Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management

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Epilepsy is common in patients with brain tumours and can substantially affect daily life, even if the tumour is under control. Several factors affect the mechanism of seizures in brain tumours, including tumour type, tumour location, and peritumoral and genetic changes. Prophylactic use of antiepileptic drugs is not recommended, and potential interactions between antiepileptic and chemotherapeutic agents persuades against the use of enzyme-inducing antiepileptic drugs. Multidrug-resistance proteins prevent the access of antiepileptic drugs into brain parenchyma, which partly explains why seizures are frequently refractory to treatment. Lamotrigine, valproic acid, and topiramate are first-line treatments of choice; if insufficient, add-on treatment with levetiracetam or gabapentin can be recommended. On the basis of clinical studies, we prefer to start treatment with valproic acid, adding levetiracetam if necessary. Risks of cognitive side-effects with antiepileptic drugs can add to previous damage by surgery or radiotherapy, and therefore appropriate choice and dose of antiepileptic drug is crucial.

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Introduction

Epilepsy is common in patients with brain tumours, and seizure control is an important part of clinical management. In the presence of a well-controlled tumour, development of convulsions adds substantial morbidity to patients with brain tumours.[1] Seizures in patients with brain tumours are symptomatic and localisation-related, manifesting as simple or complex seizures with or without secondary generalisation. Several factors affect epileptogenesis in patients with brain tumours, including tumour type, tumour location, changes in the peritumoral environment, and genetic factors.

Difficulties in the medical management of epilepsy in patients with brain tumours include the refractoriness of epilepsy, which might be due to multidrug-resistance proteins; potential interactions between antiepileptic drugs and chemotherapeutic agents; and risk of cognitive side-effects from use of antiepileptic agents in addition to earlier brain damage from surgery or radiotherapy.[1–4]

In this Review, we focus on the clinical characteristics of seizures in patients with brain tumours. We discuss the underlying mechanisms for treatment refractoriness and the interactions between antiepileptic drugs and chemotherapy, and give guidelines on appropriate management.

Epidemiology and presentation

The incidence of brain tumours in people with epilepsy is about 4%.[5,6] Of patients with brain tumours, the frequency of epilepsy is 30% or more depending on tumour type.[7] For 30–50% of patients with brain tumours, an epileptic seizure is the presenting clinical sign of a tumour; 10–30% will develop seizures later in the disease course.[5,8–10]

Patients with brain tumours who present with seizures can be divided into two groups: children and adolescents who usually show no other neurological deficits and who commonly have a low-grade brain tumour; and middle-aged or elderly people who commonly have other neurological deficits that may be caused by high-grade tumours.[10]

Slow-growing tumours—ie, mainly low-grade gliomas—are the most epileptogenic (table 1),[5,11–15] although the high frequency of epilepsy in these patients might be related to substantially longer survival from low-grade tumours compared with high-grade tumours.[5,7,13] A seizure frequency of up to 100% is seen with dysembryoblastic neuroepithelial tumours, and of 60–85% in low-grade astrocytomas and oligodendrogliomas. In glioblastoma multiforme, the incidence of epilepsy varies from 30 to 50%.[5,8,16,17] About 25% of patients with meningioma present with seizures.[18] About a fifth of patients with meningioma without a history of epilepsy develop seizures after surgery.[18] For patients with brain metastasis, incidence of seizures ranges from 20% to 35%.[5]

Irrespective of tumour type, patients who present with seizures as the first sign of a brain tumour are at increased risk of recurrent seizures despite treatment with antiepileptic drugs.[8] Furthermore, tumour location affects the risk of epilepsy. A cortical tumour is the main predictive factor for development of epilepsy. Tumours that affect the frontal, temporal, and parietal lobes are more commonly associated with seizures than are occipital lesions.[19] Infratentorial and sellar tumours rarely cause seizures, unless they extend into the cerebral hemispheres.

	Seizure frequency
Dysembryoblastic neuroepithelial tumour[5,11]	100%
Ganglioglioma[5,12]	80–90%
Low-grade astrocytoma[12,13]	75%
Meningioma[5,12]	29–60%
Glioblastoma multiforme[5,13]	29–49%
Metastasis[5,12]	20–35%
Leptomeningeal tumour[14,15]	10–15%
Primary CNS lymphoma[14]	10%

Table 1: **Association between tumour type and seizure frequency**

Epileptogenesis by brain tumours

The precise nature of epileptogenesis in patients with brain tumours is unclear. However, several mechanisms have been proposed, and its origin is probably multifactorial. In principle, the balance between intracortical inhibitory and excitatory mechanisms must shift towards that of excitation.[20] Epileptogenic activity probably arises in the cortex adjacent to the tumour; lesions are usually electrically inert.[21]

Role of tumour type

The type of primary tumour seems to play an important part in epileptogenesis. Developmental tumours, which have a high seizure incidence, frequently show cortical dysplasia or other structural abnormalities that are associated with epileptogenic properties. These tumours consist of well-differentiated cells that can release neurotransmitters or modulators with a role in epileptogenesis. Developmental tumours and those that are slow growing might partly isolate brain regions through mechanic or vascular mechanisms, and such relative deafferentation of circumscribed cortical areas has intrinsic epileptogenic propensity.[21,22]

Thus, differences in epileptogenesis might explain the discrepancy in seizure frequency between low-grade and high-grade tumours. The slow growth of low-grade lesions might be needed for development of the focal or remote cell changes that are associated with epileptogenesis.[12,13] Rapidly progressive brain tumours (eg, brain metastasis or glioblastoma multiforme) are thought to induce epilepsy through abrupt ways of tissue damage such as tissue necrosis or deposition of haemosiderin.[14]

Role of morphology in peritumoral tissue

Morphological changes in peritumoral tissue may affect epileptogenesis; these include aberrant neuronal migration; changes in synaptic vesicles; enhanced intercellular communication through increased expression of gap-junction channels; persistent neurons in white matter; or an imbalance between inhibitory and excitatory mechanisms through changes in local concentrations of GABA and glutamate.[12,22,23] Patients with glioma who have refractory epilepsy have increased concentrations of glutamate, as shown by changes in perilesional immunoreactivity of GABA receptors and glutamate decarboxylase.[20,21,24]

Furthermore, local irritation due to infiltrative neuronal growth and the tumour mass could be epileptogenic, potentially because of the presence of hypoxic brain regions.[25] However, no clear relation has been found between seizure frequency and tumour-mass effect or oedema. Moreover, high-grade tumours are associated with a lower incidence of seizures than are low-grade tumours.[26]

Role of microenvironment

Differences in angiogenesis between healthy brain tissue and tumour tissue as a result of decreased intratumoral blood perfusion and increased metabolism cause transient or chronic hypoxia in tumours and adjacent regions. These events change the pH of interstitial fluid, cause cells to swell, and damage glial cells—all of which increase neuronal excitability and thus the potential for development of epilepsy. Under normal conditions for oxygen and glucose, tumour tissues produce more lactate than do healthy cells.[21] Because tumours have genomic and chromosomal instability, including DNA strand breaks and rearrangements, the occurrence of hypoxic brain regions are associated with changes in gene expression that have negative effects on the stability of DNA-repair mechanisms and on the likelihood of mutations. Under these conditions,[20] the astrocytic cell membrane becomes prone to inward sodium currents, leading to risk of epilepsy.

Genetic factors

In addition to the effects of tumour microenvironment on gene expression, other genes may have a role in epileptogenesis. The tumour-suppressor gene *LGI1* plays a part in glioma progression, is thought to have a role in cell invasion and migration, and has low or absent expression in cell lines from glioblastoma multiforme or other high-grade gliomas. This gene causes the rare syndrome autosomal dominant lateral temporal lobe epilepsy, which shows Mendelian inheritance. Because of the association with glioma progression and epilepsy, Brodtkorb and colleagues[27] have suggested it has a role in epileptogenesis in patients with brain tumours. However, further studies are needed to confirm such a role.

Secondary epileptogenesis

For about a third of patients, the epileptogenic focus does not correspond to tumour location. Such secondary epileptogenesis implies that an actively discharging epileptogenic focus induces similar paroxysmal activity in regions that are distant to the original site. This secondary focus is seen more frequently with temporal tumours.[28] Young age and long duration of illness are associated with an increased risk of secondary epileptogenesis. Therefore, early treatment of the primary epileptic lesion may be needed to prevent development of a secondary, potentially irreversible, focus.[11]

Epileptogenesis in patients with brain tumours is probably multifactorial and caused by different tumour types and changes in the properties of tumour-cell membranes that generate action potentials and thus affect neuronal excitability (eg, raised concentrations of aminoacids, neuroreceptor disturbances, increased gap junctions between tumour cells, and low pH microenvironment).

Epilepsy in cancer

At least 4% of patients without brain metastases or primary brain tumours (ie, those with extracranial cancer)

have seizures,[29] which are commonly caused by metabolic encephalopathies secondary to electrolyte abnormalities or organ dysfunction, or by toxic encephalopathies induced by chemotherapeutic agents or other drugs.

Furthermore, epilepsy might be secondary to radionecrosis of the temporal lobe after radiotherapy (eg, of a laryngeal tumour).[15] Also, seizures can be secondary to an infection of the brain, and opportunistic CNS infections are common in cancer as a result of the immunosuppressive effects of chemotherapy or cyclosporins.[29] Drugs that are prescribed to patients with cancer such as antidepressants (eg, tricyclics, selective serotonin reuptake inhibitors, or bupropion); neuroleptic agents (eg, clozapine, phenothiazines, or butyrophenones); antibiotics (eg, penicillin, metronidazole, or β-lactams); interferon; and intrathecal or intra-arterial chemotherapy (eg, cisplatin, vincristine, etoposide, interleukin 2, or ifosfamide) are epileptogenic, especially on disruption of the blood–brain barrier.[29]

Treatment of brain tumours and seizures

Anticonvulsive treatment is an important, but nevertheless neglected, issue in patients with brain tumours because epileptologists are not often actively involved in their care, and because neuro-oncologists usually devote most of their time to cancer treatment. Therefore, prospective studies on medical treatment of epilepsy in patients with brain tumours are scarce, despite the frequent occurrence of treatment-resistant seizures in these patients. By contrast, much is known about the surgical management of treatment-resistant forms of epilepsy, including those associated with brain tumours that are mainly low grade.

Epilepsy prophylaxis

Given the frequency of epilepsy in patients with brain tumours, prophylactic use of antiepileptic drugs might be warranted. Generally, initiation of antiepileptic treatment is justified after a first and single seizure in patients with brain tumours. However, whether an antiepileptic drug should be prescribed to patients with brain tumours who have never had a seizure is uncertain. These patients have a 20–45% chance of developing seizures later on, depending on tumour type, location, patient age, and previous cancer treatment.[8]

Prophylactic use of antiepileptic drugs has been assessed in patients who were undergoing surgery for a brain tumour. However, the results are conflicting,[30–33] and therefore the need for anticonvulsive treatment before or after neurosurgery is uncertain. Prophylactic use of phenytoin was not effective in randomised studies of patients with intracerebral metastases[34] or supratentorial primary tumours.[35] Two meta-analyses[8,19] of antiepileptic drugs in patients with brain tumours who did not have seizures suggested no efficacy as prophylaxis. A consensus statement from the Quality Standards Subcommittee of the American Academy of Neurology recommends not to use antiepileptic drugs routinely as prophylaxis in patients with brain tumours, and to withdraw these drugs in the first week after surgery if patients have never had a seizure.[8,9]

Drug treatment of seizures

Little is known about the efficacy of antiepileptic drugs in patients with brain tumours. Table 2 shows results from three descriptive studies[17,25,36] of seizure frequency and treatment in patients with brain tumours. Moots and colleagues[17] assessed seizure disorders associated with malignant gliomas in patients who were older than age 20 years (table 2). 60% of patients developed at least one seizure during the course of their illness, of whom 46% presented with seizures as the first manifestation of the disease. 15% later developed seizures despite prophylaxis with antiepileptic drugs. Frequency of refractory seizures and use of more than one antiepileptic drug were higher in patients with early-onset seizures than in those who had late onset (62% *vs* 10 %, respectively). Patients with seizures as a presenting sign of a brain tumour were younger, had less-malignant tumours, and had longer survival than patients who did not have seizures as a presenting sign—features that suggest a long time interval might be needed for seizure development.

Wick and co-workers (table 2)[25] showed that about 90% of patients with low-grade gliomas had seizures compared with 60% of those who had high-grade gliomas. 70% of patients who received carbamazepine, 51% who took phenytoin, and 44% who received valproic acid had recurrent seizures, suggesting that the latter antiepileptic drug might be first choice for patients with brain tumours. Hildebrand and colleagues[36] assessed seizure characteristics in patients with brain tumours who received various chemotherapeutic regimens (table 2). Almost 80% of patients had seizures, and the high frequency of epilepsy in this study could be due to over-representation of low-grade tumours. 12% of patients had complete seizure control with antiepileptic drugs combined with cancer treatment; 61% on first-line monotherapy continued to have seizures.[36]

Several studies have aimed to assess the effect of specific antiepileptic drugs on epilepsy frequency in patients with brain tumours (table 3).[37–41] Wagner and colleagues[37] found that add-on levetiracetam in patients with persistent seizures decreased the frequency of seizures by more than half in 65% of patients, a substantial proportion of whom subsequently received monotherapy with this drug (table 3). Three further studies[39–41] showed that add-on levetiracetam led to some patients being seizure-free or having fewer seizures than before this treatment. Side-effects associated with levetiracetam were infrequent and included dizziness, disturbed mood, fatigue, and somnolence.[42] In a small prospective study[38] of add-on gabapentin, all patients had seizure reduction and more than 50% became seizure free. These results suggest that add-on treatment

with levetiracetam or gabapentin seems to be well tolerated, and that further assessment of these drugs in patients with brain tumours is warranted.

Refractory seizures

There is no single definition for medical refractory epilepsy, although a clinically useful definition is the presence of seizures so frequent or severe that they limit daily life despite the use of antiepileptic drugs and adequate serum concentrations.[43] About 20% of patients with primary generalised epilepsy and 35% of those with partial seizures meet this definition,[43] for whom genetic causes of drug resistance probably play a major part.[44] Refractory epilepsy is commonly associated with a structural brain lesion (including a brain tumour) and with a seizure frequency of 12–50%.[2]

Antiepileptic drugs do not control seizures in some patients with brain tumours because of loss of receptor sensitivity. Additionally, multidrug-resistance proteins associated with brain tumours are a major cause of refractoriness. Patients with refractory epilepsy are commonly resistant to many antiepileptic drugs despite different mechanisms of action, which suggests non-specific mechanisms of resistance.[45] For instance, there might be overexpression of proteins that belong to the multidrug-resistance pathway. These proteins are members of the ATP-binding cassette transporter family, which form part of active membrane pumps that facilitate or block the transport of substances over the endothelial cell membrane.[46] Several of these proteins can reduce the intracellular concentration of various antineoplastic and other exogenic agents.[46]

Expression of multidrug-resistance proteins in tumour cells of patients with glioma is high, suggesting that they can diminish drug transport into the brain parenchyma.[4] In healthy brains, the multidrug-resistance gene *MDR1 (ABCB1*, P-glycoprotein) and multidrug-resistance-related protein (MRP, ABCC1) contribute to the function of the blood–brain barrier and blood–cerebrospinal fluid barrier.[45–49] *MDR1* is expressed in the apical membranes of many barrier tissues such as the intestines, liver, blood–brain and blood–cerebrospinal fluid barriers, thus contributing to plasma and cerebrospinal fluid, but also to intracellular drug disposition.

Insufficient concentration of antiepileptic drugs in the blood can be the result of an active defence mechanism by MDR1, which restricts the penetration of lipophilic substances into the brain. Carbamazepine, phenytoin, phenobarbital, lamotrigine and felbamate are substrates for this gene product (figure 1).[45,47] Research suggests that a non-specific transporter can move gabapentin out of the brain.[50] Levetiracetam does not seem to be a substrate for MDR1 or other multidrug-resistance proteins, and thus this drug might be of potential use

	Moots and colleagues[17] (n=65)	Wick and colleagues[25] (n=107)	Hildebrand and colleagues[36] (n=234)
Tumour characteristics			
Tumour types	Glioblastoma multiforme, anaplastic astrocytoma	Glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic ependymoma, grade II astrocytoma, grade II oligodendroglioma, ganglioglioma	Glioblastoma multiforme, anaplastic astrocytoma, grade II astrocytoma, gliomatosis
Seizure characteristics			
Proportion with at least one seizure during disease course	60%	68%	78%
Proportion with seizure as presenting sign for tumour	46%	68%	86%
Proportion with late-onset seizures	15%	NA	14%
Proportion with recurrent seizures	32%	NA	89%
Antiepileptic drugs			
Proportion of patients who took drug class	97%	94%	100%
Types of drug	NA	Carbamazepine, phenytoin, and valproic acid	Carbamazepine, valproic acid, gabapentin, levetiracetam, and others
Proportion of patients on monotherapy	77%	NA	56%
Surgery			
Proportion of patients who had procedure	100%	100%	59% of patients with epilepsy underwent surgery
Difference in seizure frequency before and after procedure	NA	No	NA
Chemotherapy			
Proportion of patients who had treatment	89%	NA	100% of patients with epilepsy
Cranial radiotherapy			
Proportion of patients who had intervention	92%	NA	46% of patients with epilepsy

NA=not available.

Table 2: **Retrospective studies of seizure frequency and treatment in patients with brain tumours**

for patients with intractable epilepsy. However, further study of levetiracetam is needed.[51]

Overexpression of MDR1 and MRP1 has been reported in samples of brain tissue from patients with focal cortical dysplasia and ganglioglioma, which lends support to a role for these proteins in the development of refractory epilepsy in patients with brain tumours.[52,53] Breast-cancer-resistance protein (ABCG2) is another member of the ATP-binding cassette transporter family, expression of which is increased in brain-tumour tissue compared with healthy brain tissue.[53] This protein can transport antiepileptic drugs, and thus might belong to the multidrug-resistance pathway in patients with brain tumours.[53] In vitro, however, ABCG2 had no effect on several antiepileptic drugs.[54] Theoretically, blockers of MDR1 might overcome drug resistance, and the efficacy of third-generation blockers is under assessment.[55] Furthermore, valproic acid can induce apoptosis in cells that express MDR1 and inhibit proliferation of this protein and MRP1 in tumour cells of patients with acute myeloid leukaemia.[56]

Antitumour treatment for refractory seizures

Apart from drugs, other treatment modalities for control of tumour growth should be considered, particularly if seizures continue despite use of antiepileptic drugs. These modalities include neurosurgery (with extensive resection of the tumour if possible), radiotherapy, and chemotherapy.

Surgery should be considered in patients who have medical refractory epilepsy because studies suggest that epilepsy surgery would control seizures in more than two-thirds of patients.[57] 70–90% of patients become seizure-free or have a substantial decline in seizure frequency after total excision of the epileptogenic zone due to a brain tumour with intractable epilepsy.[57–60] However, in these series the epileptogenic zone was excised together with the tumour, whereas general surgery for brain tumours resects part or all of the tumour without specific attention to the epileptogenic zone.[29,61] Cranial radiotherapy might have a positive effect on epilepsy.[61,62] Two small series[63,64] show a reduction in seizure frequency of more than 75% with a median follow-up time of 12 months or more after this procedure. Nevertheless, seizure frequency increases occasionally after surgery or radiotherapy, secondary to complications such as oedema, bleeding, or radiation necrosis.[15]

The alkylating chemotherapeutic agent temozolomide reduced seizure frequency in 50–60% of patients with glioma, and 20–40% of patients became seizure-free.[65,66] In a study of nitrosoureas,[67] all ten treated patients had a decline in seizure frequency, and 60% became seizure-free.

Side-effects of antiepileptic drugs

Cognitive impairment, bone-marrow suppression, liver dysfunction, and dermatological reactions are potential

	Prospective studies			Retrospective studies	
	Wagner and colleagues[37] (n=26)	Perry and colleagues[38] (n=14)	Maschio and colleagues[39] (n=19)	Newton and colleagues[40] (n=41)	Siddiqui and colleagues[41] (n=41)
Tumour characteristics and treatment					
Tumour type	Primary brain	Brain	Primary brain	Brain	Brain
Tumour grade	High (most patients)	High (most patients)	High (most patients)	High (most patients)	High (most patients)
Treatment	Radiotherapy, chemotherapy, corticosteroids, surgery	Radiotherapy, corticosteroids	Radiotherapy, chemotherapy, corticosteroids, surgery	Radiotherapy, chemotherapy, corticosteroids	NA
Antiepileptic treatment					
Primary drug	Valproic acid (most patients)	phenytoin, carbamazepine, or clobazam	lamotrigine, valproic acid, oxcarbamazepine, topiramate (most patients)	phenytoin, carbamazepine (most patients)	NA
Add-on drug	Levetiracetam	Gabapentin	Levetiracetam	Levetiracetam	Levetiracetam
Dose of add-on drug	2–4 g/day	0·3–2·4 g/day	1–3 g/day	0·5–3·5 g/day	1–3 g/day
Proportion of patients on subsequent monotherapy with add-on drugs	46%	0	0	44%	39%
Seizure characteristics					
Proportion with seizure reduction	65%	100%	72%	90%	27%
Proportion seizure-free	20%	57%	47%	59%	51%
Proportion with no improvement	NA	0	21%	7%	5%
Study characteristics					
Follow-up (months)	Median 9·3	Range 1–6	Range 7–50	Range 1–2	NA

NA=not available.

Table 3: **Effect of add-on antiepileptic treatment on seizure frequency in patients with brain tumours**

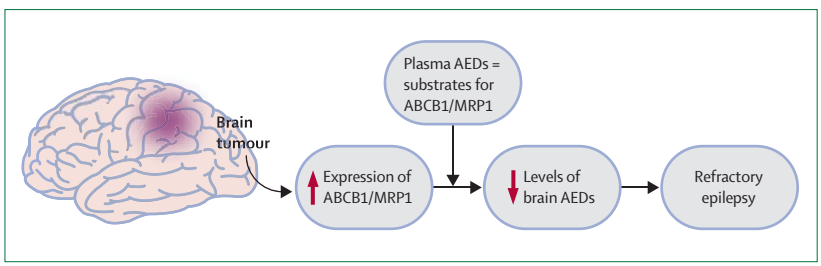

Figure 1: **Mechanism of failure of antiepileptic drugs in patients with brain tumours**
The brain tumour stimulates the expression of multidrug-resistance proteins, which prevent antiepileptic drugs (AEDs) penetrating the brain. Low concentrations of AEDs in the brain parenchyma explain the occurrence of refractory epilepsy in patients with brain tumours.

side-effects of antiepileptic drugs. Side-effects are more frequent in patients with brain tumours compared with the overall population of people with epilepsy who receive these drugs.[8,9,17] Ageing, gastric mucosal atrophy, a higher fat-to-lean body-mass ratio, and declining hepatic or renal functions increase the likelihood of side-effects through modulation of pharmacokinetics, leading to a slower metabolism.[68,69]

Severe skin reactions such as Stevens-Johnson syndrome might be associated with use of antiepileptic drugs, and occur mainly during the first 4–8 weeks after prescription of carbamazepine, phenobarbital, phenytoin, or lamotrigine.[70,71] Cases of Stevens-Johnson syndrome have been reported in patients who have received cranial radiotherapy while taking phenytoin, carbamazepine, or phenobarbital.[72,73] Mild skin rashes are frequently seen in users of antiepileptic drugs who do not have cancer or who have not had radiotherapy, although the frequency of mild skin rashes in patients with brain tumours is about twice that for patients who take antiepileptic drugs but do not have a brain tumour.[74,75]

Neurocognitive deficits are associated with use of antiepileptic drugs. In a cross-sectional study[1] of 195 patients with low-grade gliomas in the Netherlands, the presence of epilepsy and the use of antiepileptic drugs were independently associated with cognitive changes in memory, attention, and communication. Use of antiepileptic drugs in these patients was associated with a sixfold increase in deficits such as attention, psychomotor speed, or executive functions as compared to the severity of side-effects secondary to radiation of the brain.[76]

Interactions between antiepileptic and chemotherapeutic agents

Interactions between antiepileptic drugs and antineoplastic agents may lead to insufficient control of the tumour or epilepsy or to toxic effects of one or both of the agents. Drug interactions are usually pharmacokinetic and affect drug uptake, metabolism in the liver, or elimination of the drug. Furthermore, drug–drug interactions can change the volume of drug distribution and affect protein binding.

Of the two mechanisms of hepatic excretion of glucuronidation and metabolism by the cytochrome P450 pathway, the latter is the more common cause of interactions. Several antiepileptic drugs (eg, phenobarbital, primidone, carbamazepine, and phenytoin) induce cytochrome P450 coenzymes such as 3A4, 2C9, or 2C19, which leads to faster metabolism and lower plasma concentrations of agents given concomitantly that share the same metabolic isoenzyme (figure 2).

Enzyme-inducing antiepileptic drugs decrease the effectiveness of corticosteroids and several chemotherapeutic agents such as nitrosureas, paclitaxel, cyclophosphamide, etoposide, topotecan, irinotecan, thiotepa, doxorubicin, and methotrexate.[3,39,77] Oberndorfer and co-workers[78] did a retrospective study of patients with glioblastoma multiforme who were given adjuvant chemotherapy (most received lomustine), and found that overall survival of patients who received an enzyme-inducing antiepileptic drug (most received carbamazepine) was significantly shorter than for those who received a non-enzyme-inducing antiepileptic drug (most received valproic acid; 10·8 *vs* 13·9 months, respectively).[78] This finding is consistent with those noted previously,[3] suggesting that the blood concentration of chemotherapeutic drugs is decreased, and thus effectiveness of these agents is reduced, when given concomitantly with enzyme-inducing antiepileptic drugs.

Valproic acid is a broad-spectrum enzyme-inhibiting antiepileptic drug, and might reduce the metabolism of a second drug by raising plasma concentrations of this drug. Thus, valproic acid can increase the activity and toxic effects of a concomitantly given drug. Enhanced toxic effects of nitrosureas given either alone or with cisplatin and etoposide have been reported with concomitant administration of valproic acid.[9,79]

On the other hand, many chemotherapeutic agents induce coenzymes of the cytochrome P450 pathway and change the plasma concentration of concomitantly prescribed antiepileptic drugs. Cisplatin, vincristine, and doxorubicin can reduce the activity of carbamazepine and phenytoin.[80] Methotrexate, cisplatin, and doxorubicin can reduce the plasma concentration of valproic acid.[8,22] Doxorubicin and cisplatin can decrease the plasma concentration of carbamazepine or valproic acid.[81] The toxic effects of valproic acid are increased when combined with cisplatin or nitrosureas.[79] Combination of phenytoin with fluoropyrimidines (ie, fluorouracil, tegafur, and capecitabine) increases phenytoin's toxic effects, and treatment failure has been noted in combination with tegafur.[82,83] New antiepileptic drugs such as gabapentin, levetiracetam, and pregabalin do not interact with other agents as they do not influence the cytochrome P450 or other metabolic pathways. To date, no or few side-effects have been reported with levetiracetam in several series[37,40,41,84] of patients with brain tumours who received concomitant antineoplastic agents. However, further information from larger studies is needed.

Interactions between antiepileptics and dexamethasone

Dexamethasone is frequently used in neuro-oncology, mainly for the treatment of peritumoral oedema associated with brain tumours (including metastases). Phenytoin and phenobarbital shorten the half-life and thus activity of dexamethasone and prednisone.[85] Increased and decreased concentration in the blood of phenytoin have been noted with concomitant dexamethasone[86]—the former probably by competition for protein binding, and the latter by interference with hepatic metabolism. Therefore, phenytoin concentrations in patients given dexamethasone should be monitored closely—particularly during withdrawal of dexamethasone, which might lead to toxic levels of phenytoin.[85]

Practical guidelines for use of antiepileptics

Localisation-related epilepsy

There are few robust data to make conclusions about the optimum treatment for epileptic seizures in patients with brain tumours. Moreover, there may be no a priori reason why treatment of epilepsy in the setting of a brain tumour should differ from that of other types of symptomatic localisation-related epilepsy. Therefore, we think it reasonable to follow treatment guidelines for symptomatic localisation-related epilepsy, and to see subsequently whether additional guidelines are needed on the basis of studies or circumstances that apply to patients with brain tumours. These circumstances include several theoretical and practical issues for the use of antiepileptic drugs in patients with brain tumours, including pharmacokinetics, pharmacodynamics, potential for drug interactions, and side-effects.[3]

The first and second choices of antiepileptic drugs for many types of epilepsy, including that in the presence of comorbidity, have been updated and defined on the basis of a thorough statistical analysis of the individual opinions of more than 40 expert epileptologists.[87] These opinions are based on the interpretation of the outcome of clinical studies of the efficacy and tolerability of an antiepileptic drug for various types of epilepsy, and on specific problems that might arise with an antiepileptic drug. For symptomatic localisation-related epilepsy with or without comorbidity, the panel recommended the anticonvulsants carbamazepine or lamotrigine as first-line treatment.[87]

Localisation-related epilepsy in brain tumours

Although carbamazepine alone is one of the most effective antiepileptic drugs for treatment of partial epilepsy,[88] for patients with cancer it has the drawback of being an enzyme-inducer[3,89] and thus might compromise the effectiveness of concomitantly given chemotherapy.[3] Furthermore, carbamazepine is associated with a small risk of bone-marrow depression,[3] which needs careful consideration in patients receiving chemotherapy.

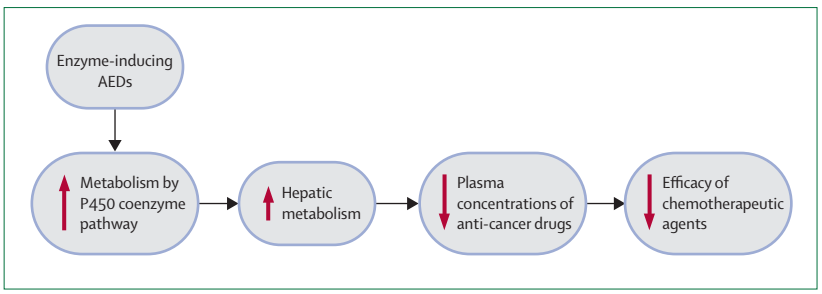

Figure 2: **Mechanism of reduced availability of chemotherapeutic agents by enzyme-inducing antiepileptic drugs**

Lamotrigine, valproic acid, and topiramate

Use of lamotrigine is well established for the treatment of symptomatic localisation-related epilepsy despite its somewhat protracted prescription formulation (ie, it can take several weeks to achieve a therapeutic dose). Other non-enzyme-inducing antiepileptic drugs should also be considered for patients with brain tumours. For instance, valproic acid and topiramate have been studied as monotherapy in patients with brain tumours.[25,42,78]

Valproic acid has a sound reputation as a broad-spectrum anticonvulsant for treatment of generalised and partial epilepsy; it has mild toxic effects and has the advantage that one can start with therapeutic dosages immediately.[88,90] Use of this drug in patients with brain tumours is well documented.[25,37] Valproic acid is associated with hepatotoxicity, and at higher doses thrombocytopenia and abnormal coagulation can occur.[91] In children and in those with drug serum concentrations of more than 100 mg/L, changes in haemostasis can occur, and the monitoring of laboratory measurements (eg, liver-function tests, platelet counts, and coagulation) every 3 months has been advocated.[91,92] However, the clinical importance of abnormal haemostatic measurements is uncertain, and neurosurgical studies have suggested that patients do not have enhanced bleeding tendencies after surgery.[93,94] Combined with chemotherapy, the enzyme-inhibiting effects of valproic acid might increase the risk of bone-marrow toxicity.[79] Nevertheless, findings on this drug further corroborate its use in patients with brain tumours.[78] Valproic acid has inherent antitumour effects through inhibition of histone deacetylase, which leads to cell differentiation, growth arrest, and apoptosis of cancer cells, including gliomas.[95–97] Valproic acid might also suppress formation of MDR1, which possibly diminishes the chances of refractoriness.[56]

Topiramate can be chosen as monotherapy, and has been tested in patients with brain tumours. However, it might have lower tolerability compared with newer antiepileptic drugs.[42,98]

Levetiracetam and gabapentin

If a first-line agent is insufficient, levetiracetam or gabapentin can be added, both of which do not interact

with other agents.[37,38,41,84] We prefer levetiracetam over gabapentin because studies suggest it has greater efficacy.[98,99] Furthermore, in patients with brain tumours levetiracetam might not be affected by multidrug-resistance proteins.[100] Several small clinical trials of levetiracetam, frequently in combination with valproic acid, in patients with brain tumours suggest good or substantial efficacy.[37,40,84] A double-blind randomised trial showed that levetiracetam as monotherapy was as effective as carbamazepine for treatment of de novo partial epilepsy, and was associated with fewer or about the same side-effects.[101]

Search strategy and selection criteria

Data for this review were identified by searches of PubMed with single or combined terms for: "brain tumour", "epilepsy", "incidence", "surgery", "chemotherapy", "cranial radiation", "epileptogenesis", "treatment", "antiepileptic drugs", "prophylaxis", "refractory epilepsy", "multidrug resistance pathway", "interactions", "side-effects", "anticancer agents", and "dexamethasone". Original research papers, clinical series, case reports, and reviews were included. Our search covered all relevant data to Jan 1, 2007.

Combining antiepileptic drugs

Although further studies are necessary, our experience suggests that valproic acid combined with levetiracetam is more active than either drug alone. This combination can have good efficacy and tolerability in fairly low doses of 1000 mg a day for each drug (MSMvB, unpublished data).[37]

Withdrawal of antiepileptics when seizure-free

In a retrospective study of 62 children with brain tumours who had discontinued antiepileptic drugs, 27% had recurrent seizures within 10 months.[61] Recurrences were associated with more than one previous craniotomy and previous whole-brain radiotherapy.[61] However, children who had infratentorial tumours and therefore a low seizure risk were included in the study, which may account for the fairly low frequency of seizure recurrence. We think that continuation of antiepileptic drugs is probably sensible in patients with seizures secondary to brain tumours because of short life-expectancy, absence of data for seizure outcome after withdrawal, and high a priori recurrence in adults.[8,17]

Conclusions

Epileptic seizures are common in patients with brain tumours, and epileptogenesis is probably multifactorial. Multidrug-resistance proteins might actively transport antiepileptic drugs out of the brain and contribute to the refractoriness of epilepsy, which is common in patients with brain tumours. A consensus statement has advised discouragement of antiepileptic drugs or their discontinuation after the first operative week in patients with brain tumours who have never had seizures.

Treatment of epilepsy in patients with brain tumours needs a multidisciplinary approach that not only involves the use of antiepileptic drugs, but also gives consideration to surgery, cranial radiotherapy, or chemotherapy (particularly with refractory epilepsy). There are few robust data for appropriate treatment of seizures in patients with brain tumours. First-line choices for treatment of symptomatic localisation-related epilepsy in patients with brain tumours are different from those for epilepsy patients in general because of increased risk of potential drug interactions, particularly with anti-cancer agents. Therefore, the use of enzyme-inducing antiepileptic drugs is discouraged. Existing brain damage from previous surgery or radiotherapy increases the risk of developing side-effects from antiepileptic drugs, and thus appropriate choice of drug is important.

Lamotrigine, valproic acid, and topiramate are first-line or second-line antiepileptic agents, although levetiracetam or gabapentin can be used as add-on treatment to a first-line antiepileptic drug. We prefer to start with valproic acid, and to add levetiracetam if insufficient. Future research is needed to assess the effects of specific antiepileptic drugs in the treatment of epilepsy in patients with brain tumours, and to define further the role of the multidrug-resistance pathway and its consequences for the management of treatment-resistant seizures.

Contributors

MSMvB did the literature search, wrote substantial parts of the review, conceived tables and figures, and has seen and approved the final version. EBW contributed to, and supervised, the discussion of pharmacology (including pharmacotherapy, side-effects, and drug interactions), and has seen and approved the final version. CJV participated in the literature search, wrote extensive parts of the review, supervised and edited the text, and has seen and approved the final version.

Conflicts of interest

EBW has received an unrestricted educational grant from Pfizer. CJV has received investigational grants from Janssen Cilag, UCB, Pfizer, and GlaxoSmithKline and has received speakers fees from Schering Plough. MSMvB has no conflicts of interest.

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