AEDs in brain tumor related epilepsy.

One of the main problems in treating tumor-related epilepsy is drug–drug interaction with cancer therapy. The interaction can occur from absorption to elimination of the drugs [1]. Hepatic metabolism and excretion are associated with most clinically significant drug–drug interactions. Enzyme-inducing drugs trigger faster elimination whereas enzyme-inhibiting drugs decrease the metabolism of the second drug. For example, phenobarbital, carbamazepine, oxcarbazepine and phenytoin, can act as enzyme inducer, thus increase the metabolism and clearance of many oncological treatments including corticosteroids, paclitaxel, cyclophosphamide, etoposide, topotecan, nitrosoureas, adriamycin and methotrexate [1].

Among the first generation AEDs, valproic acid, perhaps owing to its histone deacetylase inhibition activity, receives more attention in tumor-related epilepsy. In vitro and in vivo studies have shown that combining valproic acid and the chemotherapeutic agent temozolomide induces cancer cell

Table 1 Post-resection seizure outcome for brain tumors associated epilepsy Reproduced with permission from Englot et al. [36]

Tumor type	Approximate seizure freedom rates (%)	Seizure reduction/freedom predicators
Glioneuronal tumors	70–90	Gross total resection, early surgery, absence of generalized seizures
Low-grade glioma	65–80	Gross total resection, early surgery, localized EEG
Meningioma	60–80	Less peritumoral edema
High-grade glioma	77	Better pre-operative seizure control, improved functional status post operatively

apoptosis [65, 66]. European Organization for Research and Treatment of Cancer trial of temozolomide and chemoradiation showed that glioblastoma patients who received valproic acid had a 3 months longer median survival than patients who received chemoradiation alone [43, 67]. However, a post-hoc analysis of three randomized trials in glioblastoma found no overall positive effect of valproic acid [68], and increased side effects such as thrombocytopenia and/or neutropenia have been reported in high-grade glioma patients who received valproic acid and fotemustine-cisplatin regimen [69]. More research on the efficacy of valproic acid and its interactions with chemotherapy are needed.

Among the second generation AEDs, levetiracetam, because of its safety profile, has received the most attention [37]. For example, patients with glioma-related epilepsy who were treated with levetiracetam have reported seizure freedom up to 91% and significant seizure reduction (≥ 50%) up to 100% [70]. Furthermore, two studies have found levetiracetam to be equal or more effective than other AEDs in tumor related epilepsy [38, 39], and Rossetti et al. have reported that levetiracetam and pregabalin have comparable antiepileptic efficacy in brain-tumor patients with at least one seizure [50].

In addition to levetiracetam, there have also been recent studies on lacosamide, mostly as an adjunctive therapy, in patients with brain tumor-related epilepsy, and similar seizure-freedom and seizure-reduction rates were seen [47, 48, 71]. There is currently a clinical trial evaluating the use of lacosamide for seizure prophylaxis in patients with high-grade glioma who have not had a seizure (NCT01432171).

The limited available evidence on the use of anti-epileptic in brain tumor related epilepsy precludes the creation of best-practice guideline and consensus statement [72]. However, based on the ILAE's recommendation and published reports on the use of various anti-epileptics in tumor-related epilepsy, we propose considering levetiracetam and valproic acid monotherapy as first-line therapy in brain tumor patients with at least one seizure. Levetiracetam has Level I evidence for focal-onset epilepsy and multiple studies demonstrating efficacy and safety profile in tumor-related epilepsy. Valproic acid, while it carries as Level II evidence for focal-onset epilepsy, has been studied in tumor-related epilepsy, and as discussed above, may improve survival in patients with glioblastoma multiforme when combined with chemo-radiation treatment [65, 66], but see [68]. If seizure control is not achieved by levetiracetam or valproic acid monotherapy, combination valproic acid levetiracetam therapy [73], addition of pregabalin [50] or lacosamide [47] may be considered. Other AEDs that have been examined specifically in brain tumor related epilepsy include oxcarbazepine and topiramate. Two small studies by Maschio et al. showed efficacy of oxcarbazepine in reducing brain tumor related epilepsy [52, 53]. However, when choosing oxcarbazepine, one must consider its enzyme inducing property and the potential interaction with chemotherapeutic agents. Topiramate has also been shown to reduce brain tumor related epilepsy, especially as an adjunctive therapy, with variable efficacy [14, 55]. Importantly, plasma concentrations of oxcarbazepine and topiramate are not affected by chemotherapeutic agent temozolomide, which is a common brain tumor chemotherapy [74]. Other AEDs, including zonisamide, lamotrigine and benzodiazepines such as clobazem and clonazepam, are generally well tolerated and can be considered. However, they have not been examined specifically in brain tumor-related epilepsy. Table 2 describes the suggested dose, mechanisms of action, side effects and references on the various drugs that have been examined specifically for brain tumor-related epilepsy. Currently, there is no evidence-based guideline or consensus on the duration of treatment for brain tumor-related epilepsy. AAN is preparing to release a practice advisory on the timing of antiepileptic medication withdrawal in seizure-free patients with epilepsy, but not specifically for brain tumor-related epilepsy. We recommend patient-provider discussions about medication taper after 12–24 months of seizure-freedom and/or after tumor resection.

Discussion and future directions

Seizures are common in patients with brain tumors, either as the presenting symptom or sequelae. The available literature suggests that tumors exert effects on the surrounding non-tumoral tissue to increase the risk for epileptogenesis. Various studies have implicated the size, location, and the intrinsic properties of the tumor as well as peri-tumoral changes in inter-cellular communication, in the pathogenesis of tumor-related epilepsy. Surgical approaches to brain tumor patients with epilepsy require careful delineation of the primary goal in the context of a multi-disciplinary discussion. In aggregate, the available data provide no compelling data for prophylactic AED in brain tumor patients without epilepsy. In tumor patients with epilepsy, first generation AED (phenytoin and valproate) and second generation AEDs (levetiracetam, lacosamide, pregabalin, oxcarbazepine and topiramate) show comparable efficacy, though the second generation AEDs demonstrate more favorable safety profiles. Future research will help to customize individualized treatment paradigms including surgical and medical approaches for tumor-related epilepsy.

Table 2 Suggested dosing regimen, mechanisms of action, known side effects and references on anti-seizure medications that have been examined in brain tumor-related epilepsy

Drug	Dose	Mechanisms of action	Significant side effects	References
Levetiracetam	Starting at 1000 mg/day in divided doses, increase to effect or a maximum of 3000–4000 mg in divided doses pending seizure control	Unknown. Regulates synaptic vesicle glycoprotein, SV2A and presynaptic calcium channels	Irritability, dizziness, drowsiness	[37–42]
Valproic acid	Starting at 10–15 mg/kg/day in divided doses, increase by 10–15 mg/kg/day in weekly interval to effect or tolerable therapeutic serum level (50–150 mg/l) is achieved	Enhance GABA effects and may inhibit glutamate/NMDA-mediated excitation	Liver toxicity, hyperammonemia, thrombocytopenia, weight gain, hair loss	[43–46]
Lacosamide	Starting at 100 mg in divided doses, titrate up by 50 mg weekly to effect or up to 300–400 mg daily	Enhances slow inactivation of voltage-dependent sodium channels	Dizziness, nausea, blurred vision	[47–49]
Pregabalin	Starting at 150 mg in divided doses, titrate up by 150 mg daily to effect or a maximum of 600 mg in divided doses	Modulates Q-type voltage gated calcium channel	Dizziness, lethargy, ataxia and cognitive side effects	[50, 51]
Oxcarbazepine	Starting at 600 mg in divided doses, titrate up by 300 mg every 3 days to effect or a maximum daily dose of 2400 mg	Sodium channel inhibition	Drug rash and hyponatremia	[52–54]
Topiramate	Starting at 25 mg daily, increase by 25 mg weekly to 100 mg in divided doses. Can continue to titrate by 25 mg weekly to a maximum of 400 mg daily dosing	Affects voltage-dependent sodium channel, enhances gamma-aminobutyric acid activity and affects carbonic anhydrase enzyme	Open-angle glaucoma, cognitive side effects, nephrolithiasis, metabolic acidosis	[14, 55, 56]

Compliance with ethical standards

Conflict of interest Drs. Chen, Chen, Crawford and Wang declare that they have no conflict of interest.

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