ORIGINAL RESEARCH PAPER

Volume-7 | Issue-6 | June-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

"ROLE OF SEIZURE PROPHYLAXIS IN BRAIN TUMOR PATIENTS: A DILEMMA".

Oncology

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ABSTRACT

The risk of seizures with primary brain tumors or brain metastases is about10–100%. Frequency of seizures depends upon tumor histology, location and their growth pattern. More common in low grade tumors, supratentorial and cortical based tumors. About 25% patients have seizures at initial presentation. There is no controversy regarding the use of antiepileptic drugs (AEDs) in patients with brain tumors who present with seizures but the prophylactic use of AEDs in brain tumor patients, who do not have seizures, continues to be debated. Most of trials used enzyme inducing AEDs for seizure prophylaxis and were having small sample size. These trials show no benefit of seizure prophylaxis. In this article we emphasize the need for a large multi-centric randomized controlled trial with sufficient statistical power and testing of newer antiepileptic drugs with better pharmaco-dynamic profile into the trials, to get the solid evidence by which we can formulate the individualized recommendation regarding seizure prophylaxis keeping tumor characteristics, patient characteristics and newly available antiepileptic drugs (AEDs) in our mind.

KEYWORDS

Seizure prophylaxis, Antiepileptic drugs, Brain tumor

Introduction

The worldwide incidence of central nervous system tumors is around 2.9–5.3 cases per 100,000 person-years for children and adolescents[1]. The lifetime risk of brain tumors is about 0.7%; however, the reported incidence rates vary substantially[2]. Seizures due to brain tumors constitute 6–10% of all cases of seizures as a whole, and 12% of acquired seizures[3].

The risk of seizures with primary brain tumors or brain metastases is 10–100%[4]; the frequency of seizures differs with different tumor histologies, and with different tumor natural histories and growth patterns[5] (more common in slow growing tumors). Seizures are more common in patients with low grade astrocytomas and low-grade oligodendrogliomas than patients with glioblastomas, brain metastases or meningiomas[6]. It is more in haemorrhagic brain tumors. It also depends on tumor location as seizures are more common in supratentorial, cortical location with a higher incidence in tumors involving the temporal, frontal or parietal region[7-9]).

Other risk factors for seizures, besides tumor histology and location, include the size of the tumor, the extent of tumor resection, and age at operation older than 40 years[10].

Approximately 25% of patients with newly diagnosed primary or secondary brain tumors have seizures as a presenting symptom. If not at initial presentation still there is a 20 % risk of seizures at some point during the course of disease.

There is no controversy regarding the use of antiepileptic drugs (AEDs) in patients with brain tumors who present with seizures. However, the prophylactic use of AEDs in brain tumor patients, who do not have seizures, continues to be debated. Seizures can be particularly destructive in the patient with an intracerebral neoplasm that's why majority of radiation oncologists, neurologists, and neurosurgeons in a 1996 study routinely used AEDs to prevent new-onset seizures in patients with cerebral tumors[11] in spite of no evidence to support this practice.

We conducted a literature research under the headings included "prophylactic AEDs, Seizures and brain tumors" and we found that several randomized controlled trials (RCT) and meta-analyses have tried to resolve this dilemma regarding the prophylactic use of AEDs in brain tumor patients.

Prophylactic AED prescription before or after surgery in seizure-free brain tumor patients (children and adults) is not recommended based on available evidence. This recommendation applies to both patients with primary brain tumors and with metastases (*Glantz et al*; 2000[12]; *Kong et al*., 2015[13]).

Sirven et al.[14] published a meta-analysis evaluating studies comparing prophylactic anticonvulsant treatment to placebo or to no anticonvulsant treatment in patients with brain tumours and no history of seizures. The analysis included five trials with a total of 403 patients [15-19]. Pooling of the data showed no benefit for prophylactic anticonvulsant treatment for early-onset seizures within 1 week of treatment initiation and for long-term prophylactic anticonvulsant treatment also. A subgroup analysis was done which shows that patients with primary glial tumours, cerebral metastases, and meningiomas showed no significant benefit for prophylactic anticonvulsant treatment. The authors concluded that there is little evidence to support the use of anticonvulsant prophylaxis in adult patients with brain tumours with no history of seizures.

Glantz et al[12] conducted a meta-analysis of the four RCTs and concluded that prophylactic anticonvulsants did not meaningfully reduce the risk of seizures in seizure-naïve patients with newly diagnosed brain tumours. These authors also noted that adverse effects associated with anticonvulsants were a particular concern in the given patient population. They recommended against the routine use of anticonvulsants for primary prophylaxis in newly diagnosed patients with brain tumours or brain metastases [12].

The recommendations of the American Academy of Neurology do not advise routine AED prophylaxis because of the lack of efficacy and the potential side effects of AEDs. The same guidelines state: "In patients with brain tumors who have not had a seizure, tapering and discontinuing AEDs after the first postoperative week is appropriate, particularly in those patients who are medically stable and who are experiencing AED-related side effects"[12].

But possibly, some selected groups of patients, such as those with cortically based hemorrhagic melanoma metastases, may benefit from prophylactic AED use (*Goldlust et al*., 2012)[20].

Besides being ineffective in seizure prophylaxis in patients with cerebral tumors, AEDs may also pose more risk of complications because of mutual interactions between enzyme-inducing AEDs and other drugs, commonly used in these patients. Corticosteroids and the chemotherapeutic agents bischloroethylnitrosourea, cisplatin, carboplatin and taxol can reduce AED serum concentrations by enzyme induction or reduction in bioavailability. Conversely, Phenytoin levels are increased by concomitant use of 5-fluorouracil. Valproate can inhibit the metabolism of nitrosoureas and etoposide, causing clinical toxicity, and Phenytoin may increase the dose requirement for corticosteroids and tamoxifen[21-22].

In addition, AEDs have the risk of potentially serious allergic reactions in patients receiving treatment for brain tumors. Skin rashes with Phenytoin or carbamazepine have been reported in 25% of patients with malignant gliomas[23]. Severe Erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis have been described with patients taking Phenytoin. Some of these rashes begin within the treatment field on the scalp which suggests that the radiation

may play a direct role in enhancing an allergic response, perhaps by depressing T-suppressor activity[24] However, no study has examined the prophylactic effects of any of the newer generation of AEDs, and the risks of allergic reactions as well as complications related to drug interactions which may be different with some of these drugs.

Discussion: Only five RCTs have tested the effects of anticonvulsants for the primary prophylaxis of seizures in patients with newly diagnosed brain tumours. No studies have been disease-specific, and all trials were heterogeneous as per inclusion of mixture of different primary and secondary brain tumour, inclusion criteria and the anticonvulsants used. So we should conduct a trial in special subgroups of brain tumors like anaplastic oligoastrocytoma, tumours near the motor strip, with cortically based tumours, or with hemorrhagic tumours having high incidence of seizures to assess the role of prophylactic use of AEDs in these subgroups separately. Perhaps at least high-risk patients can benefit from AED prophylaxis[25]. In the study of *Wychowski et al*.[26] (2013) AED prophylaxis did not reduce tumor-related epilepsy but prevented status epilepticus in patients with glioblastoma.

The anticonvulsants tested in these RCTs were of the class of enzyme-inducing anticonvulsants. These agents are expected to have pharmacodynamics interactions with other medications commonly used in the treatment of patients with brain tumour. In particular, interactions between enzyme- inducing anticonvulsants and chemotherapy are of significant concern. No studies have tested the newer generation of anticonvulsants. They have fewer adverse effects and minimal drug interactions eg. Levetiracetam[27], Talampanel, Perampanel etc. These agents have some anti tumor effect also[28]. Diego et al. reports the efficacy of prophylactic levetiracetam in preventing seizures at 3 and 6 months following surgery in patients with high grade gliomas[29] but due to small sample size this study provides only level III evidence.

So, in general, there is no benefit of seizure prophylaxis in brain tumor patients. Therefore clinicians must individualize treatment for these patients. To reach treatment decisions, tumour-related factors such as location must be integrated with patient preferences and quality of life, plus concomitant medications.

Conclusion: We conclude that seizure prophylaxis offers no benefit to brain tumour patients or benefit may be minimal at best. In the absence of benefit, we should not recommend prophylactic anticonvulsants for patients with brain metastases or primary brain tumour because the evidence is insufficient therefore treatment must be individualized.

Newer antiepileptic drugs, with better pharmaco-dynamic profile, should be tested in clinical trials to assess their efficacy in seizure prophylaxis.

A well-conducted large multi-centric RCT with sufficient statistical power is the only way to obtain the evidence either for or against the prophylactic use of AEDs in practice in general and in patients with brain tumors in particular.

Most important is, we should make the individualized recommendation for seizure prophylaxis keeping tumor characteristics, patient characteristics and newly available antiepileptic drugs (AEDs) in our mind.

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