Epilepsy & Behavior xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Peritumoral epilepsy: Relating form and function for surgical success

Christopher J.A. Cowie [a,b], Mark O. Cunningham [b,*]

[a] Department of Neurosurgery, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, UK
[b] Institute of Neuroscience, The Medical School, Framlington Place, Newcastle University, Newcastle upon Tyne, UK

ARTICLE INFO

Article history:
Accepted 9 May 2014
Available online xxxx

Keywords:
Tumor
Epilepsy
Oscillations
Microcircuit
Neocortex

ABSTRACT

Seizures are a prominent symptom in patients with both primary and secondary brain tumors. Medical management of seizure control in this patient group is problematic as the mechanisms linking tumorigenesis and epileptogenesis are poorly understood. It is possible that several mechanisms contribute to tumor-associated epileptic zone formation. In this review, we discuss key candidates that may be implicated in peritumoral epileptogenesis and, in so doing, hope to highlight areas for future research. Furthermore, we summarize the current role of antiepileptic medications in this type of epilepsy and examine the changes in surgical practice which may lead to improved seizure rates after tumor surgery. Lastly, we speculate on possible future preoperative and intraoperative considerations for improving seizure control after tumor resection.

This article is part of a Special Issue entitled "NEWroscience 2013".

1. Introduction

Tumor-associated epilepsy (TAE) is a debilitating condition, causing distress and adversely affecting the quality of life of those suffering from brain tumors [1–3]. Furthermore, in patients who have had tumor surgery, both the presence of postoperative seizures and the antiepileptic medication used to treat them have been shown to have a detrimental neuropsychological effect [2]. In rare cases, TAE can be even more devastating, giving rise to sudden unexpected death [4]. Despite its major clinical and social impact, the underlying pathophysiological causes of TAE are poorly understood, and, as a result, its treatments, both pharmacological and surgical, are of limited efficacy. Epilepsy associated with tumors has been shown to have a greater refractivity to antiepileptic drug treatments, and, in those who have had surgery for their tumor, seizures may persist postoperatively [5,6].

Seizures can often be the presenting symptom in patients with brain tumors, whether primary or metastatic and whether intraaxial or extraaxial [7]. In some cases, seizures occur even before the tumor is sufficiently established to be correctly identified on computed tomography and magnetic resonance imaging [8]. In patients presenting with other different neurological sequelae, seizures may occur after the diagnosis has been made and, although less likely, even after treatment with surgery or adjuvant therapy [9,10]. The probability that seizures will be associated with a CNS tumor depends upon the tumor type and grade and its location within the brain or, if extraaxial, its location within the cranial vault [11].

The mechanism behind TAE is likely to be multifactorial, and a number of hypotheses have been proposed. Recent work has explored the role of changes in peritumoral tissue in seizure generation. This has revealed metabolic and pH changes, alterations in levels of neurotransmitters and their receptors, and disruption of localized neural networks in the region of brain tissue surrounding the tumor. This review discusses the pathophysiology behind TAE, the factors affecting the frequency and type of the seizures, and the available treatments and their efficacy.

2. Methods

A literature search was performed in MEDLINE through Web of Knowledge (Thomson Reuters) searching for publications between 1990 and 2014. Search criteria were the keywords peritumoral + epilepsy. This search yielded 70 results, 9 of which were review articles. The authors then screened the results and excluded 18 papers that were not relevant before identifying further salient published work from the reference lists of the 52 included.

3. Factors governing seizure frequency: tumor type

The frequency and type of seizures associated with TAE depend predominantly upon the type of tumor giving rise to the seizures and the location of that tumor within the brain or, in the case of meningiomas, the location within the skull. All types of primary and secondary brain tumors may present with seizures [12–14]. Even in those patients

* Corresponding author at: Institute of Neuroscience, The Medical School, Framlington Place, Newcastle University, Newcastle upon Tyne NE2 4HH, UK. Tel.: +44 191 2088935.
E-mail address: mark.cunningham@ncl.ac.uk (M.O. Cunningham).

http://dx.doi.org/10.1016/j.yebeh.2014.05.009

Please cite this article as: Cowie CJA, Cunningham MO, Peritumoral epilepsy: Relating form and function for surgical success, Epilepsy Behav (2014), http://dx.doi.org/10.1016/j.yebeh.2014.05.009

who do not suffer from seizures prior to tumor surgery, there is the potential for them to develop TAE in the postoperative period, particularly those with meningiomas [5,15].

Glioneuronal tumors, primarily arising in children and young adults, have the highest seizure rate, with 85%–92% of dysembryoplastic neuroepithelial tumors (DNETs) and 63%–91% of gangliogliomas presenting with seizures [6,7,16–18]. Glioneuronal tumors, as their name suggests, consist of both dysplastic neurons and neoplastic glial cell elements [19]. Within the tumor, hyperexcitable regions of dysplastic neurones develop, and it is thought that this causes their high degree of epileptogenicity [20].

In tumors of glial origin, low-grade gliomas (World Health Organization (WHO) grades I and II) are more likely to be associated with seizures, with recent studies showing that astrocytomas have a seizure rate of 50%–81%, and oligodendrogliomas have a seizure rate of between 46% and 78% [7,9,10,21]. These tumors grow slowly, invading the surrounding tissue causing gliosis and chronic inflammatory changes in peritumoral regions. Evidence of these inflammatory changes is detectable using immunohistochemical staining; a significant increase in reactive astrocytes is found in cortical peritumoral tissue from patients with chronic seizures compared with peritumoral tissue from patients with no seizures [22].

High-grade gliomas such as glioblastoma multiforme (GBM) are generally thought to be less epileptogenic with a reported seizure rate of between 22% and 62% although this may be a reflection of the shorter survival time associated with this tumor type rather than a true lower rate of tumor epileptogenicity; median survival in patients with GBM is approximately 12 months [5,7,23,24]. Although seizures are less frequent in patients with GBM, they are more difficult to treat, as they are more often refractory to medication and can persist after surgery [25]. It is thought that high-grade gliomas give rise to seizures as a result of localized tissue destruction, ischemia, and necrosis [11,22,26]. Because of their growth rate, high-grade tumors are also likely to effect epileptogenic changes in the peritumoral region due to mass effect and as a result of local neuronal network disruption [22]. A hypothesis previously put forward is that seizure activity may be linked to hemosiderin deposition after microhemorrhage from friable tumor vessels present in high-grade gliomas [1]. Increased levels of extracellular iron ions (Fe^{3+}) has been shown experimentally to induce paroxysmal epileptiform activity [27]. However, a recent study showed no relationship between seizure frequency and the presence of hemosiderin on histological examination of samples from 20 patients with GBM [25].

Meningiomas are among the least epileptogenic intracranial tumors with a reported seizure rate of between 13% and 26%, which may be due to the fact that they are extraaxial and, therefore, do not infiltrate the brain parenchyma [15,28].

4. Factors governing seizure frequency and semiology: tumor location

Aside from tumor type, the other most important factor in determining its epileptogenicity is its location. Studies and reviews vary in opinion as to whether frontal, temporal, or parietal lobe tumors are most likely to be associated with seizures, but most agree that occipital lobe lesions are the least epileptogenic [7,11,22,29–32]. In their review of 2342 patients with TAE from mixed tumor types, Hamasaki et al. reported a frontal predominance in tumor location, specifically in cortical regions close to the motor cortex [7]. Michelucci et al. reviewed 100 patients with seizures related to primary brain tumors and found that 60% were located in the frontal lobe, with temporal and then parietal lobes as the next most common locations [31]. When tumors are grouped by type, different tumor histology is more likely to be related to specific brain regions. Glioneuronal tumors are most commonly located in the temporal lobe and cause predominantly complex partial seizures [6,19,33]. High-grade gliomas are most likely to involve multiple brain regions but, when confined to single lobes, are found most commonly in the temporal and frontal lobes [34]. High-grade gliomas made up the majority (79%) of a review of patients with primary brain tumors in whom the initial seizures were predominantly tonic–clonic or focal motor [31]. Location is also a factor in the propensity of meningiomas to cause seizures: convexity and parasagittal/parafalcine meningiomas close to the premotor cortex are associated with the greatest seizure rates (28%–40%), with tuberculum sella meningiomas being the least epileptogenic [15,28,35].

It may be that tumors in the anterior frontal lobe are in fact as likely to cause epileptic activity as tumors in the posterior frontal lobe and temporal lobe, but that the relative lack of eloquence of the frontal regions means that some of these seizures go undetected. Although less likely, tumors in the occipital lobe can also produce seizure activity, typically producing visual auras before a seizure [7,36]. Sellar and skull base tumors, including pituitary tumors and craniopharyngiomas, seem to be much less likely to present with seizures, with Deepak et al. showing a seizure rate of only 9% in their series of 64 patients with macroprolactinomas and Karavitaki et al. finding no seizure activity in a case series of 121 patients with craniopharyngioma [37,38].

5. Pathophysiology

The pathophysiological mechanisms that give rise to epileptic activity in brain tumors are likely to be multifactorial. The literature describes a number of hypotheses relating to the biochemical, microstructural, and electrical environment of the peritumoral area that may give rise to epileptogenesis [1,14,26,29,33,39–42]. These include the levels of neurotransmitters and altered expression of their receptors, altered expression of gap junctions and ion channels, localized pH disturbance, and the effects of disruption of the blood–brain barrier [43–47].

There is evidence to show that different mechanisms predominate in different tumor types. In tumors containing neurons such as glioneuronal tumors, disruption of neuronal function is the most likely mechanism, whether through the development of hyperexcitable regions of dysplastic neurones within the tumor or neuronal immunoreactivity to certain gap junction proteins (see below) [20,43,48]. Both of these factors are likely to contribute to the high degree of epileptogenicity displayed by this tumor type, but other mechanisms must be responsible for tumors of exclusively glial origin, with no neuronal component. Recent evidence suggests that slow growing tumors may induce changes in penumbral connectivity, resulting in the development of network architecture with suboptimal functionality and a lower threshold for seizures [49]. In contrast, higher-grade tumors may induce seizures by tissue damage (ischemia, edema, mass effect, and necrosis) [40].

6. Neurotransmitters and receptors in the peritumoral zone

Alterations in glutamate neurotransmission form a core part of the pathophysiology of epileptogenesis. This is not surprising given the excitatory nature of this neurotransmitter in the brain and, thus, its depolarizing action on the neuronal membrane potential [50]. The electrical excitability of tumor cells in gliomas was established in vitro in 1996 [51]. Previously, it had been thought that tumors arising from glial cells, unlike those from neurones, lacked the Na^+ channels that allow a membrane potential to be generated. However, Patt et al. discovered that a large number of cells in gliomas expressed Na^+ channels in sufficient quantities to allow generation of brief bursts of action potentials. Activation of glutamate (AMPA/kainate) receptors in glial tumor cell membranes caused this depolarization both in ex vivo human tumor brain slices and cultured human tumor material. These findings indicate that glioma cells may have electrophysiological properties similar to those of neurons [44]. However, evidence to support that these glia with neuron-like properties exert an epileptogenic effect is not presently available. Indeed, it is unlikely that this is the case given that the seizure foci are more often than not found within the

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