Epilepsy and brain tumors.

EPILEPSY AND BRAIN TUMORS

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ABSTRACT

Purpose of review
To present an overview of the recent findings in pathophysiology and management of epileptic seizures in patients with brain tumors.

Recent findings
Low-grade gliomas are the most epileptogenic brain tumors. Regarding pathophysiology, the role of peritumoral changes [hypoxia and acidosis, blood-brain barrier (BBB) disruption, increase or decrease of neurotransmitters and receptors] are of increasing importance. Tumor-associated epilepsy and tumor growth could have some common molecular pathways. Total/subtotal surgical resection (with or without epilepsy surgery) allows a seizure control in a high percentage of patients. Radiotherapy and chemotherapy as well have a role. New antiepileptic drugs are promising, both in terms of efficacy and tolerability. The resistance to antiepileptic drugs is still a major problem: new insights into pathogenesis are needed to develop strategies to manipulate the pharmakoresistance.

Summary
Epileptic seizures in brain tumors have been definitely recognized as one of the major problems in patients with brain tumors, and need specific and multidisciplinary approaches.

INTRODUCTION

Epilepsy is a common cause of morbidity among brain tumor patients. Clinically, tumor-related seizures are localization-related and manifest as simple or complex seizures with or without secondary generalization and respond less frequently to conventional antiepileptic therapy. The epileptogenesis in brain tumor patients is multifactorial and still not fully understood. Antineoplastic treatments (surgical resection, radiotherapy and chemotherapy, targeted agents) are increasingly recognized as effective not only for tumor control but for epileptic control as well. Old antiepileptic drugs (AEDs) have many interactions with antineoplastic agents and steroids, thus newer AEDs are employed and investigated.

EPIDEMIOLOGY AND PATHOLOGY

Overall, 20–40% of patients with brain tumors experience at least one seizure prior to the diagnosis of their tumor, and another 20–45% will develop seizures at some point following diagnosis [1,2].

The tumor location influences the risk of epilepsy [3,4]. Tumors involving the frontal, temporal and parietal lobes are more commonly associated with seizures than occipital lesions. Intractable epilepsy is particularly frequent in tumors which involve the temporo-mesial and insular structures [5–7]. Cortical tumors have a higher incidence of associated epilepsy than noncortical deeper

lesions, and lesions entirely within the white matter are rarely epileptogenic. Proximity to the rolandic fissure and the central sulcus increases seizure frequency.

The frequency of seizures differs widely according to the different tumor types.

Glioneural tumors, such as gangliogliomas and disembryoplastic neuroepithelial tumors (DNTs), are typically associated with a chronic pharmacoresistant epilepsy in up to 90–100% of patients [8••]. They occur predominantly in children and young adults, and in the temporal lobe. These tumors are designated by the last WHO classification [9] as grade I tumors, thus most patients have a favorable outcome after surgical resection alone, with only rare cases of gangliogliomas that recur and/or undergo malignant transformation [10,11]. Among DNTs two histological variants have been identified: the simple variant is characterized by the glioneural element, whereas the complex variant contains additionally glial nodules resembling astrocytomas or oligodendroglial tumors. From a clinical point of view, patients with complex DNT variants have an earlier seizure onset than patients with simple variants, and complex DNT variants are more likely to be located outside the temporal lobe [12•]. Sometimes the differential diagnosis between these grade I tumors and the most common grade II gliomas is challenging due to sampling problems. The brain tissue adjacent to a ganglioglioma or a DNT may frequently show an atypical cortical architecture, referred to a malformation of cortical development or cortical dysplasia [8••,13•]; conversely, the presence of adjacent cortical maldevelopment is distinctly uncommon in grade II gliomas. Moreover, a dual pathology, such as incidental second lesion controlateral to the epileptogenic lesion or hippocampal sclerosis in conjunction with the epileptogenic lesion, may occur. Other rare grade I gliomas, such as supratentorial pilocytic astrocytomas, pleomorphic xanthoastrocytomas and angiocentric gliomas that prevail in children and young adults, frequently cause seizures [8••].

Diffuse low-grade gliomas (grade II astrocytomas, oligodendrogliomas and oligoastrocytomas) have seizures in 60–88% of patients [4,14•]. The rare protoplasmic astrocytoma, which is predominantly cortical-based, can be linked to chronic epilepsy. Moreover, among grade II astrocytomas, a subtype characterized by long-term epilepsy, longer survival and lower recurrence rate has been described [15]. This subtype, called isomorphic astrocytoma, is characterized by low cellularity, lack of mitotic activity, highly differentiated astrocytic cells, and absence of nuclear p53 accumulation, and glial MAP2 and CD34 expression. Among low-grade gliomas, seizures are much less frequent (47 versus 85%) in older patients (>=60 years) compared to younger patients [16•].

The frequency of seizures decreases significantly in high-grade gliomas [30–50% in glioblastoma (GBM)] [17,18]. About 25% of patients with meningiomas present with seizures [19]. The lowest seizure frequencies are observed in brain metastases (20–35%), neoplastic meningitis (10–15%) and primary CNS lymphomas (10%) [3].

Tumor location and histology can be correlated: the majority of glioneuronal tumors occur in the temporal lobe, whereas low-grade gliomas tend to grow close to eloquent areas [20].

No correlation has been found between seizure activity and the metabolic rate of the tumor measured by PET with methionine [14•].

A recent magnetic resonance volumetric analysis [21•] has reported that among high-grade gliomas tumors presenting with seizures were smaller than tumors presenting with nonseizure neurological symptoms, whereas among low-grade gliomas tumors presenting with seizures were larger than tumors presenting with nonseizure neurological symptoms.

PATHOGENESIS

The pathogenesis of tumor-related seizures is multifactorial and still not fully understood [22,23,24•]. In this regard, the role of peritumoral changes is of growing importance [25••].

Role of tumor type

There is evidence that the mechanisms of epileptogenesis vary for different tumor types, thus explaining the differences in seizures frequency.

Intrinsic epileptogenicity of glioneuronal tumors is supported by electrocorticography, surgical and immunocytochemical studies, suggesting the presence of a hyperexcitable neuronal component [26]. The cells of these developmental tumors can overexpress neurotransmitter receptors and neuropeptides, compromising the balance between excitation and inhibition [24•]. The associated dysplastic disorganization of the adjacent cortex may contribute to the mechanism of seizure generation. An extensive inflammatory reaction with accumulation of microglial cells in the perilesional areas has also been suggested [27].

Slow-growing tumors could produce an epileptogenic milieu by partial deafferentation of cortical regions, thus causing a denervation hypersensitivity [3]. Moreover, recent studies [28,29], using magnetoencephalograpy to investigate the functional connectivity between brain regions, have suggested that low-grade gliomas, by infiltration of white matter and not only infiltration of the cortex, could modify the natural balance and synchronization of normal networks (‘small-world’ networks), and cause random networks that might have a lower threshold for seizures [30].

Differently from low-grade gliomas, high-grade tumors, such as GBMs, induce seizures via abrupt tissue damage due to necrosis, bleeding with subsequent hemosiderin deposition and edema. The putative mechanism of epilepsy in extrinsic tumors, such as meningiomas, is more likely related to peritumoral edema that, for instance, explains the high frequency of preoperative seizures in supratentorial tumors [19].

Role of changes in peritumoral tissue

Morphologically, neuronal density in the hippocampus of patients with mesial temporal lobe epilepsy and gliomas is normal; however, peritumoral cells may have an anomalous phenotype. Morphologic changes include aberrant migration with persistent neurons in the white matter, and pyramidal neurons with fewer inhibitory and more excitatory synapses [25••]. Intercellular connections between adjacent glial cells occur via connexin transmembrane gap junction proteins: altered expression of connexins in tumor cells and reactive astrocytes of the perilesional cortex of patients with low-grade gliomas and epilepsy has been found by immunohistochemical studies [31].

The peritumoral microenvironment in brain tumors is substantially different from that of normal brain tissue. Modern neuroimaging techniques have provided new evidence: MRS has demonstrated decreased levels of N-acetylaspartate, a marker of neuronal viability and function, in lesional epileptogenic cortex [32]. Several alterations may predispose to seizure generation. Tumor hypoxia and interstitial acidosis, extending into the peritumoral tissue, can induce glial cell swelling and damage. A functional consequence of acidic pH can be a deregulation of sodium and calcium influx across cell membranes. Further, the influence of pH on the activity of AEDs is uncertain. Changes in ionic concentrations can also contribute to neuronal excitability. Disruption of the blood–brain barrier (BBB) leads to abnormal extravasation of plasma proteins and other substances; thus it can increase excitability and induce seizures. It is known that focal disruption of the BBB leads to the

development of a seizure focus [33], and that osmotic BBB disruption with intra-arterial mannitol, in conjunction with chemotherapy, may be complicated by seizures [34].

Role of neurotransmitters and receptors

Brain tumors and the peritumoral tissue have been found to have altered expression of neurotransmitters and their receptors. A greater concentration of glutamate, the major excitatory amino acid neurotransmitter in the brain, has been found in brain tumor samples from patients with active epilepsy [25••,35]. Moreover, it has been recently hypothesized that, when invading normal tissue, glioma cells react to spatial constraints by releasing high level of glutamate into the extracellular space which induces seizures and later causes excitotoxic neuronal cell death, thereby facilitating invasion and migration [36–38]. Both ionotropic and metabotropic glutamate receptors have been shown to be overexpressed either in glioma cells and peritumoral astrocytes [39–41]. Activation of these receptors by glutamate could down-regulate [gamma]-aminobutyric acid (GABA)-mediated inhibitory stimuli as a second mechanism by which seizure activity could increase. Alterations in GABA levels, the main inhibitory neurotransmitter, may also contribute to tumor-associated seizures, but it remains unclear whether decreased inhibition or new characteristic excitatory activity, together with altered receptor subtype expression, may be responsible for neuronal hyperexcitability [25••].

Molecular–genetic findings

Recent molecular–genetic findings have been described in glioneuronal tumors. A common role for the PI3K-mTOR pathway in the pathogenesis of glioneuronal tumors, focal cortical dysplasias type IIB and cortical tubers has been suggested [42]. Gene expression profiling of epilepsy-associated gangliogliomas has revealed altered levels of expression of genes involved in immune system, synaptic transmission and cell cycle control [43]. Overall, it remains to be demonstrated that tumor-associated epilepsy and glioma growth have common genetic pathways [44].

Secondary epileptogenesis

Secondary epileptogenesis is a phenomenon predominantly seen in younger patients with slow-growing tumors of the temporal lobe and long history of seizures. It implies that an actively discharging focus has the capability to induce a similar paroxymal activity in areas of the brain that are distant to the original site.

IMPACT OF SURGERY

Tumor surgery allows seizure control in many patients with low-grade gliomas, including those with pharmacoresistant epilepsy: the percentage of seizure-free patients in the major series ranges from 65 to 82% [5–7,45–50,51•]. Across all studies, the most significant factors associated with seizure freedom are completeness of tumor resection and short preoperative duration of tumor-associated epilepsy. In the large series of Chang et al. [7] 89% of patients were seizure-free at 6 months following gross total resection (i.e. resection of FLAIR abnormalities on MRI) as compared to only 57% after subtotal resection. Among other prognostic factors, age more than 40 years, frontal location and gemistocytic differentiation have been associated with poorer seizure outcome [6]. Long-term seizure control seems better in patients with gangliogliomas or DNTs (94%) than in patients with other gliomas (79%) and those with cortical dysphasia (68%) [52].

When patients become seizure-free after tumor surgery, it means that the cortex surrounding the tumor probably loses the ability to independently initiate and propagate seizures once the tumor has been removed; in other words the epileptogenic zone does not extend substantially beyond tumor borders. Conversely, when the epileptogenic zone includes significant extratumoral cortical areas,

patients (15–20%) still suffer from refractory epilepsy, even after (sub)total tumor resection [5,48]. In this setting a more comprehensive approach aiming at the identification and removal of the epileptogenic zone as well (i.e. epilepsy surgery) will result in improved epilepsy outcome. Seizure outcomes after lesionectomy versus epilepsy surgery in patients with medically intractable seizures have been compared by several authors, and all have shown a significant improved control after epilepsy surgery [53,54•].

IMPACT OF RADIOTHERAPY

Few studies have analyzed the impact of radiotherapy on tumor-related seizures. Stereotactic interstitial irradiation may improve seizure control in 40–100% of unresectable low-grade gliomas [55,56], and this could be due to an increased benzodiazepine receptor density [56]. Gamma-knife radiosurgery for mesiotemporal tumor-related epilepsy, aiming to also irradiate the presumed epileptic foci surrounding the tumor, can be effective as well [57]. Moreover, radiosurgery has been of value in patients with gelastic or generalized seizures related to hypothalamic hamartomas [58,59]. Conventional radiotherapy has been reported to be effective in seizure control in 75–100% of patients with medically intractable epilepsy and low-grade gliomas [60,61] and malignant brain tumors [62]. Patients may become seizure-free (25–55%), and the median duration of seizure control is about 12 months, but can be as long as 8 years [60]. Recurrence or increase of seizures is more commonly associated with tumor progression. Both after interstitial and conventional radiotherapy of low-grade gliomas the seizure reduction may begin early during radiotherapy and is not always associated with a tumor response (‘shrinkage’) on CT/MRI. In fact, among patients who had a significant reduction of seizures after radiotherapy, 1/4 patients in the series of Rogers et al. [60] and 13/19 of the series of Rudà et al. [61] had a stable disease only on CT/MRI. Thus, in addition to a reduction of tumor size, further hypotheses regarding the effect of ionizing radiations on seizure control include damage to epileptogenic neurons in the peritumoral tissue or metabolic changes of the microenvironment [60]. An indirect suggestion of the efficacy of radiotherapy on epileptic seizures comes from the EORTC 22845 phase III trial that compared adjuvant postoperative radiotherapy versus observation in low-grade gliomas: at 1 year, 25% of patients who were irradiated had seizures compared to 41% of patients who were not irradiated [63].

IMPACT OF CHEMOTHERAPY AND TARGETED THERAPIES

The activity of chemotherapy with alkylating agents [procarbazine (PCV), temozolomide] in low-grade gliomas, either as salvage treatment after surgery and radiotherapy or as upfront treatment after surgery in symptomatic/progressive patients, is well established [64•]. Seizure improvement is more commonly obtained in 50–65% of patients (Table 1) [65–74], with 20–40% becoming seizure-free. In general, clinical improvement is more frequent than objective radiological responses: the majority of these patients have nonenhancing lesions on MRI and tend to show a minor response on a stable disease on T2 or FLAIR images. As in the case of radiation therapy, recurrence or increase of seizure frequency is associated with tumor progression. There are no data in the literature regarding the response of epileptic seizures to chemotherapy in malignant tumors.

A recent study has reported a significant reduction of epileptic seizures, in association with MRI improvement, in subependymal giant-cell astrocytomas (SEGAs) in tuberous sclerosis after treatment with the mTOR inhibitor everolimus [75].

Reference	No. of pts with seizures/no. of total patients	Chemotherapy regimen	Seizure response
[65]	6/9	PCV	100%
[66]	12/26	PCV	50%
[67]	8/10	PCV	87%
[68]	22/33	PCV	53%
[69]	31/43	TMZ standard	48%
[70]	27/29	TMZ standard	55%
[71]	60[a]	TMZ standard	Up to 51%
[72]	149[a]	TMZ standard	Up to 58%
[74] (ongoing study)	17/31	TMZ dose-dense	65%

CCNU, vincristine; PCV, procarbazine; TMZ, temozolomide.
[a] Number of patients with epilepsy not reported.

Table 1 Seizure response to chemotherapy in low-grade gliomas

EFFICACY OF ANTIEPILEPTIC DRUGS

The knowledge on optimal antiepileptic therapy in patients with brain tumors is limited and, to date, there are no firm evidence-based guidelines regarding the management of seizures in neuro-oncologic patients. Although many randomized trials on anticonvulsants have been carried out over the last 15 years, there is a lack of large prospective studies or randomized trials comparing the efficacy of old and new AEDs in brain tumor patients [76•,77•]. Overall, employing conventional AEDs, first-line treatment fails in about 60% of patients, whereas in the remainder 60% will experience a second failure in monotherapy or polytherapy [78]. Hildebrand et al. [79] reported a complete control of seizures in 12.6% of patients following valproate, carbamazepine, gabapentin, lamotrigine and clobazam in association with chemotherapy; moreover AEDs, combined with specific antitumor treatments, significantly reduced the rate of seizure generalization.

In the last 10 years, new AEDs have been introduced and show promise, as add-on or first-line treatment of epilepsy, both in terms of efficacy and tolerability. Table 2 [80–86,87•–89•] shows the published series on the efficacy of new AEDs in brain tumor patients. Overall, employing newer AEDs, the rate of response is commonly superior to 50%, and the percentage of seizure-free patients ranges between 20 and 91%. Most series are on levetiracetam [82–84,88•]. Wagner et al. [82], using levetiracetam as add-on in a prospective series of 26 patients, obtained a significant (more than 50%) reduction of seizure frequency in 65% of patients. Another two prospective studies [84,88•] have reported a response rate of 72 and 60%, respectively. Side effects were mild and consisted in occasional occurrence of somnolence, especially at the beginning of treatment, fatigue and dizziness. Moreover, the authors [82,84,•] reported no laboratory abnormalities in patients with concomitant chemotherapy (temozolomide or fotemustine). Considering all these studies on levetiracetam, the results provide good evidence of safety and efficacy: maybe this could be related to some peculiar characteristics of the drug, such as the ability to prevent the impairment of astroglial regulatory properties under inflammatory condition [90]. Levetiracetam does not cause induction or inhibition of the P450 enzyme system or other enzyme systems, has no active metabolites and exhibits almost no protein binding: these factors allow the drug to avoid significant interactions with other medications. Thus, together with the lack of cognitive side effects [91], levetiracetam has now become the drug of first choice in patients with epilepsy and brain tumors.

Some studies, with small numbers of patients, have studied gabapentin, tiagabine and pregabalin [80,81,86]. Perry and Sawka [80] explored the role in add-on of gabapentin in 14 brain tumor patients (mostly high-grade gliomas) with intractable seizures: complete control of seizures occurred in 8/14 patients (57%), seizures frequency was reduced in all patients and efficacy persisted over time. Preliminary studies have suggested a possible ‘cause-specific’ efficacy of tiagabine (TGB) in patients with drug-resistant partial epilepsy and cerebral glial tumors. Striano et al. [81] explored the effect in add-on of tiagabine in a group of 11 patients with glial tumors and long-lasting (3–40 years), drug-resistant, partial epilepsy. Seven out of 11

Table 2 Efficacy of new antiepileptic drugs in brain tumor-associated epilepsy

Reference	Study	No.	AED	Antineoplastic, concomitant treatments	Histology	Response ratio	Seizure-free ratio
[80]	Prospective	14	Gabapentin Add-on	RT in 4/14 Radiosurgery 1/14	8 HGG 1 LGG 4 MTS 1 MEN	100%	57%
[81]	Prospective	11	Tiagabina Add-on	n.r.	1 GBM 9 LGG 1 PA	63%	27%
[82]	Prospective	26	Levetiracetam Add-on	RT + TMZ (GBM)	18 HGG 8 LGG	65%	20%
[83]	Retrospective	41	Levetiracetam Add-on	Majority RT; some TMZ, 2 MTX	12 GBM 13 AA 7 MTS 7 LGG 2 PCNSL	90%	58%
[84]	Prospective	19	Levetiracetam Add-on	RT, chemotherapy	12HGG 6 LGG 1 MEN	72%	47%
[85]	Prospective	47	Topiramate 33/47 add-on 13/47 first choice	38/47 chemotherapy (TMZ, PCV, fotemustine, other) 20/47 RT	28 HGG 13 LGG 4 MEN 2 MTS	20%	56%
[86]	Retrospective	9	Pregabalin Add-on or monotherapy	RT + TMZ (GBM)	6 GBM 2 LGG 1 PCNSL	100%	67%
[87•]	Prospective	6	Zonisamide Add-on	Chemotherapy in 3/6 (fotemustine)	3 LGG 1 HGG 2 Gliomatosis	83%	
[88•]	Prospective	82	Levetiracetam First choice	n.r.	13 LGG 69 HGG	60%	73/82
[89•]	Retrospective	13	Lacosamide 11/13 add-on 2/13 first choice	n.r.	4 GBM 5 LGG 1 Pineoblastoma 1 DNET 1 gliomatosis 1 PA	77%	46%

AA, anaplastic astrocytoma; DNET disembrio neuroepithelial tumor; GBM, glioblastoma; HGG, high-grade glioma; LGG, low-grade glioma; MEN, meningioma; MG, mixed glioma; MTS, metastases; n.r., not reported; O, oligodendroglioma; PA, pilocytic astrocytoma; PCNSL, primary CNS lymphoma.

patients responded (64%) with 3/11 seizure-free. Tolerability of tiagabine was good in all but two patients who experienced nausea and tiredness. This efficacy could be related to a selective blockade of GAT-1 transporter by the drug. Pregabalin [86] was studied in a retrospective series of nine consecutive patients, most with GBM: all patients experienced at least a 50% seizure reduction and 6/9 (66%) became seizure-free. However, 45% experienced side effects (mainly fatigue) leading to a discontinuation of the drug in 25%. Topiramate [85] showed efficacy in a series of patients with heterogeneous tumor histology (mostly high-grade gliomas): seizure reduction was observed in 76%, being 56% seizure-free. Considering separately patients in which topiramate was employed as add-on and those in which it was employed as first-line therapy, the difference in terms of response to treatment was not significant. Three of 47 patients had severe side effects that required topiramate discontinuation.

More recently, two small series have studied the role of the new AEDs zonisamide [87•] and lacosamide [89•]: they both seem promising with a rate of response of 83 and 77%, respectively. Whereas with lacosamide the most common toxicity was mild dizziness, with zonisamide 2/8 patients experienced side effects such as sexual dysfunction and drowsiness; however, further studies in a larger number of patients are needed.

In general, all series have limitations, such as small number of patients, retrospective nature and heterogeneity regarding patient characteristics: they grouped together different histologies (high and low-grade gliomas, metastases, meningiomas, other), patients under antineoplastic treatment or in follow-up, patients with stable or progressive tumor and patients with different ‘activity’ of the epilepsy (from one

seizure at the time to diagnosis to ‘intractable seizures’). Moreover, in some series the antitumor treatments were not detailed. In conclusion, due to the different natural history, concomitant treatments and pathophysiology of seizures, future studies aiming to investigate the role of new AEDs should be focused on specific tumor categories.

SIDE EFFECTS OF ANTIEPILEPTIC DRUGS

Side effects of AEDs are more common among brain tumor patients than in patients with nontumoral epilepsy [3,92–94]. Skin rashes are about twice that for patients who take AEDs without a brain tumor. Severe skin reactions, such as Stevens–Johnson syndrome, may occur mainly during the first 4–8 weeks of administration of carbamazepine, phenobarbital, phenytoin or lamotrigine (especially in association with radiotherapy). Shoulder–hand syndrome is particularly frequent in patients with brain tumors treated with phenobarbital. Bone marrow suppression (lymphopenia after carbamazepine, thrombocytopenia after valproic acid, agranulocytosis after lamotrigine) should be considered in patients treated with concomitant chemotherapy. Neurocognitive deficits are associated with the use of AEDs, in particular old AEDs: in a cohort of patients with low-grade gliomas, the presence of epilepsy and the use of AEDs (carbamazepine, phenytoin, valproic acid, phenobarbital) were associated with cognitive changes [95]. Compared with healthy controls, glioma patients had significant reduction in information processing speed, psychomotor function, attentional functioning, verbal and working memory, executive functioning, and HRQOL. The reduction in cognitive domains, except for attentional and memory functioning, could primarily be attributed to the use of AEDs, whereas the decline in HRQOL could be ascribed to the lack of complete seizure control. The authors concluded that low-grade glioma patients suffer from a number of neuropsychological and psychological problems that are aggravated by the severity of epilepsy and intensity of the treatment.

INTERACTIONS BETWEEN ANTIEPILEPTIC AND ANTICANCER AGENTS

Several interactions between AEDs and chemotherapy, based on shared cytochrome P450 enzyme pathways, have been reported [96]. In particular, potent inducers, such as phenobarbital, phenytoin, primidone and carbamazepine, may significantly reduce serum levels of nitrosoureas, cyclophosphamide, ifosfamide, procarbazine, vincristine, paclitaxel, irinotecan, topotecan, 9-aminocampthotecin, doxorubicin, teniposide, thiotepa, methotrexate and busulfan [97,98]. Moreover, highly protein-bound AEDs and chemotherapeutic agents (phenytoin, phenobarbital, valproic acid, cisplatin, etoposide, teniposide) may interact with each other by displacement, altering free and bound levels of both compounds. Chemotherapeutic agents may affect AED levels as well: methotrexate, doxorubicin, adriamycin and cisplatin have been reported to decrease the serum levels of valproic acid, carbamazepine, and phenytoin [78].

Among chemotherapeutic agents, temozolomide, an oral alkylating agent commonly used for treatment of high and low-grade gliomas, has minimal hepatic metabolism: one study have documented no effect of temozolomide on levels of topiramate or oxcarbazepine in chronically treated patients [99,100]. This is also true for bevacizumab, a monoclonal antibody anti-vascular endothelial growth factor (VEGF) that is active against high-grade gliomas at recurrence [100].

Small tyrosine-kinase molecules that are commonly used in extranervous tumors or in clinical trials in malignant gliomas, such as imatinib, gefitinib, erlotinib, tipifarnib, sorafenib, and so on, are metabolized by the P450 system, thus leading to interactions with enzyme-inducing AEDs (EI-AEDs) [101].

Valproic acid has distinct enzyme-inhibiting properties, and might reduce the metabolism of a second drug by raising plasma concentrations; thus, valproic acid may increase the bone marrow toxic effects of

concomitant chemotherapeutic drugs. Enhanced toxic effects of nitrosoureas, given alone or in combination with cisplatin and etoposide, have been reported with concomitant administration of valproic acid [102].

Also, metabolism of corticosteroids is highly sensitive to enzyme induction [96]. EI-AEDs may increase the metabolism of various steroids, including cortisol, prednisone, dexamethasone (usually employed in brain tumor patients in order to control peritumoral oedema), resulting in inadequate clinical response.

Antiepileptic drugs and outcome

As the EI-AEDs enhance the metabolism of concurrent chemotherapeutic agents, their serum levels may be inadequate, leading to a reduction of efficacy of treatment. Whether this phenomenon impacts the outcome of patients is not well established. Two studies have focused on this issue in GBM patients, with conflicting results. Oberndorfer et al. [103] evaluated in a retrospective analysis 168 patients with histologically confirmed GBM. All were treated with surgery, radiotherapy and chemotherapy (first-line: CCNU in the majority of patients, dacarbazine/fotemustine, PCV, temozolomide). Eighty of them experienced seizures during the course of the disease and were treated with EI-AED (54%) or non-EI-AEDs (46%). A significant difference in survival was found between the group of patients receiving non-EI-AEDs (13.9 months) and the group receiving EI-AEDs (10.8 months). Limitations of this study include the retrospective nature, the variety of chemotherapy regimens (both at first and second-line) and lack of adjustments for prognostic factors. In a larger study, Jaeckle et al. [104•] performed a correlative analysis of AED use with outcome, using a cross-sectional database of 620 patients with GBM, treated within North Central Cancer Treatment Group (NCCTG) trials. Both overall survival and PFS were longer in EI-AEDs patients compared with non-EI-AED patients (12.3 versus 10.7 months and 5.6 versus 4.8 months, respectively). The reason remains unknown, but this study confirms that, in clinical studies, treatment arms may need stratification for the proportion of patients receiving EI-AEDs.

EPILEPSY PROPHYLAXIS

Antiepileptic therapy in patients with brain tumors is generally recommended after the occurrence of a first seizure [3]. Two meta-analyses have found no evidence to support prophylaxis with phenobarbital, phenytoin or valproic acid in patients with no history of seizures [94,105]. Tumor pathology (primary brain tumors, metastases, meningiomas) does not show any effect on response to prophylactic AEDs [94,105,106]. A recent Cochrane review [107] has pointed out several pitfalls of both meta-analyses and trials that were reviewed. Clinical heterogeneity between and within trials, misclassification of levels of evidence and a selective bias in the reporting of outcome (especially adverse events), all weaken the strength of evidence and recommendations. Hence, the authors prefer to state that ‘the evidence for seizure prophylaxis is inconclusive, at best’. Nonetheless, regarding implications for practice, they agree with the American Academy of Neurology (AAN) Subcommittee [94] that recommended not to use AEDs routinely as prophylaxis in patients with brain tumors and to discontinue AEDs after 1 week from surgery when used as a perioperative prophylaxis. However, the reality is that many physicians still prescribe prophylactic AEDs [108], and this is particularly true for prophylaxis of perioperative seizures.

It is unclear whether newer AEDs may have any benefit in preventing seizures. Two retrospective trials only are available. The first trial [109] evaluated oxcarbazepine for prevention of early postoperative seizures: they occurred in less than 3% of patients, similar to data reported for old drugs; moreover, oxcarbazepine was well tolerated with rapid titration. The second study [110] compared levetiracetam with phenytoin after supratentorial neurosurgery: the incidence of early and late seizures was similar in both groups, but

significantly fewer adverse events occurred with the use of levetiracetam, resulting in a higher retention rate after 1 year.

MECHANISMS OF RESISTANCE TO ANTIEPILEPTIC DRUGS

Patients with refractory epilepsy are commonly resistant to many AEDs despite different mechanisms of resistance [111]. AEDs may fail to control seizures because of loss of receptor sensitivity [3]. The major reason for resistance of epilepsy to AEDs is overexpression of proteins, belonging to the ATP-binding cassette (ABC) transporter family, such as P-glycoprotein (P-gp, MDR1), MRP1 and MRP5, that actively transport a variety of lypophilic drugs out of the brain capillary endothelium at the level of the BBB. These proteins are called ‘multidrug-resistance proteins’. An overexpression of these proteins has been reported in tumor cells of patients with glioma [112] and in samples of brain tissue from patients with ganglioglioma [113], and could lead to a diminished drug transport into the brain parenchyma.

Moreover, seizures are known to up-regulate P-gp expression by releasing glutamate [114]. A number of AEDs, including phenytoin, phenobarbital, carbamazepine, lamotrigine, and felbamate, are substrates for P-gp [115]. Levetiracetam and valproic acid do not seem to represent a substrate for P-gp or other MRPs [115,116], making these drugs attractive in brain tumor-associated epilepsy, but more data are needed. It has been suggested that valproic acid might even reduce the expression of MRP1 via its histone deacetylase-inhibiting effects [117].

New imaging studies with a P-gp-specific radioligand are ongoing to ‘in vivo’ investigate the role of P-gp and its polymorphisms in drug-resistant epilepsy [118•].

CONCLUSION

Tumor-associated epilepsy is an important clinical problem. Low-grade gliomas are the most epileptogenic brain tumors. In this patient population early total/subtotal surgical resection shows a strong tendency to predict better seizure outcome. This supports early operation not only based on oncological considerations, but also to avoid the risk of chronic epilepsy and optimize the patient's quality of life. Radiation and chemotherapy can be proposed as a first-line choice, instead of AED polytherapy, when uncontrollable seizures develop during follow-up, even if a true tumor recurrence is not evident. Advances into the distinct pathophysiologies of epilepsy associated with different tumor histologies will promote an even more rational choice of therapies, including prophylaxis.

REFERENCES AND RECOMMENDED READINGS

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 677).

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