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Chapter 10

Tumor Associated Epilepsy

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1. Introduction

Epilepsy in the general population occurs with an incidence of 44 per 100,000 person-years in a population based study [1]. Symptomatic etiologies such as vascular injuries, infection, and neoplasm are usually associated with a higher incidence of seizures and epilepsy. In the cancer population, seizures arise mainly as a result of an infiltrative neoplastic process in the brain. However, cancer treatment, metabolic causes, and paraneoplastic disease can also cause seizures in this population despite the absence of a structural lesion. The etiology of epilepsy in brain tumor patients includes primary malignancies and metastatic disease to the brain. A multifaceted approach is required for treatment of seizures including surgery, radiation treatment, chemotherapy, and antiepileptic drugs. A combination of treatments has the potential of adverse effects and generally requires a multidisciplinary team.

This chapter will review the causes of epilepsy in cancer patients, incidence, treatment, the role of electroencephalogram (EEG) and antiepileptic prophylaxis in this group of patients. The factors which predispose seizures in these patients will also be reviewed, such as tumor grade, histology and brain tumor morphology.

2. Incidence

The cumulative incidence of seizures in the general population is almost 10% by age 74. More than 4% of the population has one unprovoked seizure by age 74 and 3% will develop epilepsy [2]. Symptomatic etiologies such as brain tumors account for a higher percentage (30%-49%) of all unprovoked seizures and epilepsy. Although brain tumors account for 4% of all epilepsies, symptomatic seizures can occur in up to 85% of patients depending on tumor type and location. In 30%-50% of patients with brain tumors a seizure is the presenting clinical sign.

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However, up to 30% will develop seizures later in the course of their disease [2]. In the cancer population seizures can occur for numerous reasons including primary brain tumors, brain metastasis, paraneoplastic syndromes, and other etiologies such as toxic/metabolic, infection, or from a reaction to cancer treatment [3]. Drug interactions and adverse drug effects are important considerations in this population as many treatments may have neurologic adverse effects and seizures are one such problem.

Incidence rates of epilepsy based on etiology including brain tumors, traumatic brain injuries, central nervous system (CNS) infections, cerebrovascular disease, and other causes have been determined [4]. Symptomatic etiologies such as brain injuries and brain tumors account for a higher percentage (30%-50%) of all unprovoked seizures and epilepsy.

The incidence of seizures in patients with systemic cancer is estimated to be 5%, but for patients with an intracranial neoplasm, seizure incidence may be as high as 30% [5,6]. There are several factors which affect the incidence of seizures in brain tumor patients and these include age, location of the lesion, histology, and the grade of the tumor. With regard to age, there is a higher incidence in young patients and those over age 65 which mirrors the incidence of epilepsy in the general population [7,8]. The reason for this finding is likely the higher incidence of low grade brain tumors in children versus adults and the subsequent longer survival rate [9].

3. Etiology

Location, grade, histology and tumor morphology are important contributors to seizure incidence.

Cortical location is an important determinant for the development of seizures as neural generators are located in the cortex. Rarely do subcortical or infratentorial lesions cause seizures. Location in the temporal, frontal, and parietal lobes are more likely to result in seizures than occipital or subcortical lesions. Location near the rolandic fissure can also result in seizures [8,10].

Grade of the tumor is an important determinant as low-grade lesions are more likely to be associated with seizures. Chronicity of the lesion and subsequent secondary epileptogenesis appear to play a role in the devolvement of seizures. Morphological characteristics of low-grade lesions portend higher seizure incidence when compared to high-grade tumors. In one study examining morphological characteristics, low grade gliomas tended to be larger in patients presenting with seizures. This contrasted with patients with high grade gliomas where patients who presented with seizures had smaller tumors. Location in the temporal lobe was associated with higher seizure incidence for low-grade tumors [11].

Histology is an important contributor to the development of seizures and subsequent tumor associated epilepsy as low-grade tumors are more often epileptogenic. Chronicity of the tumor has been shown to be directly correlated with the incidence of seizures [12]. There are several reasons for this: slow-growing tumors may isolate and deafferentate focal regions of normal

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tissue and prevent normal regulation. Low-grade brain tumors such as gangliogliomas and dysembryoplastic neuroepithelial tumors can have an almost 100% incidence of seizures whereas the incidence rate is 60%-85% in low-grade astrocytomas and oligodendrogliomas (Fig. 1) [13].

4. Causes of seizures

4.1. Brain tumors

Primary brain tumors. As discussed, tumor histology and grade of tumor are important contributors to the development of seizures in primary brain tumor patients.

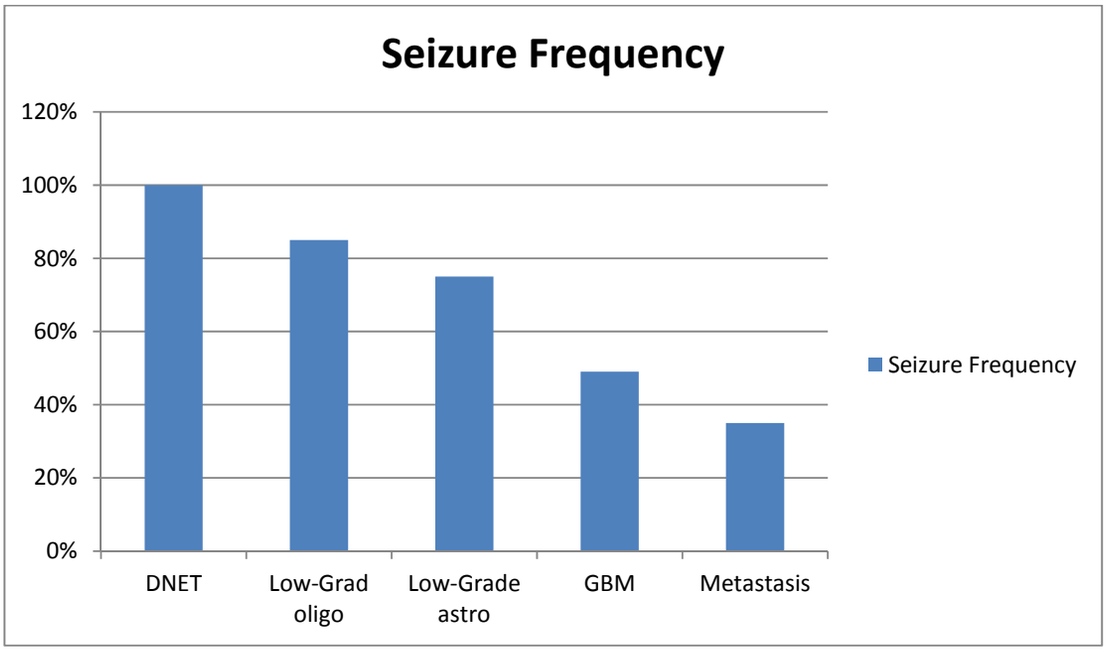

Figure 1. Seizure Frequency Based on Tumor Type

Neuronal tumors have a higher incidence of seizures. One possible reason is that the population of neurons could be epileptogenic within the tumor whereas in the glial tumors the seizure focus is generally in the peritumoral brain tissue [8].

Glial neuronal tumors also have a high incidence of seizures which is more likely due to cortical involvement of the tumor. Secondary epileptogenesis can occur in up to one-third of brain tumor patients where the epileptogenic focus does not correspond to the tumor location. The process by which this occurs can be described as an actively discharging epileptogenic region that induces a similar paroxysmal activity in the region distant from the original site. This phenomenon has been seen in animal models and it is believed that it occurs in humans as well. Secondary epileptogenesis can be seen in low-grade brain tumors in the temporal lobe which have associated hippocampal sclerosis [14].

Several other factors can affect epileptogenesis including imbalance between excitatory and inhibitory pathways. Higher levels of excitatory neurotransmitters such as glutamate can result in excitability of cortical neurons and therefore seizures [15]. Alkaline pH levels in peritumoral brain tissue can also lead to epileptogenesis by disrupting levels of intracellular and extracellular Na.

Morphologic changes in the peritumoral brain tissue such as aberrant neuronal migration, persistent neurons and white matter, and changes in synaptic vesicles can result in seizures in brain tumor patients. Changes in receptor binding sites for excitatory and inhibitory neurotransmitters (GABA, NMDA) can affect epileptogenicity [16]. One example of this phenomenon is seen in gliomas as they have been shown to have higher concentrations of inotropic glutamate receptors which can lead to neuronal hyperexcitability with resultant seizures and possible cell death [17].

Metastatic lesions account for a smaller percentage of patients with intracranial neoplasms who go on to develop seizures and epilepsy. Systemic cancers which occur more commonly, such as lung and breast cancer, tend to have a higher incidence of brain metastasis and subsequent seizures. Some cancers have a higher predilection for central nervous system metastasis such as melanoma and, depending on location, may have a higher seizure frequency [18].

4.2. Treatment-related causes of seizures

Chemotherapy. Various chemotherapeutic agents can be toxic to the central nervous system either directly or through other mechanisms which result in epileptogenesis or lower seizure threshold.

Agents such as cytarabine, methotrexate, high-dose cisplatin, bevacizumab, ifosfamide, vincristine, and nitrosoureas can cause seizures by direct central nervous system toxicity when given systemically or in the case of methotrexate when given intrathecally [19].

Radiation therapy. For patients undergoing whole brain radiation for brain metastasis, leptomeningeal disease, and for primary brain tumors, seizures can occur as a direct result of radiation. Complications can occur acutely such as during radiation treatment. They can occur early within weeks to months after radiation or they can occur late, 1-2 years after receiving radiation treatment from radiation necrosis [19, 20].

4.3. Toxic/metabolic

Medication toxicity or withdrawal can result in symptomatic seizures. This can occur with numerous different agents including antimicrobials, antipsychotic medication, antidepressant medication, and, of course, antiepileptic drug medication.

Conditions which can cause seizures even in patients without cancer can also contribute to seizures in those with a brain tumor such as renal or liver failure. Electrolyte disturbance including disturbances of sodium, calcium, magnesium and glucose can precipitate seizures.

Glucose disturbances in particular can also result in focal neurologic disturbances such as seizures or stroke-like syndromes [21].

4.4. Paraneoplastic syndromes

There are several paraneoplastic syndromes which have been characterized and which seizures are one symptom. Paraneoplastic limbic encephalitis has been associated with numerous antibodies including anti-Hu, anti-Ma2, CRMP5, and amphiphysin. Recently, antibodies have been associated with encephalitis and seizures in patients who may or may not have a neoplasm. One such antibody has been the NMDA receptor antibody which was initially described in women with ovarian teratoma but has also been found in children without cancer [22].

5. Treatment

Treatment will be discussed for patients with brain tumor epilepsy. In general, treatment for patients with systemic cancer without intracranial lesions will consist of antiepileptic drugs only. In patients with intracranial lesions, there is a multifaceted approach which includes antiepileptic drugs, surgery, chemotherapy, and radiation therapy.

5.1. Antiepileptic drugs

Antiepileptic drugs are a mainstay of treatment for seizures of any etiology. In patients with cancer this is also true, but a consideration of drug interactions and drug metabolism is important as patients receiving chemotherapy, with or without corticosteroids, can have untoward drug interactions in combination with antiepileptic drugs [23]. This is usually the case for some of the first generation antiepileptic drugs which can be hepatic enzyme inducers, specifically of the cytochrome P-450 pathway. Drug interactions can also occur with antiepileptic drugs that are enzyme inhibitors. A benefit of the second and third generation antiepileptic drugs is that many are not metabolized through the same hepatic pathways as chemotherapy agents or corticosteroids. In addition, there is less protein binding with these agents which makes them more suitable for treatment in patients receiving concurrent chemotherapy (Table 1).

Enzyme-inducing antiepileptic drugs can decrease the effects of corticosteroids and in turn corticosteroids can also alter the metabolism of antiepileptic drugs resulting in decreased serum levels [24]. Enzyme-inducing antiepileptic drugs can also have an effect on the serum drug levels of chemotherapeutic agents such as nitrosureas, paclitaxel, cyclophosphamide, etoposide, doxorubicin, and methotrexate. Temozolomide, an alkylating agent commonly used for treating high-grade gliomas, has minimal CYP metabolism. One study documented no effect of temozolomide on levels of topiramate or oxcarbazepine [25].

Treatment of seizures with antiepileptic drug therapy in brain tumor patients has been evaluated in several retrospective trials (Table 2). Use of older antiepileptic drugs with

Enzyme inducers (CYP 450)	Non-enzyme inducers
Phenytoin	Gabapentin
Carbamazepine	Lamotrigine
Phenobarbital	Valproic acid (enzyme inhibitor)
Primidone	Felbamate (enzyme inhibitor)
Oxcarbazepine	Levetiracetam
	Pre-gadolinium
	Tiagabine
	Topiramate
	Zonisamide
	Lacosamide

Table 1. List of antiepileptic drugs comparing those metabolized through the CYP 450 pathway and those that are not

adjunctive treatment with agents such as levetiracetam, lamotrigine, or topiramate have been reviewed and shown to be safe and efficacious in the brain tumor population. There are varying degrees of success with reports of seizure reduction in many patients and a smaller percentage achieving seizure freedom. Follow-up in these studies has been variable and difficult to compare.

Side effects of antiepileptic drug treatment are an important consideration. In patients with brain tumors who have undergone craniotomy, radiation treatment, and who may or may not be receiving chemotherapy, additional toxicity from antiepileptic drugs can be additive. Common side effects such as cognitive impairment, bone marrow suppression, liver dysfunction, electrolyte abnormalities, and dermatologic reactions are important considerations in patients receiving this antiepileptic drug therapy. Side effects are more frequent in patients with brain tumors compared to the overall population with epilepsy as was noted in the 2000 AAN Practice Parameter [33].

A benefit to the newer antiepileptic drugs is that there are fewer interactions with chemotherapy, they can be used in clinical trials aimed at treatment of brain tumors, and at times there can be a better side effect profile. However, side effects from antiepileptic drugs can be seen more often in patients with brain tumors. This is likely because patients with brain tumors have fixed neurologic deficits which can be worsened in the setting of drug toxicity of any kind.

Treatment with antiepileptic drugs in the cancer population should be similar to treatment for anyone with localization related epilepsy. Monotherapy should be the goal with the lowest possible dose to control seizures and to avoid adverse side effects. Drugs which control focal seizures with secondary generalization are desired and agents such as lamotrigine, carbamazepine, and oxcarbazepine are generally well-tolerated [34]. Other agents which can have an

Author	N	Type	Grade	Primary AED	Add-on AED	Seizure Free (%)	Seizure reduction (%)
Hildebrand et al[26]	234	R	HGG	VPA, CBZ, GBP, LMT, others		13	NA
Maschio et al.[27]	14	P	HGG, LGG	LEV, VPA, LTG, others	LCS	43	78
Wick et al.[28]	107	R	HGG, LGG	PHT, VPA, CBZ		30	
Wagner et al.[27]	26	P	HG	VPA	LEV	20	65
Mashio et al.[30]	19	P	HG	LTG, VPA, TPM, OXC	LEV	47	72
Newton et al[31]	41	R	HG	PHT, CBZ	LEV	59	90
Mashio et al.[25]	47	P	HG, LG, BM	PHT, CBZ, PB	TPM	56	76
Perry et al.[32]	14	P	HG	PHT, CBZ, Clobazam	GBP	57	100

N- number of patients; R- retrospective; P- prospective; HGG- high grade glioma; LGG-low grade glioma; HG- High grade; LG- low grade; BM-brain metastases; LEV-levetiracetam; VPA-valproic acid; LTG- lamotrigine; GBP-gabapentin; CBZ-carbamazepine; OXC-oxcarbazepine; LCS-lacosamide; TPM-topiramate; PB-phenobarbital

Table 2. AED drug trials in brain tumor patients

effect on this population such as topiramate or valproic acid can be used. However, cognitive side effects with topiramate may limit its dosing and therefore its efficacy. Valproic acid would appear to be a good agent; however, it can cause drug interactions and liver toxicity. In patients already receiving chemotherapy, the potential for liver toxicity and thrombocytopenia can be a problem with valproic acid [35]. Valproic acid does have possible antitumor effects due to inhibition of histone deacetylase (HDAC) [36]. There is recent evidence that in patients with glioblastoma undergoing standard treatment, radiation treatment with concurrent temozolomide, receiving valproic acid for the treatment of seizures may be a survival benefit [35]. However, prospective studies examining this issue have yet to be performed. Whether this survival benefit was seen due to HDAC effects or hepatic enzyme inhibitory properties was unclear. In contrast, a study examining 620 patients with newly diagnosed glioblastoma found an overall survival benefit and progression-free survival in patients who received an enzyme inducing agent versus those who did not [37]. The role of enzyme inducing AEDs on survival has not been established in the brain tumor population but is something that should be prospectively analyzed in new clinical trials.

Levetiracetam and gabapentin have ideal properties in that neither is liver metabolized and there are few if any drug interactions. In several retrospective studies, levetiracetam has been well-tolerated in brain tumor patients but can be associated with mood disturbances [29, 30, 38]. Cognitive side effects and fatigue are also seen with use of this agent which can be compounded in patients who have received brain radiation.

5.2. Surgery

There are generally two approaches to surgery for brain tumor patients. The first and most important is gross total resection of either the primary brain tumor or a metastatic lesion. A secondary consideration can be additional removal of a seizure focus (lesionectomy) for patients who present with seizures as a symptom of their brain tumor. Circumstances which can limit lesionectomy are the location of the seizure focus in an eloquent area of cortex. In the brain tumor population, surgery is almost always geared towards gross total resection which has shown on its own to improve outcomes from a seizure standpoint [39]. However, there remains a significant population of patients who undergo brain tumor surgery and continue to have seizures postoperatively. Patients with lesions near the motor cortex are more likely not to be surgically "cured" as the lesion causing seizures is unlikely to be amenable to surgical resection. Therefore, these patients remain with symptomatic partial epilepsy.

In tumor associated epilepsy, seizures generally arise from the peritumoral brain tissue and not from the mass. Tumor tissue is generally electrically inert and does not give rise to seizures. Electrocorticography (Ecog) performed intraoperatively may assist in identifying a seizure focus and aid the neurosurgeon in removal of the lesion. A study reviewing 35 patients with intractable temporal lobe epilepsy due to benign lesions (ganglioglioma, DNET, cavernoma) found 3-year post-operative seizure rates to be improved in patients who underwent Ecog with additional removal of spike-positive areas [40]. However, there is no universal standard established.

For temporal lobe lesions, the additional resection of mesial structures may be beneficial in some cases. A series with patients with low grade temporal lobe tumors (DNET, ganglioglioma) with associated hippocampal sclerosis suggest that lobectomy with hippocampectomy is preferable to tumor resection alone [41]. Overall, prognostic factors which favor control of epilepsy with surgery are a shorter duration of epilepsy prior to surgery, a single focus on EEG, a single lesion on neuroimaging, and complete tumor resection [10,41,39].

5.3. Chemotherapy

Chemotherapy is one of the primary treatment modalities for all types of metastatic and primary central nervous system tumors. The use of chemotherapy can result in seizure reduction for patients with primary brain tumors. Recent studies retrospectively reviewing the use of temozolomide or nitrosoureas in patients with low grade glioma have shown a reduction in seizures with some patients achieving seizure freedom [42-44].

Additionally, in patients with subependymal giant cell astrocytomas with tuberous sclerosis complex, the mTor inhibitor, everolimus, has been associated with reduction of subependymal tumors and subsequent improvement in seizures. Whether this agent is antiepileptogenic in itself or causes a reduction of tumor bulk which improves seizures remains to be seen [45].

5.4. Radiation therapy

Treatment for glioblastoma with surgery followed by radiation with concurrent temozolomide has been established as a standard of care. There have been small studies which have shown

that radiation treatment for malignant lesions has also resulted in improvement in seizures independent of antiepileptic drug adjustment [46, 47]. The EORTC 22845 randomized trial of long-term efficacy of early versus delayed radiation treatment for low grade brain tumors revealed an improvement in seizure frequency at one year post treatment. Although later data points were not collected, this study shows what has been evident in clinical practice which is that radiation treatment for low-grade brain tumors can improve seizure frequency [48].

6. Antiepileptic drug prophylaxis

6.1. Postsurgical patients

The role of prophylactic anticonvulsant medications in the perioperative period has been reviewed for numerous tumor types including primary brain tumors and brain metastasis. Prophylaxis appears effective for preventing early postoperative seizures but does not appear to affect the delayed development of epilepsy [49]. Current practice is to use prophylactic anticonvulsants during the first week after surgery and then to discontinue after that time period [50]. The data on these recommendations are derived from the older anticonvulsants, phenytoin, phenobarbital, and valproic acid. The newer generation antiepileptic drugs have not been studied as rigorously in this setting and therefore recommendations for their use is limited. However, recent studies using levetiracetam in this setting have been promising in that there are few if any drug interactions and minimal adverse effects related to the use of this drug [51,52]. Certain tumor types may not benefit from the use of prophylactic anticonvulsants in the perioperative period, such as meningioma, as seen in a recent meta analysis [53]. Prospective studies are needed to determine the validity and efficacy of prophylactic anticonvulsants in the perioperative period with newer generation antiepileptic drugs. In view of the minimal drug interactions and favorable side effect profile of these drugs, they may have a role in early seizure prophylaxis after craniotomy.

6.2. Brain tumor patients

Both the American Academy of Neurology and the Association for Neurologic Surgeons/ Congress of Neurologic Surgeons recommend against routine prophylaxis with antiepileptic drugs for patients with primary brain tumors or brain metastasis without a history of seizures [33,54]. Treatment is recommended only after patients with brain tumors experience a seizure.

7. Role of Electroencephalogram in brain tumor patients

Altered mental status is a common clinical manifestation in patients with brain tumors and seizures are one cause of altered mental status. In patients with overt clinical seizures, the diagnosis is usually not in question and therefore treatment can be started immediately for this potentially life-threatening problem. However, in patients with subtle clinical signs of seizures or nonconvulsive seizures, the diagnosis is often not clear without the use of an EEG.

The workup in patients in whom seizures are suspected can be accomplished with routine bedside EEG or long-term monitoring (LTM) with continuous video EEG recording. The use of LTM has increased, especially in intensive care unit (ICU) settings. One study reported seizures in 110 (19%) of 570 critically ill patients who had continuous video EEG, most of whom were in an ICU setting. Of note, 101 of these patients had nonconvulsive seizures. Therefore, in that setting, seizures would have been missed had EEG not been used [55]. Clinical suspicion should be high in patients with structural brain lesions with altered mental status and an EEG may be beneficial for evaluating these patients.

8. Conclusion

Epilepsy in cancer patients can be from numerous causes including the cancer itself, cancer treatment, or toxic metabolic etiologies. Numerous factors contribute to the development of epilepsy in these patients. Adverse effects due to cancer treatment and antiepileptic drugs should be recognized early as patients with brain tumors and epilepsy are more likely to experience adverse effects. Treatment will be multifaceted and include antiepileptic drugs, surgery, chemotherapy, and radiation treatment. A multidisciplinary approach is usually needed for treatment of these complicated patients.

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