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Neurological and Medical Complications in Brain Tumor Patients

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Abstract

Purpose of Review Patients with brain tumors are susceptible to multiple complications that can affect their survival or quality of life. The scope of these complications is widening due to prolonged overall survival and improved therapies. In this review, we discuss the most common complications in this patient population focusing on the recent literature. We specifically concentrated on tumor-related epilepsy, vasogenic edema, infectious, vascular, chemotherapeutic, radiation, endocrine, and cognitive complications.

Recent Findings Molecular biomarkers play a role in epileptogenicity in brain tumor patients, and anti-epileptic drugs may cause neuro-cognitive side effects independent of other factors. The pathophysiology of vasogenic edema remains complex and poorly understood. Limited data suggest that newer oral anticoagulants appear to be safe and effective in venous and arterial thrombo-embolic complications.

Summary Brain tumor patients are prone to a wide variety of complications, including some related to new therapies. Optimal management of these complications improves quality of life, and in some cases overall survival.

Keywords Brain tumors · Complications · Seizures · Stroke · Radiation necrosis · Cognitive impairment

Introduction

Many patients with brain tumors develop long-term sequelae with an impact on survival or quality of life. The more common complications include epilepsy, strokes and other vascular complications, cognitive impairment, vasogenic edema, radiation necrosis, fatigue, endocrine, and infectious complications. In this review, we focus on major advances in these areas.

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Tumor-Related Epilepsy

Seizures are common among patients with brain tumors with an overall incidence ranging from 35 to 70% [1]. Given this high percentage, the use of prophylactic antiepileptic drugs (AED) has been an area of debate although routine use of AEDs was not recommended per American Academy of Neurology (AAN) practice guidelines [2]. A recent meta-analysis including 1073 seizure naïve patients with brain tumors undergoing craniotomy showed no significant therapeutic benefits of prophylactic treatment [3]. Among those patients who received prophylaxis, levetiracetam had a lower incidence of side effects (7.5%) compared to phenytoin (15.5%). However, the use of prophylactic AEDs remains common practice among neurosurgeons. In low-grade glioma, prevalence of epilepsy is high reaching up to 90% [4]. Multiple studies confirmed higher epilepsy prevalence in low-grade glioma patients with isocitrate dehydrogenase (IDH) mutations, confirming that molecular characteristics of tumors play a role [5•]. IDH mutation reduces ketoglutarate to 2-hydroxyglutarate (2HG) instead of converting isocitrate to ketoglutarate. This leads to a significant increase in 2HG levels in IDH mutant tumors. 2HG is similar to glutamine structure and can activate *N*-methyl-D-aspartate

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(NMDA) receptors and hence epileptogenicity [6••]. Selection of an AED depends largely on provider preference in addition to pharmacokinetic, pharmacodynamic, and adverse effects profile of each drug (Table 1) and not on the tumor type itself. We prefer to avoid hepatic microsomal enzyme inducers or inhibitors initially. Valproate (VPA) is known to be a histone deacetylase inhibitor, a class of drugs with antineoplastic properties. An unplanned secondary analysis of a large treatment trial suggested improved survival in glioblastoma (GBM) patients with a dose-dependent effect [7], although subsequent analyses have not borne this out, and currently, its use is justified mainly for seizure control [8]. Perampanel is a highly selective non-competitive amino-3-hydroxy5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptor antagonist without enzyme-inducing properties and has been shown to be safe and effective in glioma-associated epilepsy [9•]. Recently, it has been shown that neuron–glioma interactions include AMPA-dependent synapses suggesting potential therapeutic anti-tumor effect using AMPA antagonists [10•].

Levetiracetam remains one of the most commonly prescribed AED in patients with tumor-related epilepsy due to its efficacy and side effect profile. A recent study prospectively examined the prevalence and magnitude of neuropsychological adverse effects in an observational multicenter setting including 259 patients with brain tumor–related epilepsy [11••]. The study showed that frontal lobe tumor localization and levetiracetam treatment were independently associated with a 7-fold increased risk of developing neuropsychological adverse effects and those with frontal lobe tumors on levetiracetam were the most affected; this effect did not seem to be dose related.

Withdrawal of antiepileptic drugs in patients with low-grade glioma is often challenging due to the high seizure incidence, and currently, large prospective studies on this issue is lacking [12–14]. A recent study evaluated the risk of seizure recurrence in low-grade and anaplastic glioma and included 71 patients where 25 patients continued on AEDs and 46 off AEDs with a median follow-up of 2.2 years. All patients had clinically and radiographically stable disease for 12 months in addition to freedom from seizures for at least 24 months from last seizure or 12 months from treatment (surgery, radiation, or chemotherapy). The decision to withdraw was also shared between the patient and the neuro-oncologist, but no further testing such as electroencephalogram was required. Of the 46 patients off AEDs, 12 (26%) had seizures of whom 7 had progression of tumor. Thus, withdrawal of AEDs in selected low-grade glioma patients is reasonable [15].

Vasogenic Edema

Management of vasogenic edema remains challenging for both primary central nervous system (CNS) malignancies and metastases. Its pathophysiology remains complex with increased blood–brain barrier permeability being a key factor. Multiple factors and potential therapeutic targets are involved including vascular endothelial growth factor (VEGF), nitric oxide (NO), arachnoid acid metabolites, and aquaporins [16]. However, steroids by far remain the most frequently used agent to date. Most neurosurgeons maintain dexamethasone at frequencies of 3 to 4 times daily while neuro-oncologists at twice a day. Dexamethasone's biological half-life lasts up to 54 h, and thus, administration more than twice daily is unnecessary in the outpatient settings [17]. It is recommended to taper steroids as soon as possible as they may decrease the effectiveness of treatment and shorten survival in glioblastoma patients [18•]. Bevacizumab is used for management of cerebral edema of different etiologies and is gaining popularity with more supportive evidence [19]. Steroid use can also be problematic in brain metastases from underlying malignancies treated with immunotherapy as it may reduce efficacy of checkpoint inhibitors [20], though the importance of this observation is debated [21]; the use of bevacizumab as a steroid sparing agent can be considered in such cases [22].

Infectious Complications

Infectious complications are not uncommon in brain tumor patients. An often challenging issue is ring-enhancing lesions on T1-weighted MR images or residual post-operative enhancement that raise the question of local infection or neoplasm. In the absence of supportive clinical findings, treatment approach is mostly guided by imaging findings especially with recent advances in MR scans. Apparent diffusion coefficient (ADC) value is known to be helpful in differentiating abscesses from necrotic tumors as the ADC value of pus is usually low in the cavity compared to tumors where it is usually high [23]. However, it is estimated that 5–21% of brain abscesses show high ADC values [24]. Recently, there has been interest in susceptibility-weighted imaging (SWI) and in the presence of intralesional susceptibility signal (ILSS) where findings of fine linear or dot-like low-signal intensity structures within the lesions indicate the presence of paramagnetic substance that may be associated with tumor necrosis, microhemorrhages, and tumor vascularity [25]. SWI sequences have recently been shown to be complementary to ADC for differentiation between abscesses, necrotic glioblastomas, and necrotic metastatic brain tumors although these findings require further validation [26•]. Another infection encountered in neuro-oncology patients is Pneumocystis pneumonia associated with the use of temozolomide and corticosteroids [27]. Other very rare infections related to immunosuppression may be seen and include herpes reactivation [28], CMV-related infections [29], and Aspergillosis [30] (Table 2).

Table 1 Commonly prescribed AEDs

AED	Principal mechanism of action	Interactions	Target dose	Adverse effects	Idiosyncratic effects
Phenytoin	Sodium channel blocker	Hepatic enzyme inducer	200–400 mg/day guided by serum concentration	Somnolence, dizziness, ataxia, blurry vision, gum hyperplasia, irritability.	SJS, lupus like reaction, hepatitis, blood dyscrasia
Carbamazepine	Sodium channel blocker	Hepatic enzyme inducer	Up to 800 mg/day	Nausea, headache, dizziness, fatigue, hyponatremia, weight gain, decreased bone density, mild leukopenia	SJS, TEN (more likely with HLA-B1502 allele), lupus like reaction, hepatotoxicity
Oxcarbazepine	Sodium channel blocker	Hepatic enzyme inducer	Up to 1200 mg/day	Similar to Carbamazepine (25% cross-reactivity). More likely to cause hyponatremia	Similar to Carbamazepine
VPA	Multiple	Hepatic enzyme inhibitor	Up to 2000 mg/day	GI side-effects, tremors, alopecia, weight gait, PCOS, insulin resistance, hyperammonemia	Liver/pancreatic failure, thrombocytopenia, birth defects
Levetiracetam	SV2A modulation	n/a	Up to 4000 mg/day	Somnolence, dizziness, fatigue, irritability, depression	None established
Brivaracetam	SV2A modulation	More interactions than levetiracetam	Up to 200 mg/day	Somnolence, dizziness, fatigue, irritability	None established
Lamotrigine	Sodium channel blocker	Decrease OCP efficacy	4.5–7.5 mg/kg/day guided by serum concentration	Dizziness, blurry vision, ataxia, headaches, insomnia	SJS, TEN, DRESS
Topiramate	Multiple	Decrease OCP efficacy	Up to 400 mg/day	Somnolence, dizziness, mental slowing, memory disturbance, weight loss, kidney stones	Hepatic failure, glaucoma
Lacosamide	Sodium channel blocker (enhances slow inactivation)	n/a	Up to 400–600 mg/day	Somnolence, dizziness, diplopia, headaches, tremors	None established
Zonisamide	Multiple	n/a	Up to 600 mg/day	Somnolence, ataxia, dizziness, decreased appetite, paresthesia, weight loss, kidney stones, apathy	Rash
Perampanel	Noncompetitive AMPA glutamate receptor antagonist	Decrease OCP efficacy	8–12 mg/day	dizziness, somnolence, headache, fatigue, ataxia, blurred vision, aggression and hostility	DRESS
Clobazam	Potentiate GABAergic neurotransmission	n/a	Up to 40 mg/day	Drowsiness, dizziness, withdrawal seizures	None established

AED antiepileptic drug, *VPA* valproate, *GI* gastrointestinal, *SJS* Stevens-Johnson syndrome, *TEN* toxic epidermal necrolysis, *DRESS* drug reaction with eosinophilia and systemic symptoms, *PCOS* polycystic ovary syndrome, *AMPA* amino-3-hydroxy5-methyl-4-isoxazolepropionic acid, *OCP* oral contraceptive, *n/a* not available

Table 2 Selected organ-specific complication of commonly prescribed glioma chemotherapies and steroids

Organ system	Temozolomide	Lomustine	Procarbazine	Bevacizumab	Steroids
Cardiovascular/ Respiratory	Peripheral edema	Pulmonary fibrosis	Hypotension, peripheral edema	Hypertension, peripheral edema, venous thromboembolism	Hypertension, peripheral edema
Renal	UTIs	Azotemia, nephrotoxicity	Polyuria	Increased serum creatinine	Sodium and water retention
Endocrine	Weight gain	Alopecia	Gynecomastia	Ovarian failure, hyperglycemia	Cushingoid appearance, hyperglycemia
Gastrointestinal	Nausea, vomiting, constipation, diarrhea	Stomatitis	Nausea, vomiting, constipation	Nausea, GI perforation, gingival hemorrhage	Peptic ulcers
Hematologic	Secondary malignancies, bone marrow suppression	Secondary malignancies, bone marrow suppression	Secondary malignancies, bone marrow suppression	Immunosuppression, thrombocytopenia	Immunosuppression
Musculoskeletal	Myalgia, weakness	n/a	Myalgia, weakness	Arthralgia	Myopathy
Ophthalmic	Blurred vision	Optic atrophy	Accommodation disturbance	Disease of lacrimal apparatus	Cataracts, glaucoma
Psychiatric	n/a	n/a	n/a	n/a	Mood disorders, anxiety

UTI urinary tract infection, *n/a* not available

Vascular Complications

Glioma patients carry one of the highest risks of venous thromboembolism (VTE) among cancer patients, with rates up to 25–39% [31–33]. A recent retrospective study showed that thromboembolic complications in brain tumor patients are responsible for 22% of readmission within 30 days of surgery [34]. VTE can be challenging to treat and is associated with worse survival especially with comorbid intracranial conditions such as strokes or tumors susceptible to hemorrhage [33]. In glioma patients, the risk of spontaneous intratumoral hemorrhage is reported between 2 and 8% [35]. However, given the available evidence, closely monitored anticoagulation therapy seems to be safe in primary CNS tumors as well as in metastases. Low molecular weight heparin (LMWH) is the preferred agent over warfarin, although recent evidence suggest bleeding risk may be higher with anticoagulation in primary brain tumors compared to metastases overall [36, 37]. Novel direct oral anticoagulants (DOACs) appear to have slightly lower risk of bleeding compared to warfarin or LMWH in general population; a recent small retrospective study suggests acceptable safety in primary brain tumors and metastases [38]. Bevacizumab increases the risk of cerebral infarcts as well as hemorrhages in cancer patients generally independent of other risk factors [39]. A recent small retrospective study investigated the risk of ischemic strokes and hemorrhages in patient treated for recurrent GBM with or without bevacizumab failed to demonstrate an association between bevacizumab and CNS vascular events [40]. However, in the AVAGlio study for newly diagnosed GBM, the risk of intracranial hemorrhage in the bevacizumab arm was higher [41]. Therefore, it is recommended to avoid bevacizumab in tumors that have more than petechial hemorrhages. Other neurological vascular complications do occur in cancer patient such as posterior reversible encephalopathy syndrome (PRES) and has been reported with primary CNS tumors or metastases on different treatments, particularly anti-VEGF agents, and should always be considered in the right clinical context with supportive radiological findings [42–44].

Endocrine and Fertility Complications

Endocrinopathies and hypothalamic-pituitary axis dysfunction are not uncommon in brain tumor patients with an incidence that may exceed 30% if the radiation field involves the hypothalamus and pituitary gland. Dysfunction typically starts within a few years of radiation and is radiation dose dependent [45], manifesting as decreased production of growth hormones (GH), thyroid stimulating hormones (TSH), adrenocorticotropic hormones (ACTH), and gonadotropins. The incidence is high in childhood brain tumor survivors with largest cohort to date (27.3 years) showing incidence of GH,

thyrotropin, ACTH, and gonadotropins deficiencies of 72.4%, 11.6%, 5.2%, and 24.4%, respectively [46•]. Thus, long-term attention to pituitary function is essential in childhood/young adult cancer survivors [47]. Patients with brain tumors are at risk of infertility due to either a direct tumor effect or secondary to chemo and/or radiation therapy; unfortunately, the magnitude of this risk is poorly studied in the brain tumor patient population. Fertility risk and preservation counseling should be discussed with all patients of reproductive age prior to treatment [48].

Cognitive and Behavioral Complications

Patients with brain tumors are prone to cognitive impairment secondary to the neoplasm or its treatment. However, strong evidence suggests that even prior to treatment, a significant proportion of patients with non-CNS malignancies experience cognitive impairment prior to treatment (up to 30%) with higher prevalence during and after treatment reaching up to 75% of patients [49–53]. The underlying pathophysiology is complex and poorly understood but likely involves inflammatory cytokines, brain infiltrating immune cells, tumor-derived extracellular vesicles, blood-brain barrier integrity, and other probable mechanisms [54]. Genetic factors such as the role of the APOE ε4 allele also may be implicated although the evidence is inconsistent [55]. Chemotherapy plays a major role in cognitive impairment, and numerous studies have reported alterations in brain structure and function following chemotherapy [56, 57]. Whole brain radiation therapy (WBRT) is also well established to cause more pronounced cognitive impairment compared to focal radiation [58].Memantine has been studied in a randomized controlled trial of patients undergoing WBRT for brain metastases. Although the study, which had low statistical power due to deaths, did not meet its primary end point, it did show trends favoring memantine arm on different cognitive tests [59]. RTOG 0933 showed that hippocampal avoidance during WBRT (HA-WBRT) preserver memory and quality of life in comparison to historical controls and is the preferable method of WBRT delivery [60•]. Additionally, the recently published phase III trial NRG oncology CC001 investigated brain metastases patient undergoing HA-WBRT plus memantine on one arm and WBRT plus memantine on the other arm. A total of 518 patients were evaluated, and the HA-WBRT arm showed better preservation of cognitive function with no difference in survival [61••]. Stereotactic radiosurgery to the surgical cavity post resection for brain metastases appears safe with no significant cognitive decline or impairment in quality of life parameters and has been shown to be superior to WBRT in cognitive function preservation with no changes on overall survival [62, 63].

The management of cognitive impairment in cancer patients remains challenging. Psychostimulants has been studied with variable results and with some criticism regarding methodological flaws. Donepezil for example has been shown in smaller studies to show evidence of effectiveness but failed in others although in phase III trial there was modest improvement in patients with more severe cognitive impairment pretreatment [64, 65]. An 8-week course of Armodafinil during radiation treatment of glioma patients did not show effectiveness in a pilot study [66]. Other non-pharmacological treatment such as cognitive behavioral therapy (CBT) and cognitive rehabilitation may be helpful in selected patients [67].

Conclusion

New advances in the management of brain tumors have improved survival and quality of life but also added to the complexity of taking care of this patient population for the practicing neuro-oncologist. Long-term cognitive impairment and its relation to AEDs remain a major issue, and further studies are needed.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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