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# Glioma-Associated Epilepsy

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Kost Elisevich

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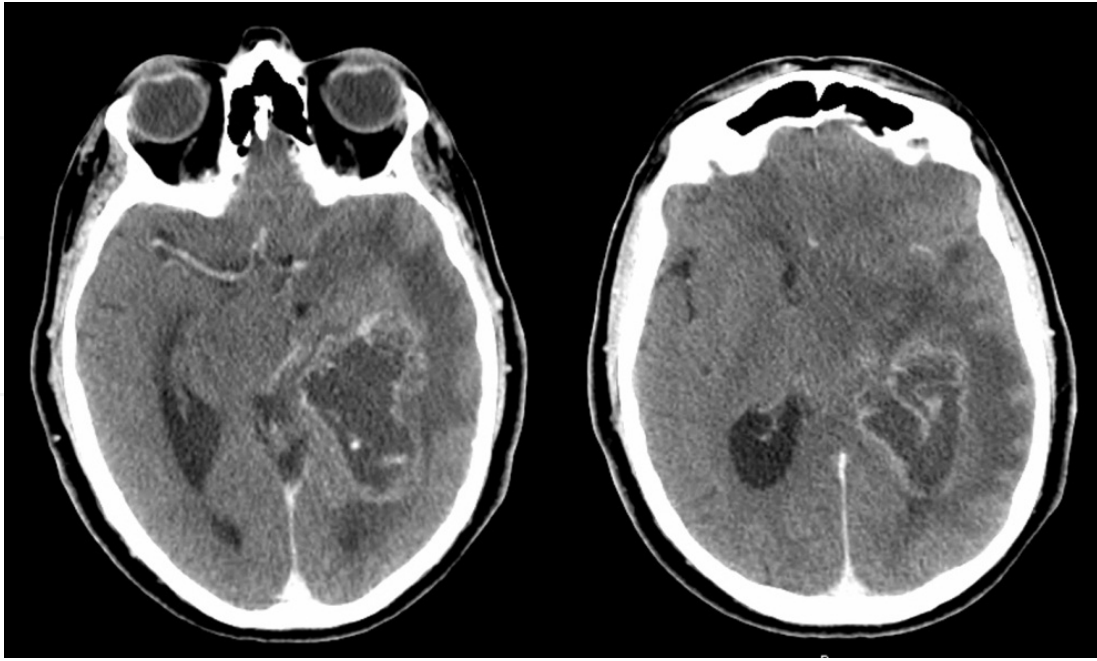
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## 1. Introduction

Hughlings Jackson, in the nineteenth century, first noted that epilepsy could be the only clinical manifestation of a primary brain tumour [1] (Figure 1). Among patients with epilepsy, the incidence of brain tumours is about 4% [2] whereas the prevalence of epilepsy among patients with brain tumours is over 30% [3]. Seizures will herald the presence of a cerebral glioma in 20-45% of patients [4,5] and another 15-30% of patients will develop seizures during the course of the condition [6]. In particular, epilepsy occurs in over 80% of patients with low-grade gliomas [7] and 30-60% of those with high-grade gliomas [8]. Factors which favour epileptogenesis in low-grade tumours appear related to slow growth kinetics coupled with cerebral location [9,10]. The relative risk for a cerebral tumour following a diagnosis of epilepsy approaches 20-fold overall compared with control and, when differentiated between malignant and benign tumours, it is about 26-fold and 10-fold, respectively [11]. It is highest for those aged 15-44 years at the time of diagnosis of the epileptic condition and will persist for several years afterward.

Apart from the adversity brought about by the growth of a cerebral tumour, a tumour-associated epilepsy adds further disadvantage for the patient with its impact on the quality of life and on the course of treatment. Epilepsy in brain tumour patients is often refractory to pharmacological therapy. The unpredictability of seizure occurrence, particularly those associated with a loss of consciousness, denies patients the ability to move freely in society, promoting a sense of isolation. Adverse effects of antiepileptic medications, particularly when taken in combination in those cases that are difficult to bring under control, may add to the burden of those imposed by therapy dedicated to the tumour itself. Debate has also arisen over the effect of some enzyme-inducing antiepileptic medications upon such therapy as certain of these agents will induce hepatic P450 microsomal enzymes that could accelerate the metabolism of chemotherapeutic agents. Particular attention must be given to the view that, in addition to the optimal removal of tumour, surgical intervention should be dedicated, as best



**Figure 1.** Axial contrast-enhanced computed tomography (CT) images identify a large left temporo-occipital glioblastoma. This 58 year old man acquired a medically intractable complex partial epilepsy 3 years previously and was investigated then by noncontrast CT imaging which showed no abnormality. The presence of an implanted cardiac defibrillator precluded magnetic resonance imaging.

as possible, to the elimination of the associated epilepsy with the ultimate aim of withdrawing the antiepileptic medical regimen altogether. This requires a greater perspective upon the neurobiology of this attendant condition in order to effect as best an outcome as possible for the patient.

As more is becoming known of tumor biology and the putative factors underlying epileptogenesis, a periodic review of the current status of glioma-associated epilepsy in this context is mandatory. This chapter will review the principal clinical features of the epileptic condition, its neurobiology as it pertains to etiological mechanisms, in particular, and the therapeutic options, both medical and surgical, that seek to control it.

## 2. Neurobiology

The fundamental characteristic of epilepsy is the presence of recurrent, usually unprovoked seizures that, when viewed electrographically, consist of paroxysmal, self-limiting, excessive and synchronous discharge of a population of neuronogial elements comprising a coherent network, often limited in its topography. These elements are contained predominantly in the cerebral cortex and, at the cellular level, manifest as unrestrained excitation attributable to deregulatory mechanisms affecting membrane depolarization and repolarization. It is important that we attempt to understand the phenomenon of epilepsy from a cellular and molecular level by addressing the constituent elements that give rise to a region of excitability

and from a network perspective to establish the relatedness of neuronogial populations that interact with one another to perpetuate the condition.

Previous literature regarding localization-related epileptogenicity referred to irritative and ictal onset zones wherein the former designated the cerebrocortical area that generated interictal spikes and the latter, that area responsible for initiating actual seizure activity. The two zones, although related, were not necessarily congruent as in a perilesional environment. This conceptualization is being supplanted by the realization of multiple limited functional connectivities that exist in the brain which itself is seen as a complex integrated master network. These connectivities are defined by statistical interdependencies or coherences as identified by neurophysiological time series, particularly by electroencephalography (EEG) and magnetoencephalography (MEG) [12,13]. In essence, the strength of connections among network nodes and their directionality may define for us the extent of epileptogenic territory. An altered functional connectivity has been proposed in the case of both mesial temporal lobe epilepsy [14] and tumour-associated epilepsy [15] patients. A pathologically increased theta or low frequency band connectivity was found to be related to increased seizure activity in brain tumour patients raising some consideration as to whether such findings may shed light on peritumoural epileptogenesis. Greater appreciation of such local network behavior and the integration of EEG, MEG and resting state functional MRI will allow a more definitive interpretation of seizure vulnerability and a better disclosure of perilesional epileptogenicity as it relates to network topology for use in the planning of surgical intervention.

At the cellular level, it is insufficient to describe epileptogenicity as a neuronal phenomenon as the intimacy of neuronogial interaction declares an inseparability of function of these two essential cell types. The impact of astrocytes on neuronal function through influences upon synaptic function and plasticity, provision of energy and regulation of local blood flow and blood-brain integrity is profound [16]. Protoplasmic astrocytic processes surround neuronal synapses and form gap junctions among one another [17] allowing electrotonic communication through a local syncytium. Astrocytes bear sodium and potassium channels and demonstrate excitability through regulated increases in intracellular calcium concentration [18,19]. These elevations can be triggered by glutamate released during neuronal activity propagated to neighbouring astrocytes via gap junctions and, in turn, cause the release of glutamate from astrocytes into the extracellular space triggering receptor-mediated currents in neurons remote from the original site of stimulation [20-24]. Higher concentrations of glutamine have been found in gliomas [25] and glioma cells have been shown to take up and release glutamine [26, 27] providing a potential reservoir of precursor for glutamate production in the peritumoural area. Otherwise, glutamate uptake has been demonstrated to be 100-fold lower in human glioma cells compared to that in astrocytes and has been attributed to a reduction of sodium-dependent glutamate transporters and an upregulation of cystine-glutamate exchange [28].

In fact, marked glutamate release in murine brain slices implanted with human-derived glioma cells has been shown to induce epileptiform hyperexcitability in adjacent brain tissue [29]. Administration of sulfasalazine, an inhibitor of glutamate release, to tumour-bearing mice reduced ictal behavior compared with untreated controls. Certain antiepileptic agents will also block astrocytic calcium signaling pointing to a mechanism underlying epileptogenicity [30].

Synaptic interstitial homeostasis is provided by astrocytic processes through the maintenance of fluid, pH and transmitter balance. The aquaporin 4 (AQP4) water channel and transporters for potassium uptake [31, 32], proton shuttling mechanisms [33] and transporter-mediated clearance of synaptic glutamate, glycine and gamma aminobutyric acid (GABA) [34] coupled with the ability for an astrocytic gap junction-mediated syncytium to dissipate detrimental accumulation of all such elements [35] argues for the essential nature of the neuronoglia relationship. Glutamate also modulates astrocytic glycogen storage [36] and neuronal activity may influence the passage of glucose metabolites through this same syncytium [37]. Reactive astrocytosis in a peritumoural environment may contribute to epileptogenesis through the release of glutamate [38, 30], compromise of blood-brain barrier integrity through production of vascular endothelial growth factor [39], production of excess reactive oxygen species [40], accentuation of inflammation through cytokine production [41, 139] and through AQP4 overactivity [32]. In the end, there are several putative epileptogenic mechanisms involving the neuronoglia relationship which, individually or in concert, may promote and sustain ictal behavior. Both the local infiltrative and structurally disruptive process of gliomatous invasion and the altered neurochemistry of the peritumoural environment undoubtedly combine to bring about the epileptogenicity.

Reduced numbers of both GABA- and somatostatin-containing interneurons in the area adjacent to low-grade gliomas [42] suggests a change in peritumoural neuronal phenotype and an alteration in the excitatory-inhibitory balance. A similar reduction in somatostatinergic neurons has been demonstrated in the human hippocampus in mesial temporal epileptogenicity [43, 44] and in animal models of experimental epilepsy [45]. Other cellular alterations demonstrated in animal models have raised suspicion regarding similar evolution in human peritumoural epileptogenicity. Particular attention has been given to synaptic vesicle protein 2A, a membrane glycoprotein present in synaptic vesicles of neurons and a calcium regulator in neurotransmitter release [46], as it is the binding site for the antiepileptic, levetiracetam [47]. It has been shown to have a low distribution in the cerebral cortex and hippocampus of spontaneously epileptic rats [48] and its removal in knockout mice promotes severe seizure development [49]. Expression of SV2A in human peritumoural cortex in both low- and high-grade gliomas, however, was no different between those patients identified with epilepsy and those without, suggesting different mechanisms of regulation of SV2A than in the models examined (50).

Further attention has turned to signaling pathways that trigger epileptogenesis following a cerebral insult. In particular, serine/threonine kinase (mTOR) activates several downstream processes involved in protein synthesis, ribosomal biogenesis, cell growth and proliferation [51]. As a consequence, it will respond to aberrant events in order to initiate a cellular reaction and, indeed, has been found to be dysregulated in neurological disease including brain tumours [52, 53]. Inhibition of mTOR by rapamycin attenuates the development of epilepsy and interferes with epileptogenesis in the kainate model [54]. Its delivery even following an induced status epilepticus succeeded in blocking the chronic phase of mTOR activation demonstrating not only an antiepileptic but an antiepileptogenic effect.

The influence of inflammatory factors in the mediation of epileptogenesis has also been addressed in recent years. Seizures themselves are known to induce an upregulation of cyclooxygenase-2 (COX-2) in neurons and, particularly, in non-neuronal cells [55]. This agent is known to promote neurodegeneration of somatostatin-expressing GABAergic interneurons, intensify cytokine reactivity and underlie the loss of integrity of the blood-brain barrier after seizure activity [56]. Its involvement in the peritumoural region may explain the loss of GABAergic neurons [42], in particular, and suggest a role in the mechanism for the epileptogenic process here.

### 3. Clinical presentation

The standardized mortality ratio (SMR; ratio of observed and expected deaths) for patients with recurrent seizures attributed to an acquired lesion such as a brain tumour during the first two years is 4.3 [57]. The frequency of status epilepticus, with its attendant risk of morbidity and mortality, increases from 3.8% in all patients with epilepsy to 9% in those with an underlying lesion. Three primary factors influence the risk of acquiring epilepsy in the presence of a cerebral glioma – glioma type, location and proximity to the cerebral mantle [10, 58]. As many as 80% of patients with oligodendrogliomas or gangliogliomas experience seizures. Anaplastic astrocytomas carry a risk of 68% [59], similar to astrocytomas, and the risk for glioblastomas is 29% to 37% [59, 10, 58]. The transitional histopathology of astrocytomas and anaplastic astrocytomas, with the latter likely to retain regional features of the more epileptogenic low-grade neoplasm, may explain the similarity in risk.

The propensity toward epileptogenicity by cerebral region varies considerably with the motor-sensory region most susceptible and the occipital region less so [10, 60]. The motor-sensory cortical region substantially raises the general risk of seizure occurrence for both the astrocytoma (83%) and glioblastoma (53%) [59].

The semiology of partial epilepsy may, at times, provide useful lateralizing or localizing information as to the whereabouts of a cerebral glioma. One of the more characteristic of such occurrences is the classic uncinat fit or olfactory aura brought about by a lesion situated in the uncus or lateral olfactory area in which the patient commonly experiences the recurrent spontaneous sensation of a bad odour. Lateralized elementary visual hallucinations originate typically in the vicinity of the calcarine cortex [61, 62] and gustatory hallucinations in the parietal operculum and/or insula [3, 63]. Focal motor or sensory manifestations as simple partial seizures, with or without a Jacksonian march, will also indicate the presence of a centrally located tumour as will periods of speech arrest in cases of tumours in the dominant hemisphere occupying the frontal opercular and inferior premotor or posterior temporal convexity region. In these latter circumstances, certain subtle aspects of the clinical presentation will shed further localizing information as in some loss of contralateral manual dexterity, a widening of the contralateral palpebral fissure and lapses in the proficiency of speech. Postictal manifestations may accentuate these features for variable periods of time. Although versive head deviation at ictal onset has been shown to be unreliable as a lateralizing feature [64, 65], combined contralateral head and eye deviation may have lateralizing significance [66].

A detailed rendering of lobar-specific ictal manifestations may best be presented in a tabular form for completeness (Table 1); however, as the majority of both low- and high-grade gliomas appear in the fronto-temporal distribution, our particular attention may be drawn to the anterior cerebral hemispheres to review some of the more common ictal features.

<b>Frontal</b>	<p><b>Orbitofrontal:</b> olfactory hallucinations, experiential sensations, gestural automatisms, autonomic features, speech arrest (likelihood of spread to mesial temporal area)</p> <p><b>Dorsolateral:</b> generalized event without warning, possible contraversive tonic head and eye motion (likelihood of spread to rolandic area and transcallosally)</p> <p><b>Cingulate:</b> complex motor gestural and sexual automatisms, mood changes, urinary incontinence (likelihood of spread transcallosally and to temporal lobe)</p> <p><b>Supplementary:</b> abduction and lateral rotation of upper arm with elbow flexion and tonic head rotation to involved limb, vocalization, bicycling, scissoring of legs (likelihood of spread transcallosally)</p> <p><b>Perirolandic:</b> focal clonic motor activity, possible Jacksonian march</p>
<b>Temporal</b>	<p><b>Mesiobasal:</b> experiential sensations with epigastric features, déjà vu, memory flashes, behavioural arrest, staring with oroalimentary automatisms (likelihood of spread to frontal and insular areas)</p> <p><b>Opercular:</b> auditory hallucinations, focal motor and sensory symptoms, vertigo (likelihood of spread to insula and parietal area)</p> <p><b>Convexity:</b> complex visual hallucinations, vertigo, speech arrest (likelihood of spread to mesial temporal and parietal areas)</p>
<b>Parietal</b>	<p><b>Inferior:</b> speech arrest/dysphasia, vertigo, arm/facial sensory and motor activity, tonic posturing, head deviation</p> <p><b>Superior:</b> metamorphosia, asomatognosia, arm/leg sensory and motor activity, tonic posturing, vertigo</p>
<b>Occipital</b>	Elementary contralateral visual phenomena – scotoma, hemianopia, phosphenes, object distortion

**Table 1.** Semiologies of Lobar Epilepsies

In the case of frontal lobe ictal origin, the tendency for rapid dissemination of discharge both ipsi- and contralaterally and to generalize confounds our ability to localize or even lateralize the condition. The seizure may manifest in a variety of forms – primary generalized, absence, simple and complex partial [67-71]. Auras tend to be less frequent than in temporal lobe epilepsy and, when present, rather nonspecific [72,70]. Prominent motor features with focal tonic-clonic activity, adverse head and eye deviation and stereotypic motor automatisms (i.e., fencing posture, scissoring) may develop [73, 74, 69, 63, 71, 70] and secondary generalization without evidence of focal onset occurs often, particularly in the case of seizures arising in the dorsolateral frontal convexity [75, 63, 72]. There is also some vulnerability toward status epilepticus of the convulsive [76] or of the complex partial [71] variety. By contrast, brief tonic and absence-like seizures may occur [77]. Frontopolar seizures without spread are commonly clinically silent whereas posterior spread may result in a loss of consciousness, focal tonic motor activity and generalization [71]. Orbitofrontal seizures are typically complex partial in nature and may be mixed with motor and gestural automatisms, olfactory hallucinations and

autonomic signs, perhaps through connections with the mesial temporal structure via the uncinate fasciculus. Seizures of cingulate origin may also be complex partial in nature with similar motor and gestural automatisms in addition to sexual automatisms, mood changes and urinary incontinence [78, 71]. Finally, supplementary motor seizures tend to be brief but frequent and may manifest as an abduction and external rotation of the contralateral arm and flexion of the elbow with the head directed toward the postured arm while the legs may be flexed, extended or elevated [63]. Either vocalization or speech arrest may be apparent while the patient remains conscious. Alternating locomotor activity, as in bicycling, may also be witnessed. Many frontal lobe seizures, particularly of convexity origin and exclusive of generalized events, are characterized by a rapid postictal recovery with little evidence of fatigue.

Epilepsy of temporal lobe origin is commonly of a complex partial variety and, in the case of a mesial origin, may be heralded by an aura of an experiential sort, followed or accompanied by impaired consciousness, behavioural arrest, staring and subsequent automatic behaviour as with oroalimentary automatisms (i.e., chewing, lip-smacking, swallowing) [79]. A postictal fatigue of variable duration, sometimes profound, often follows. Those complex partial events arising from an extratemporal source often begin with semipurposeful motor activity and commonly do not manifest a behavioural arrest or stereotypical automatisms [80, 81]. Auras appear in 80% of patients with a mesial temporal epileptogenicity and may be characterized by epigastric sensations, déjà vu experiences and memory flashes [82]. Additional features to those described above include uni- and bilateral tonic-clonic or dystonic posturing. Seizures arising in the temporal opercular area may cause auditory hallucinations in addition to focal motor or sensory experiences, depending upon subsequent spread of activity. Vestibular and complex visual hallucinations may characterize the more posteriorly situated temporal convexity ictal semiology. Language disturbance in the form of speech arrest, in particular, in the ictal or postictal state, will often declare dominant hemispheric involvement.

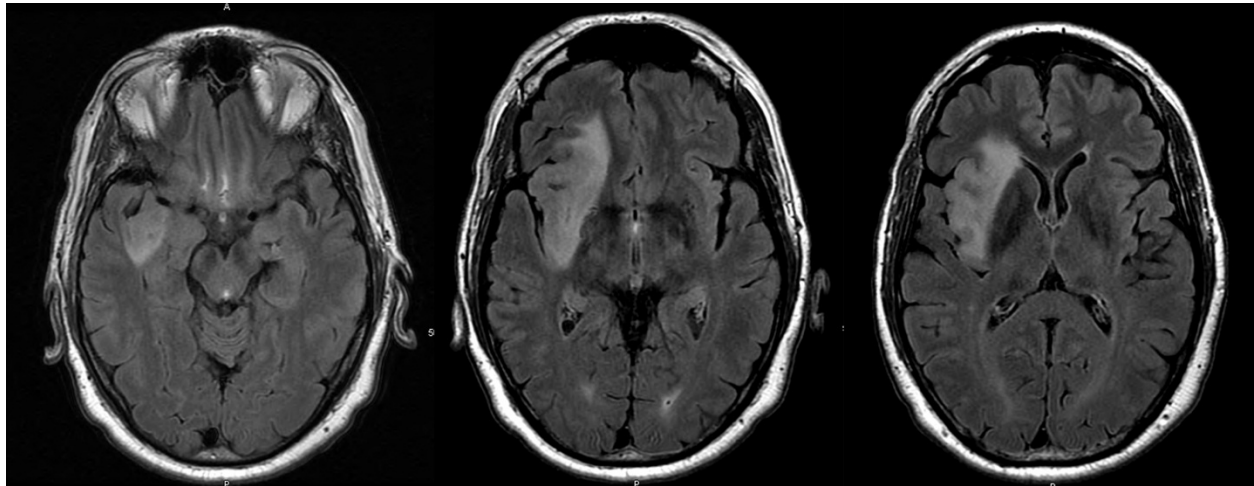
#### **4. Antiepileptic medical management**

Apart from the issue of refractory seizures, patients with epilepsy attributable to a glioma are threatened by potential interactions between antiepileptic and chemotherapeutic agents and risks associated with toxicity of either.

All gliomas, whether low- or high grade, must be assessed for surgical resection in order to optimize survival [83, 84, 85]. The literature has supported the notion of aggressive removal, to the extent allowable, in any region of the brain and, to this end, the inclusion of the immediate peritumoural region in the resection volume affords the opportunity of removing sufficient epileptogenic tissue to reduce or eliminate the presenting epilepsy or deny its further evolution (*Figure 2*). Postoperative antiepileptic medical prophylaxis is advised for patients with supratentorial gliomas. In a study of anaplastic gliomas, 36% of patients without preoperative indication of epileptogenicity experienced a postoperative seizure [86]. In a nonrandomized study, the incidence of all seizure types was lower in the early postoperative



stage (21% vs 39%) in patients receiving antiepileptic treatment compared with those left untreated [87]. Moreover, no impairment of consciousness was witnessed in those treated compared to 18% of those untreated, suggesting that a putative subclinical epileptogenicity was averted. Postoperative complications (i.e., hemorrhage, worsening edema) raise the likelihood of seizures during the initial 48 hour period by over two-fold, including status epilepticus even in the presence of antiepileptic medical coverage [9]. Late postoperative seizures were found to occur in 34% of those patients who had presented preoperatively with seizure activity. Although a significant difference was not substantiated, the incidence of late-onset epilepsy appeared lower in the treated patients (12% vs 21%) in the same study. The interval between surgery and the first postoperative seizure was less than six months in 52% of patients and the majority harboured a malignant glioma. Maintenance of therapeutic levels is essential in judging the efficacy of treatment and maximizing serum levels to individual tolerability is required before consideration is given to adding a second agent.



**Figure 2.** Axial magnetic resonance imaging identifies a predominant right insular tumour in a 62 year old man with a 3 year history of medically intractable complex partial epilepsy. Acute nausea followed by behavioural arrest, orolimentary automatisms and a postictal drowsiness began manifesting at an almost daily frequency with no distinct electroencephalographic features. Resection of this grade 2 oligoastrocytoma resulted in cessation of seizures

The risk of late postoperative seizure recurrence and a declared epileptogenicity may be judged by a number of factors. These include, primarily, the extent of glioma removal with the consequent reduction of tumour burden and elimination or reduction of vasogenic edema. The proximity to cortical regions prone toward epileptogenicity where such regions have been left intact (i.e., dominant mesial temporal region, motor-sensory region) must also be taken into consideration. Exclusive of the inability to optimally remove the tumour and/or a sufficient portion of the peritumoural region, the duration of preoperative epileptogenicity, postoperative complications (i.e., cerebrovascular compromise, intracerebral hemorrhage) and difficulties in maintaining adequate serum antiepileptic medication levels will also influence the outcome.

Several antiepileptic agents have appeared over the past two decades that have shown efficacy and greater tolerability in patients with brain tumour-related epilepsy [88-92]. The side effect profile of the traditional antiepileptic medications such as phenobarbital, phenytoin, carbamazepine and valproic acid was such [93, 94, 5, 95] that it seemed often to take precedence over the desire to reduce seizure activity [96]. The administration of phenobarbital, phenytoin or primidone can markedly lower serum levels of carbamazepine and both valproic acid and lamotrigine will increase the serum concentrations of an active metabolite, carbamazepine-10,11-epoxide. On the other hand, the half-life of phenytoin can be significantly shortened and the serum level of valproic acid may be reduced when delivered with carbamazepine. Finally, agents such as calcium channel blockers, erythromycin and propoxyphene may elevate plasma levels of carbamazepine when given concurrently. The incidence of severe rash (14%) accompanying therapy with these agents is higher in patients undergoing radiation and chemotherapy [93] and cognitive decline more pronounced [95]. Moreover, phenobarbital, phenytoin and carbamazepine are potent inducers of P450 microsomal enzymes, particularly, CYP 3A4 and CYP 2D6, and will putatively enhance metabolism of chemotherapeutic agents degraded by these enzymes resulting in the reduction of plasma levels and reduced efficacy [97, 98]. Some controversy regarding this effect has arisen, however, with some studies declaring improved outcomes in the presence of enzyme-inducing antiepileptic medications [99, 100]. Nevertheless, a decline in the use of the latter has occurred in recent years in favour of the newer non-enzyme-inducing antiepileptics such as levetiracetam, lamotrigine and vigabatrin which are relatively devoid of P450 microsomal enzyme induction or inhibition. Oxcarbazepine and topiramate are weak inducers of CYP 3A4 and weak inhibitors of CYP 2C19 and zonisamide has shown variability but overall weak inducing and inhibiting effects [101]. Valproic acid has been shown to be a potent inhibitor of microsomal enzymes and may increase the toxicity of chemotherapy [101].

A total of 14 new antiepileptic medications have been approved by the Federal Drug Administration (FDA) since 1992. These newer medications are safer, more tolerable, have, in general, fewer interactions with one another and require less monitoring. Moreover, several medications are under development which target other mechanisms underlying epileptogenicity other than those which currently effect voltage-gated Na and Ca channels and GABA inhibition. For instance, 2-deoxyglucose inhibits glycolysis and appears to have both antiepileptic and antiepileptogenic effects. Both ezogabine and ICA-105665 affect voltage-activated (KCNQ) potassium channels and are the first such agents dedicated to this ion channel. Targetting receptors for the neuropeptide, galanin, also shows promise as an antiepileptic. An AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonist, peramppanel, appears effective in patients with refractory partial epilepsy and is in the late stages of clinical development. Because of the interest in neuroinflammation as a promoter of epileptogenicity, an active inhibitor (VX-765) of caspase 1, the enzyme responsible for the production of interleukin-1-beta, has been investigated and found to show longterm antiepileptic effects that may be relevant.

Of particular interest has been the discovery of an antiepileptic effect brought about by topoisomerase inhibition [102]. Given the antineoplastic efficacy of DNA topoisomerase 1

inhibition, such an agent would be particularly useful in patients with cerebral glioma-associated epilepsy. Type 1 DNA topoisomerase (Top1) binds with DNA and relaxes the helix at the time of torsional stresses associated with its replication and transcription [103]. In a situation where transcription is generating supercoiled DNA to sustain high levels of RNA synthesis, as in an area of excitability, such inhibition would be detrimental to the epileptic process. Reduced Top1 activity could result in the inhibition of gene transcription critical for efficient synaptic transmission or possibly result in an enhanced apoptosis of those cellular elements involved in epileptogenic circuitry [104].

In the absence of postoperative seizure occurrence or recurrence for a period of 3 – 6 months and in the absence of both imaging evidence of tumour recurrence and EEG evidence of epileptiform features, a tapering regimen for the antiepileptic medication may be contemplated. Where a patient has presented with a single ictal event preoperatively, the decision, as dictated above, may be reached comfortably. In the case where there is uncertainty regarding the veracity of a patient's statement as to the absence of clinical seizure activity, the presence of artefactual changes that may obscure tumour recurrence in potentially epileptogenic territory on followup imaging and/or an inability by the electroencephalographer to adequately survey the cerebral cortex for hidden epileptogenicity, the decision to taper medication must be tempered accordingly.

## 5. Surgery

Tumour resection alone results in good postoperative seizure control in those patients presenting with a glioma-associated epilepsy [105, 9, 106]. As is often the case, a variable amount of epileptogenic cortical tissue is removed in the process of optimizing the removal of a glioma with its ill-defined border, affording the patient a good seizure outcome postoperatively. When the peritumoural tissue removal is not satisfactory, postoperative seizure control remains effectively unchanged [107, 108, 9, 106, 109, 58]. Image-guided stereotactic lesional resection achieves a longterm seizure-free outcome in 57% of cases [108] whereas the inclusion of peritumoural tissues in the resection volume raised this metric beyond 80% [110, 111]. The realization that the peritumoural environment is critical in the promotion of most epileptic manifestations has prompted the use of intraoperative electrocorticography in cases of low grade gliomas, in particular, to increase the likelihood of capturing those responsible cortical areas in the resection volume [112-116]. In a review of 45 patients with low grade gliomas and intractable epilepsy, 53% were rendered seizure-free and no longer requiring antiepileptic medical management after a mean followup of 54 months [112]. An additional 38% were seizure-free but still required medical management, although reduced. A meta analysis of studies addressing the benefit of resecting additional epileptogenic tissues showed that, in the case of low grade gliomas, seizure-free outcome was 63%, in marked contrast to the 18% seizure-free outcome achieved by lesionectomy alone [117]. Persistence of epileptiform activity following resection of an epileptogenic area is associated with seizure recurrence [118] and, hence, postresection electrocorticography has been promoted also [112]. When addressing specifically complex partial epilepsy in the context of temporal lobe tumors, the use of

electrocorticography clearly favoured outcome [119]. When a lesionectomy alone was performed, a seizure-free status of 18.8% was achieved compared with a 92.8% seizure-free outcome when electrocorticography was used.

At times, in cases of low grade gliomas, the source of some of the epileptogenicity may be remote from the tumor [106, 120]. Such occurrences may only be documented, in most circumstances, with prolonged inpatient extraoperative electrocorticography and reflect the engagement of an epileptogenic network type of activity in which remote nodes of epileptic activity may attain sufficient independence to perpetuate clinical manifestations despite removal of the original offending lesion. Indeed, resection of a remote epileptogenic site in the presence of an unresectable tumour has resulted in the relief of the epileptic condition [121].

Both the glioma type and its cerebral location typically determines its epileptogenic potential. Although oligodendrogliomas are found more commonly in the frontal region (35%), their epileptogenicity is better expressed in the temporal and temporoparietal regions where about 80% will promote an epilepsy [122]. A distinct clinicopathological group of patients with a protracted history of epilepsy attributable to the occurrence of a limbic or neocortical glioma has been identified [123]. Most such gliomas were confined to the temporal (63%) and occipital (18%) lobes and occupied limbic or perilimbic locations. The majority (61%) were identified as low grade tumors although 17% were anaplastic despite a stable clinical history of epilepsy with a mean of 15 years duration. Following resection of the tumour, 82% of the group of 60 patients studied were seizure-free after one year. A similar group, consisting typically of low grade gliomas, has been studied more recently [124] and characterized by a low cellularity, lack of mitoses and the absence of certain protein expression, such as the microtubule-associated protein (MAP2) which is critical in neurogenesis. The protein stabilizes microtubules that are enriched in dendrites, implicating a role in stabilizing dendritic shape during neuronal development. Microtubular assembly is therefore an essential step in neurogenesis. Patients are reported to have 50% fewer recurrences at 7.5 years followup and an 80% ten year survival.

Complex partial epilepsy in the context of a temporal lobe tumour must always raise suspicion of a dual pathology with an associated atrophy of the ipsilateral hippocampus resulting from cell loss, particularly in the CA4 region [125, 126]. In a series of 17 patients harbouring temporal lobe tumours presenting with complex partial epilepsy, 12 were found to have gliomas of which four were mixed gliomas (astrocytoma-oligodendroglioma), three were low grade astrocytomas and two were classed as cellular astrocytomas [126]. Neuronal densities throughout all the hippocampal subfields including the granule cell layer were diminished. Medially placed tumours were associated with the more dramatic changes than laterally placed tumours. Where an atrophic hippocampus has been identified, resection of both the lesion and the hippocampus is more likely to result in a seizure-free outcome [127].

## **6. Effect of ionizing radiation**

Experience over the last several decades has indicated that ionizing radiation is capable of reducing both the clinical and electrographic expression of partial epilepsy [128-132]. The

radiosurgical treatment of cerebral arteriovenous malformations with an associated epilepsy has been shown to have an antiepileptic effect even in the absence of angiographic evidence of obliteration of the malformation [129]. In this latter series, seizures had ceased altogether in 55% of cases and a seizure-free interval had been maintained for a duration of followup of 2 – 8 years. In a review of patients presenting with glioma-associated epilepsy of long term, three of four patients with frontal lobe tumours who had undergone biopsy and conventional radiation therapy were found to be seizure-free during a followup of four years [106]. In the same series, 83% of 23 patients who had undergone a resection followed by radiation therapy also became seizure-free. In the shorter interval, recurrent seizures attributable to malignant gliomas have been shown responsive to ionizing radiation [133]. Five of nine patients harbouring a biopsy-proven malignant glioma and manifesting an intractable partial epilepsy responded to treatment with a seizure-free outcome for the duration of their survival and the remainder showed a reduction in frequency of greater than 75%.

Radiosurgical application in the case of nonlesional partial epilepsy has also been shown to be beneficial in the longterm [134, 135], enough so that its use in the treatment of partial epilepsies remains an option. Whether lesionally-associated or not, there is much yet to be understood regarding the radiobiology of the effect upon the epileptic condition [136- 138].

## 7. Summary

Importantly, seizures will herald the presence of an underlying glioma, particularly in the adult, and will result in intervention before any other clinical manifestation is realized. This alone may afford the patient an opportunity to delay or avoid the inevitable loss of function that occurs with the further growth of the tumour and its further malignant transformation. Surgical intervention constitutes the most effective means by which an often intractable glioma-associated epilepsy may be brought under control. The extent of peritumoural resection is critical in this intervention and the use of intraoperative electrocorticography, particularly in the case of a longstanding epilepsy, provides the necessary objective criteria by which the surgeon will appreciate the location and extent of the epileptogenic surround. Cerebrocortical mapping in the presence of electrographic monitoring allows the surgeon to optimally perform such a resection by avoiding eloquent structure and concurrently reduce the tumour burden further in the infiltrative zone.

There is great promise in future antiepileptic pharmaceutical applications as they apply specifically to glioma therapy. Dual antiepileptic-antineoplastic effects may be realized. Better understanding of the biology underlying the antiepileptic effect of ionizing radiation may ultimately be used to guide therapy specifically to certain peritumoural areas where epileptogenicity is expressed.

The presence of epilepsy diminishes the quality of life for the patient with a glioma and dedicated effort is required to assure that the patient benefits maximally from intervention not only to reduce tumour burden but to eliminate the epileptogenicity.

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