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Review

Tumour associated epilepsy and glutamate excitotoxicity in patients with gliomas

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ABSTRACT

Tumour associated epilepsy (TAE) is common, debilitating and often not successfully controlled by surgical resection of the tumour and administration of multiple anti-epileptic drugs. It represents a cause of significant lost quality of life in an incurable disease and is therefore an important subject for ongoing research. The pathogenesis of TAE is likely to be multifactorial and involve, on the microscopic level, the interaction of genetic factors, changes in the peritumoural microenvironment, alterations in synaptic neurotransmitter release and re-uptake, and the excitotoxic effects of glutamate. On a macroscopic level, the occurrence of TAE is likely to be influenced by tumour size, location and interaction with environmental factors. The optimal treatment of TAE requires a multi-disciplinary approach with input from neurosurgeons, neurologists, radiologists, pathologists and basic scientists. This article reviews the current literature regarding the incidence, treatment, and aetiology of TAE.

1. Introduction

Seizures are common in the clinical course of patients with gliomas, and are the presenting feature in up to 88% of low-grade gliomas and up to 50% of gliomas overall; in 10–45% of patients, seizures develop later in the disease [1–4]. Tumour associated epilepsy (TAE) can be defined as seizures which can be directly attributed to the presence of a supratentorial glioma. TAE is an important subject for research, as the seizures themselves, as well as the antiepileptic drugs (AED) used in their treatment, are a significant cause of lost quality of life. Seizure control is of paramount importance particularly in patients with low-grade gliomas, who are often young, otherwise neurologically intact, and have a relatively long life expectancy, with uncontrolled seizures being the major impairment to their quality of life. However, even in higher-grade gliomas, adequate seizure control is a vital palliative measure.

Multiple theories regarding the causal mechanisms for TAE have been proposed, including peritumoural oedema and ischaemic changes, denervation hypersensitivity, pH changes, alterations in neuronal and glial ion channel and transporter protein expression, neurodegeneration, and an imbalance between excitatory and inhibitory mechanisms mediated via changes in local glutamate and gamma-amino-butyric acid (GABA) concentrations [5–7]. While the cause of TAE is most likely to be multifactorial, there is increasing evidence to implicate disturbances in the homeostasis of glutamate, the major excitatory neurotransmitter in the mammalian central nervous system, as playing a key role in its pathogenesis [5,6,8].

2. Epidemiology of TAE

Epilepsy has an overall prevalence of 5–10 per 1000 in the general population [9], but it is far more common in patients with gliomas. Many patients with gliomas suffer from drug resistant epilepsy, defined by The International League against Epilepsy as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" [10]. Low-grade gliomas are associated with a higher risk of seizures than higher-grade tumours [1,2,4,11]. This is possibly because of differing molecular profiles between these tumour types, but chronicity of the lesion and the much longer survival time of

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patients with lower-grade tumours may also be a factor, allowing time for epileptogenic changes to occur in the peritumoural brain.

There have been many large series reporting rates of seizures occurring in patients with gliomas, with the incidence varying widely (Table 1). Seizures are the presenting feature in 59–88% of all World Health Organization (WHO) grade II gliomas. By histological subtype, seizures are reported as a presenting feature in 60–100% of astrocytomas, 70–100% of oligoastrocytomas and 61% of oligodendrogliomas [1,5,12–22]. Seizures are less common in WHO grade III gliomas, but are still the presenting feature in 46–89%. Overall seizure frequency is reported as 39–100% in anaplastic astrocytomas, 33% of anaplastic oligoastrocytomas and 43–57% of anaplastic oligodendrogliomas [1,5,12–20]. Up to 36% of patients with anaplastic astrocytomas will have their first seizure after surgery [23]. In contrast seizures are the presenting feature of 25–36% of WHO grade IV gliomas, although 31–63% of patients will still experience seizures at some stage in their disease [1,5,12–20]. Although the focus of this review is on gliomas, it should also be noted that seizures are reported in up to 20–35% of patients with cerebral metastases and between 25–44% of patients with benign meningiomas [5,7,14,18–20].

3. Seizure types

Generalised tonic-clonic and complex partial seizures (focal dyscognitive seizures) are the most common seizure type in TAE, reported in 18–33% and 16–36% of patients, respectively [3,20,24]. Simple partial seizures (focal seizures without impairment of consciousness) are reported in 4.4–20%, while secondary generalisation, whether from simple or complex partial seizures, occurs in 6.7–17.8% [3,20,24] (Table 1). These seizures not only have the capacity to cause injury, but are also a significant source of anxiety and lost quality of life in patients with an incurable disease, as discussed below.

4. Treatment of TAE: Surgery and AED therapy

The main therapeutic strategies for treatment of TAE are surgical excision of the tumour, and treatment with AED [2,7,15]. There are a number of older series analyzing TAE outcomes post-surgery in adult and paediatric patients; differences in methods of reporting, AED prescription, histopathology, extent of surgical resection and use of post-operative radiotherapy make comparison difficult (Table 1). Reported rates of seizure freedom post-operatively range from 40–91% [5,20,24–29]. For example, Berger et al. presented a retrospective series of 45 patients with gliomas and drug resistant epilepsy who underwent surgery (13 WHO grade II astrocytomas, 14 oligodendrogliomas, nine oligoastrocytomas and nine gangliogliomas). At a mean follow-up of 50 months, 41 (91%) were seizure free, and 24 (53%) were seizure free and not taking any AED [24].

Danfors et al. presented a retrospective series of 101 patients with WHO grade II gliomas: 34 astrocytomas, 49 oligodendrogliomas and 18 oligoastrocytomas. Seizure was a presenting feature in 88%. AED use and response was not analysed, but only 54 of 88 (61%) of those who presented with seizures were prescribed an AED in the early phase. In a multivariate analysis, patients with seizures as a presenting feature had a better prognosis than those without seizures (overall survival [OS], 8.8 years *versus* 5.2 years, $p = 0.006$) [21]. In both of these series, neither the extent of resection nor the AED used were noted.

A more recent study by Rosati et al. presented a series of 176 patients with newly diagnosed glioma of mixed grades. Seizures were the presenting feature in 88/176 (50%) patients, of whom 82 (47%) developed ongoing TAE and were treated with levetiracetam monotherapy. At a mean follow-up of 13.1 months (range 10 months–2.9 years), 73 (89%) remained seizure free on levetiracetam monotherapy [19]. In a multivariate analysis there was no correlation seen between drug resistance and patient age, Karnofsky Performance Status score, tumour location, tumour grade or extent of surgery [19].

Glantz et al. performed a meta-analysis of 12 studies, including four randomised controlled trials, of AED prophylaxis in patients with brain tumours, including cerebral metastases and meningiomas. Seizures as a presenting feature was reported in 26% (range 14–51%), and prophylactic AED were used in 63% of patients with primary central nervous system (CNS) tumours and 32% with metastases. It was reported that 42% of patients treated with AED had sub-therapeutic drug levels. None of these 12 studies showed evidence of prophylactic AED use prior to surgery being effective in decreasing seizure incidence (odds ratio [OR] 1.09, 95% confidence interval [CI] 0.63–1.89; $p = 0.8$) or in increasing seizure free survival (OR 1.03, 95% CI 0.74–1.44; $p = 0.9$) or OS (OR 0.93, 95% CI 0.65–1.32; $p = 0.7$). Not only did this meta-analysis include patients with cerebral metastases and meningiomas, but in three of the 12 studies the AED used was not recorded. When the prophylactic AED was noted, it was often phenytoin, phenobarbital or "other". Despite these problems, based on this meta-analysis, the American Academy of Neurology recommends that AED be tapered and ceased 1 week after surgery if no seizures have occurred [30]. Other authors agree that tapering and ceasing AED after the first week post-craniotomy is appropriate [31].

The side effects of AED are of particular concern in many patients with TAE: the incidence and severity of AED side effects appear to be appreciably higher (20–40%) in brain tumour patients than in non-tumour patients [30], and only 12% of brain tumour patients on AED report that they have no side effects [32,33]. Rash is the most common side effect of AED, particularly phenytoin, and occurs in 14–27% of patients [13,34], but more serious side-effects include nausea or vomiting (5%), encephalopathy (5%), myelosuppression (3%), hepatic dysfunction, ataxia and gum pain (5%) [30]. Attention impairment and cognitive slowing are also reported in many patients, and may be somewhat more common with older AED such as phenytoin, carbamazepine and valproic acid [35,36]. AED are also associated with severe skin reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis, which although rare (annual incidence of up to 1 per 10,000 people) are associated with significant morbidity and even mortality [37]. It is estimated that overall 23.8% (5–38%) of patients have side effects severe enough to warrant change or cessation of their AED [34,38]. Levetiracetam, one of the more commonly prescribed new AED used in patients with TAE is potentially associated with fewer overall side-effects than older AED, but has been reported to be associated with adverse psychiatric symptoms, including depression and anxiety (3.8%), hostility (2.3%) and emotional lability (1.7%) [19,39,40].

From the above review of the literature, it is clear that TAE is common, and that treatment with surgery and AED is often suboptimal with regards to seizure control and incidence of side effects.

5. Effect of chemotherapy and radiotherapy on TAE

Patients with gliomas often undergo treatment with chemotherapy and/or radiotherapy at some stage during their disease course, and these treatments may also impact upon TAE. The current best treatment for glioblastoma multiforme (GBM), following maximal safe surgical resection, is radiotherapy with concurrent chemotherapy (temozolomide), followed by further adjuvant temozolomide [41]. The effect of temozolomide on low-grade gliomas, while controversial, has also been investigated, although not as the