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What is New in the Management of Epilepsy in Gliomas?

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Opinion statement

Seizures represent a common symptom in low- and high-grade gliomas. Tumor location and histology influence the risk for epilepsy. Some molecular factors (BRAF V 600E mutations in glioneuronal tumors and IDH1/2 mutations in diffuse grade II and III gliomas) are molecular factors that are relevant for diagnosis and prognosis and have been associated with the risk of epilepsy as well. Glutamate plays a central role in epileptogenicity and growth of glial and glioneuronal tumors, based on the release of glutamate from tumor cells that enhances excitotoxicity, and a downregulation of the inhibitory GABAergic pathways. Several potential targets for therapy have been identified, and m-TOR inhibitors have already shown activity. Gross total resection is the strongest predictor of seizure freedom in addition to clinical factors, such as preoperative seizure duration, type, and control with antiepileptic drugs (AEDs). Radiotherapy and chemotherapy with alkylating agents (procarbazine, CCNU, vincristine, temozolomide) are effective in reducing the frequency of seizures in patients with pharmacoresistant epilepsy. Newer AEDs (in particular levetiracetam and lacosamide) seem to be better tolerated than the old AEDs (phenobarbital, phenytoin, carbamazepine), but randomized clinical trials are needed to prove their superiority in terms of efficacy.

Introduction

Seizures are frequent manifestations of glial and glioneuronal tumors [1]. Many patients with gliomas suffer from drug-resistant epilepsy, that negatively impacts quality of life and neurocognitive functions [2], ultimately leading to a psychosocial disability. The mechanisms of epileptogenesis are multifactorial and not fully understood. Novel molecular factors and biological pathways, involved in both seizure development

and tumor growth, have been identified as potential prognostic factors or even targets of therapy. Antiepileptic drugs (AEDs) still remain the mainstay of management of tumor-associated epilepsy (TAE); however, the importance of antineoplastic treatments, such as surgery, radiotherapy, chemotherapy, and targeted agents, has progressively grown, allowing a long-term control of seizures in an increasing number of patients.

A detailed discussion of current management paradigms is outside of the scope of this article. Here, we have focused on recent developments in molecular pathology, biology, and treatment options in a field, such as that of epilepsy in brain tumors, that has raised increasing interests among physicians caring of these patients.

Pathology and molecular factors

The frequency of seizures depends mainly on tumor location and histologic type.

Intractable epilepsy is particularly frequent in tumors which involve the temporo-mesial and insular structures [3–5, 6••]. Glioneuronal tumors, such as gangliogliomas and dysembryoplastic neuroepithelial tumors (DNETs), are typically associated with chronic pharmacoresistant epilepsy in 80–100 % of patients [7–10]. Seizures are usually the first and isolated clinical symptom: of these, 50–80 % are focal seizures with alteration of consciousness, with or without secondary generalization [11•]. Glioneuronal tumors occur predominantly in children and young adults, are located in the temporal lobe, and are largely grade I neoplasms with favorable outcome after surgery alone, with rare instances of recurrence and malignant transformation in gangliogliomas [12].

Regarding the molecular genetics signature, glioneuronal tumors generally lack IDH1/2 mutations, while BRAF V600E mutations have been identified in up to 50 % of gangliogliomas [13] while being more rare in DNETs [14]. The mutant BRAF V600E protein in gangliogliomas is predominantly expressed by neuronal tumor cells [15], and the expression has been associated with a worse postoperative seizure outcome [16••].

The brain tissue adjacent to a ganglioglioma or a DNET may frequently show an atypical cortical development or cortical dysplasia [7, 17]. BRAF V600E mutations can be present not only in glioneuronal tumors but also in focal cortical dysplasias that accompany glioneuronal tumors [18•]; thus, a common origin of glioneuronal tumors and focal cortical dysplasia from the same precursor cell has been hypothesized. Moreover, a dual pathology, such as hippocampal sclerosis, in association with the epileptogenic tumor, may occur. The majority of gangliogliomas of the temporal lobe, unlike those in other locations, are positive for the CD34 glycoprotein staining [19], that could represent a possible marker of dysembryoplastic differentiation, contributing to epileptogenesis [11•].

Other rare grade I gliomas (supratentorial pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and angiocentric glioma), that prevail in children and young adults, represent a cause of seizures [7]. Similarly to glioneuronal tumors, pilocytic astrocytomas and pleomorphic xanthoastrocytoma have frequently BRAF V 600E mutations [13].

Diffuse grade II gliomas, the so-called low-grade gliomas, are more common in young adults, have seizures in 70–90 % of patients, representing more often the first clinical symptom, and have an inherent tendency to progress toward higher-grade tumors. Among low-grade gliomas, seizures are much less frequent in older patients (≥50–60 years) compared to younger patients [20]. Grade II gliomas arise in the cerebral hemispheres and compared with glioneuronal tumors, focal seizures with alteration of consciousness (complex partial seizures) are less frequent than simple partial seizures and secondary generalized seizures [21]. Tumors with an oligodendroglial component are more likely to present with seizures [5]. The rare protoplasmic astrocytoma, which is predominantly based in the cortex, can be linked to chronic epilepsy. In this regard, a possible explanation is that protoplasmic astrocytes normally synchronize neuronal firing in the cortex and have been recently shown to express glutamate EAAT1/2 transporters [22] (see mechanisms of epileptogenesis).

Moreover, among grade II astrocytomas, a subtype, characterized by long-term epilepsy, longer survival, and lower recurrence risk, has been reported [23] and interestingly presents CD34 expression (as some grade I epileptogenetic tumors).

IDH1 and 2 mutations are common in diffuse low-grade gliomas (60–75 %), separating them from the glioneuronal tumors and pilocytic astrocytomas, in which they are absent or extremely rare [24]. IDH1/2 mutations have been associated with seizures as initial symptom [25•, 27], and this could be independent of tumor localization [25•]. Due to the structural similarity to glutamate, 2-hydroxyglutarate (2HG), the metabolic product of IDH1 mutation, is able to activate NMDA

receptors [28], providing evidence for an epileptogenic potential. An indirect confirmation could be that more than 50 % of pediatric patients with L-2-hydroxyglutarate-acidurea, a rare hereditary syndrome, characterized by elevated serum, urine, and CSF levels of 2HG, present with severe seizures [29]. Interestingly, a high level of IDH1 mutations has been found in protoplasmic astrocytomas [26] that are known to have a higher incidence of seizures. A candidate gene for secondary generalized seizures has been suggested to be located on a chromosome [30].

However, a relationship between molecular markers and seizure risk has not been confirmed in a large French dataset of low-grade gliomas [6••]; thus, this issue is still open.

Diffuse grade III gliomas tend to overlap with grade II tumors in terms of age of presentation, location in the cerebral hemispheres, frequency of seizures at presentation, and positivity for IDH1/2 mutations.

BRAF V 600E mutations are extremely rare in large series of diffuse gliomas [13]. Recently, four out of five BRAF V 600 E mutate diffuse grade II gliomas have been described as having long-standing, frequent, sometimes refractory, seizures, and all four tumors were located within the temporal lobe [31]. The same authors also reported two cases of glioblastoma with BRAF V 600E mutations, both presenting with focal seizures. All these data suggest the BRAF mutations occur in a setting specifically linked to epileptogenesis.

The incidence of epilepsy in patients with glioblastoma (GBM) varies between 30 and 60 % in different series: in about two thirds as presenting symptom and in one third developing during the course of the disease [11•].

It has been hypothized that the influence of gene expression on TAE is regional, e.g., gene expression could play a significant role in determining epileptogenicity in certain regions of the brain and not in others [32].

Tumor-associated seizures are more likely to occur with smaller lesions in high-grade tumors and vice versa in low-grade tumors [33]; however, among low-grade gliomas, no significant association between seizures and tumor volume or growth speed has been found [6].

Patients with preoperative seizures have been reported with a longer overall survival compared with those without seizures across the different grades of malignancy [34–36]. Seizure recurrence is generally associated with tumor recurrence [5, 37].

Epileptogenesis and tumor growth: common pathways and potential targets of therapy

Glutamate, the excitatory aminoacid neurotransmitter, is known to be excitotoxic in excess and mediate neuronal death in epilepsy, stroke, and neurotrauma.

Glutamate plays a central role in epileptogenicity and growth of glial and glioneuronal tumors [38, 39•]. Glutamate levels in the normal brain are closely regulated by membrane glutamate transporter proteins on astrocytes: a major group of these proteins is the excitatory amino acid transporters (EAATI-5), with EAAT2 being responsible for over 90 % of the active reuptake of glutamate from the synaptic cleft. Conversely, the Na^+-independent cystine-glutamate antiporter (system Xc-) is responsible for glutamate efflux from astrocytes. There is considerable evidence in preclinical models of gliomas that the release of glutamate by tumor cells, mediated by the system Xc-, outweights a reduced influx mediated by EAAT2, leading to glutamate accumulation in the extracellular space both within the tumor and in the peritumoral tissue [40]: neurotoxicity results in neuronal death, allowing the tumor to expand. These findings have been confirmed in humans. In a retrospective group of 190 patients with mixed-grade supratentorial gliomas (41 % with TAE), the mean levels of glutamate and system Xc in both tumor and peritumoral tissue were significantly higher in patients with TAE [41•]. The inhibition of system Xc by sulfasalazine, an anti-inflammatory drug, by reducing the glutamate release, has been shown to decrease the epileptiform EEG recording [42] and inhibit the tumor growth [39] in preclinical models of gliomas. Unfortunately, a phase 1–2 trial of sulfasalazine in recurrent high-grade gliomas was stopped earlier due to an increase of cerebral edema in five out of ten patients and of seizure frequency in two patients [43], maybe in relation with a decrease in serum AEDs levels. Despite these negative results, the inhibition of system Xc, whether by sulfasalazine or other compounds, has not been investigated in an early stage of the neoplastic disease or in patients with low-grade gliomas nor have the effects on seizures been specifically studied.

Glutamate reuptake by astrocytes can be compromised in presence of a high concentration of ammonia, produced when glutamine is deaminated to glutamate by glutaminase: this enzyme has been reported as being highly expressed in glioma cells [44]. In this regard, treatment with antioxidants could significantly interfere with the ammonia-induced inhibition of glutamate reuptake [45]. An increase of the glutamate reuptake by

astrocytes, either by compounds such as pentrofylline or by upregulating the expression of EAAT2 with drugs such as pioglitazone [46], could be another possibility.

A downregulation in GBM cells of glutamine synthetase could contribute to the epileptogenicity by raising the concentration of glutamate [47]. In this regard, lower levels of glutamate synthetase in brain tumor samples have been observed in epileptogenetic GBMs as compared with non-epileptogenetic GBMs [48].

Glial and neuronal tumor cells respond to glutamate through the activation of ionotropic and metabotropic glutamate receptors, which have been shown to be highly expressed [49, 50]. Glutamate receptors could trigger an electrical activity in human glioma cells. Most of the neurotoxic effects of glutamate have been attributed to the activation of ionotropic glutamate receptors, especially NMDA and AMPA subtypes. However, in high-grade gliomas, such as glioblastomas, a downregulation of AMPA receptors have been reported, suggesting a lower excitability of high-grade gliomas in a glutamate-rich environment compared with low-grade tumors [51].

Talampanel is an oral non-competitive antagonist of AMPA receptors, which is active on refractory non-tumoral partial seizures. Two phase II studies in GBM, either recurrent or newly diagnosed, have been performed in the USA [52, 53]: the trial on newly diagnosed tumors showed promising results in terms of median OS (20.3 months vs the standard value of 14.6 months) [52]. Unfortunately, the effects on tumor-associated epilepsy were not recorded in both studies.

Hopefully, perampanel, another AED with activity on AMPA receptors, that has recently entered the market of epilepsy, could represent in the future a new option to explore.

The hyperexicitability of peritumoral neuronal networks is likely not exclusively due to the elevated glutamate levels. A concomitant reduction in GABAergic inhibition of peritumoral neurons seems to contribute to the development of peritumoral epilepsy. In a mouse glioma model, it has been shown that in the cortex adjacent to tumor, there is a reduction in the number of GABAergic interneurons, a decrease in KCC2 (K^+-Cl^- cotransporter) expression with an impairment of KCC2-mediated Cl^- extrusion, and a change of GABA effect from inhibitory to excitatory [54••]. In glioneuronal tumors, several GABA receptor subunits are downregulated, suggesting an impairment of GABAergic inhibition as well [55]. All these data suggest new therapeutic targets for controlling peritumoral excitability.

An enhanced PI3K-mTOR signaling activation is critical for tumor growth in gangliogliomas [56], aggressive pilocytic astrocytomas [57], and diffuse gliomas [58] but seems to be involved in epileptogenesis as well [59•], and thus, m-TOR inhibitors could have a role for controlling both tumor growth and seizures. In this regard, there is an increasing evidence of an efficacy of m-TOR inhibitors, such as everolimus or sirolimus, on tumor growth and intractable seizures in patients with tuberous sclerosis complex with or without subependymal giant cell astrocytomas [60•, 61].

A role of the leucine-rich glioma-inactivated gene (LGI1) in epileptogenesis and glioma progression has been suggested but still needs a confirmation [62].

Current treatment of epilepsy

Surgical resection, radiation therapy with various modalities, chemotherapy, and antiepileptic drugs, all have a potential role in controlling seizures: overall, an integration of the different options is critical for a successful outcome [63–65, 66•] (Table 1).

Surgery

Seizure control after resection of glioneuronal tumors has been studied extensively. In contrast to diffuse gliomas, where the primary goal of surgery is to impact on improved PFS and OS rather than epileptologic considerations, the primary objective of surgery in glioneuronal tumors is to alleviate disabling

Table 1. Role of antineoplastic treatments for controlling seizures in gliomas

Treatment modality	Seizure freedom (%)	Median follow-up
Surgical resection		
Grade I tumors [4, 9, 67]	80–85	>6 months–8 years
Grade II tumors [5, 6••, 21, 72•]	62–67	12–34 months
Grade III–IV tumors [37]	77	14 months
Brachytherapy/radiosurgery		
Grade II tumors [63]	40–100	Up to 24 months
Conformal radiotherapy		
Grade II and III tumors [63, 81••]	32–38	12 months
Chemotherapy[a]		
Grade II tumors [63, 81••, 82•]	13–55	Up to 3 years

[a]Temozolomide

seizures and side effects of AEDs. Seizure freedom rates are significantly higher following gross total resection compared with subtotal resection [67]: among gangliogliomas, values of 96 versus 54 % are reported [68]. Duration of epilepsy of less than 1 year and secondarily generalized seizures preoperatively were factors associated with a better seizure outcome, while there were no difference between children and adults, temporal and extratemporal location, DNET and ganglioglioma, and medically controlled and refractory seizures preoperatively [67]. The incomplete removal of the cortical dysplasia adjacent to tumors represents an important cause of failure [69].

Among diffuse low-grade gliomas, the extent of resection is an independent predictor of control of the epileptic seizures at 6 and 12 months following surgery, and gross total resection is strongly associated with seizure freedom (62–67 % range) [5, 6••, 21, 35, 70]. Simply partial seizures are associated with less favorable control. An early resection has been suggested in the context of recurrence [71]. A recent study has investigated the seizure outcome following surgery in a series of 52 insular low-grade gliomas with preoperative drug-resistant epilepsy [72•]. At 12 months following surgery 67 % of patients were seizure-free (Engel class I), 8 % had rare seizures (class II), 15 % a meaningful improvement (class III), and only 10 % showed no improvement (class IV). Seizure freedom significantly prevailed among patients who had seizures for less than 1 before surgery (88 %) compared with a preoperative seizure history of more than 1 year (12 %), and among patients with monthly seizures compared with those with daily seizures: these findings confirm previous reports suggesting an early surgical resection of low-grade gliomas (LGG) [5] even if they are small and not showing progressive.

In line with the other studies, the series of Ius et al. [72] confirmed the importance of the extent of resection (measured by postoperative tumor volume) as predictor of seizure control: seizure outcome was worse for patient with an EOR <70 %, and no or little postoperative seizure improvement occurred in cases with a prevalent infiltrative growth pattern. Interestingly, the authors reported that the patients in whom preoperative EEG demonstrated epileptic activity had a worse seizure outcome at 1-year follow-up.

Among high-grade gliomas, an extensive resection is associated with improved seizure control, with seizure freedom at 12 months of 77 % in a large

recent series [37], while less extensive resections are associated with a higher risk of recurrence [73].

An extensive surgical resection allows a reduction AEDs use [74•], and patients who achieve a condition of seizure freedom following gross total resection are candidates for AEDs discontinuation [5, 70, 72•]. However, factors predicting the safety of discontinuation are still not well known [20]. The prophylactic use of AEDs in patients with no preoperative seizures is still a controversial issue. An increased risk of intraoperative seizures during awake surgery has been either reported [75] or denied [76, 77•]. Patients with tumors located in the supplementary motor area could have a higher incidence of intraoperative seizures [78•]. However, in the absence of data from prospective randomized trials, most authors favor a perioperative prophylaxis in patients undergoing awake craniotomy. It must be noted that in all studies, surgical resection was performed using intraoperative functional cortical and subcortical mapping allowing extensive resection while preserving eloquent areas. The role of electrocorticography for improving seizure outcome with surgery still needs to be defined [79, 80].

Radiotherapy

The role of radiation therapy as a means of improving seizure control in diffuse gliomas, especially in low-grade gliomas, has been suggested since many years. Old studies reported a seizure control in 40–100 % of patients with inoperable tumors by using either interstitial or γ-knife irradiation, and a usefulness of conventional radiotherapy has been described in inoperable or incompletely resected LGG [63]. A recent retrospective study has analyzed the seizure outcome following conformal radiotherapy in a cohort of 43 patients diagnosed with grades II and III gliomas and medically intractable epilepsy [81••]. A significant reduction of seizure frequency (reduction ≥50 % from baseline) was obtained in 72 % of patients at 3 months and in 76 % at 12 months. Seizure reduction was observed more often among patients displaying an objective tumor response on MRI, but patients with no change on MRI has a significant seizure reduction as well. Seizure freedom (Engel class I) was achieved at 12 months in 32 % of all patients and in 38 % of patients with grade II tumors. This study also demonstrated that early versus delayed radiotherapy at tumor progression are equally effective in seizures control. Prospective studies are needed to precisely define the role of radiation therapy for management of seizures in high-risk LGG. Conversely, there are no data on seizure control following RT or RT+TMZ in glioblastomas.

Chemotherapy

The efficacy of chemotherapy with alkylating agents (PCV, TMZ) in treating LGG either at recurrence following radiotherapy or as initial treatment in symptomatic/progressive patients is well established [63]. Overall, a seizure improvement has been reported in 48–100 % of patients, with 20–40 % becoming seizure-free. As already observed with radiotherapy, clinical improvement is not reflected by radiographic response on MRI which is often unchanged or demonstrates only minor responses. In a recent retrospective study on 102 patients, 44 % of patients achieved a 50 % reduction of seizure at 6 months after the start of TMZ [82•]. Interestingly, responding patients showed

a significant longer progression-free survival of 24 months compared with only 12 months in patients without seizure reduction, and this translated into a superior overall survival as well. Moreover, the prognostic effect of seizure reduction was independent of age, histology, neurological symptoms, and previous antitumor therapies. Studies, that prospectively collect the data regarding epileptic seizures following both radiotherapy and chemotherapy, are needed. In particular, when analyzing the potential prognostic effect of response of seizures to treatments, molecular makers of known prognostic significance (1p/19q codeletion, IDH1/2 mutation) must be evaluated. As seizure response could be a surrogate biomarker for certain favorable prognostic molecular signatures [83].

Last, seizure control following either radiotherapy or chemotherapy is similar in terms of rates of seizure reduction, early appearance, and lack of strict correlations with tumor response on MRI. All these findings reinforce the hypothesis that the impact of these treatments on seizures is not exclusively related to an impact on the tumor cells, but probably, other mechanisms, such as changes of microenvironment, downregulation of neuronal epileptogenicity, etc., are also involved [63].

Antiepileptic drugs

Epilepsy in patients with brain tumors belongs to the type of partial epilepsy in adults, either with or without secondary generalized seizures. For this type of seizures, the International League Against Epilepsy (ILAE) has recently updated the most appropriate AED choices, based on a meta-analysis of a large number of randomized controlled trials [84]. Levetiracetam (LEV), carbamazepine, phenytoin, and zonisamide have been classified as level A anticonvulsants, valproate (VPA) represents the only level B anticonvulsants, while gabapentin, lamotrigine, oxacarbazepine, phenobarbital, topiramate, and vigabatin are level C. In neuro-oncology, consensus exists to avoid enzyme-inducing antiepileptic drugs (EIAEDs), such as phenobarbital, carbamazepine, and phenytoin to avoid interactions with antineoplastic drugs. A recent meta-analysis by the Cochrane collaboration [85] has concluded that there is a lack of robust, randomized, controlled evidence to support the choice of antiepileptic drug for the treatment of seizures in patients with brain tumors. Moreover, it is important to realize that the excellent figures in terms of response rate of seizures to the different drugs that have been reported probably include the beneficial effects of surgery or other concomitant antineoplastic treatments.

LEV is the preferred monotherapy choice in patients with gliomas, based on numerous studies carried out either as add-on therapy or monotherapy, that reported a seizure freedom in 76–91 % of patients, a 50 % seizure reduction in up to 100 %, and a superior tolerability [86–88]. In a recent randomized comparison, LEV has yielded a seizure freedom at 12 months of 65 % compared to 75 % with pregabalin [89]. VPA monotherapy has yielded a seizure freedom in 30–78 % patients [90•]. VPA may induce or aggravate thrombocytopenia in combination with chemotherapy [91]. However, a recent study on a cohort of GBM patients receiving RT+TMZ (Stupp regimen) did not show any significant difference between LEV and VPA in terms of neutrophil granulocytes, lymphocytes, and thrombocytes decrease [92•]. Moreover, both LEV and VPA (at a lesser extent) could improve verbal memory in high-grade glioma patients [93].

Lacosamide is a third-generation AED that has a novel mechanism of action of selectively enhancing slow inactivation of voltage-gated sodium channels. It is approved by FDA and EMA as add-on treatment of partial-onset seizures in adults with epilepsy. Lacosamide has many good properties for use in patients with brain tumors. It has a favorable pharmacoresistant profile that includes low protein binding, a 13-h half-life that allows twice daily administration, rapid and complete oral assumption not affected by food intake, no induction or inhibition of hepatic enzymes, and a very low potential for drug interactions. Lacosamide is available also in an intravenous form with easy 1:1 dose conversion to/from the oral preparation. A recent study [94•] on 70 patients with primary brain tumors (mainly gliomas) with seizures has reported a decrease of seizure frequency in 66 %: the activity was even greater (73 %) in the subset of patients who suffered from seizure unresponsive to previous therapy. Lacosamide showed activity regardless of the prior AED class. No data on seizure freedom rate were reported. Toxicities were mild. Future prospective trials should confirm these preliminary interesting data. In our experience, when seizure control is insufficient with monotherapy of LEV or VPA, polytherapy combining the two drugs is preferred; in case this combination lacks activity, our policy is to add lacosamide, before trying alternative AEDs (lamotrigine or zonisamide). Status epilepticus, which is more likely associated with frontal tumors and advanced disease, appears paradoxically more responsive to simple AED regimens than tumor-associated epilepsy [95]. Our preliminary experience suggests an important activity of i.v. lacosamide in treating status epilepticus resistant to phenytoin and valproate.

In glioma patients with seizure freedom after antitumor therapy, the question emerges whether AEDs should be continued, particularly in case where antitumor treatment has been successful. Few studies suggest that in this subgroup of patients, a safe withdrawal of AED medication is feasible [96, 97], but overall, the benefit versus risks and timing of a withdrawal of AEDs in patients with gliomas are still unclear. A prospective observational study is ongoing in Netherlands [97].

The use of VPA in patients with GBMs has recently drawn attention because of its potential beneficial antitumor activity as a histone deacetylase inhibitor. Some clinical papers have suggested an improvement of survival when using VPA in combination with TMZ [90•, 98–100]; however, this hypothesis has not been confirmed in studies investigating prospectively this question.

Compliance with Ethics Guidelines

Conflict of Interest
Roberta Rudà and Riccardo Soffietti declare no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by the authors.

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