# Chapter 3
# Neuro-oncologic Emergencies


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## Introduction

Primary central nervous system (CNS) tumors are the second most common pediatric cancer diagnosed in the United States each year. Comprising approximately 22% of new cases of pediatric cancer per year, CNS tumors are second only to pediatric leukemia in incidence. Brain and CNS tumors are the most common solid tumor in children with an annual age-adjusted incidence rate of 5.47 per 100,000 population [1, 2]. While brain and CNS tumors are the second most common pediatric cancer, they account for the majority of cancer-related mortality in children [3].

However, survival of pediatric patients with primary brain tumors has increased over the years, but the treatment of brain tumors has the potential for significant and life-threatening neurologic complications. It is imperative that critical care professionals recognize and appropriately treat common neurologic emergencies associated with these tumors. These emergencies can be the result of direct effects of the CNS tumor (increased intracranial pressure, seizures, spinal cord compression), indirect effects (CNS infection), or complications of various treatment strategies (chemotherapy toxicity, radiation necrosis, pituitary damage). Prompt diagnosis and treatment of these emergencies may not only be lifesaving but can preserve neurologic function both in the short term and have long-lasting effects on overall quality of life.

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## Increased Intracranial Pressure/Hydrocephalus/Herniation

In children with primary CNS tumors, a frequent emergency that develops is increased intracranial pressure (ICP). This can arise because of hydrocephalus, vasogenic edema, or combination of the two. If not addressed adequately, increased intracranial pressure can progress to irreversible neurologic deficits, herniation, and death.

The Monro-Kellie doctrine serves as the basis of understanding the pathophysiology of increased intracranial pressure. The intracranial volume ranges from 1400 to 1700 mL. The brain constitutes roughly 80% of that volume, with blood and cerebrospinal fluid (CSF) each comprising an additional 10% [4]. Given the fixed volume of the cranial vault, owing to the rigid skull surrounding it, the Monro-Kellie doctrine states that an increase in volume of the brain, blood, or CSF must trigger a decrease in one or both of the other components. When the system fails to compensate appropriately, there is a resultant increase in intracranial pressure.

One cause of increased ICP commonly encountered in children with primary CNS tumors is hydrocephalus. This occurs due to obstruction of the CSF outflow system. For example, pineal tumors may block CSF outflow from the 3rd ventricle resulting in dilatation of the lateral ventricles, or posterior fossa tumors can obstruct the 4th ventricle resulting in dilatation of the entire ventricular system. As CSF cannot drain adequately, its volume within the cranial vault increases and therefore results in increased ICP.

A common symptom of elevated intracranial pressure is headache. The classic description of headache associated with elevated ICP is one that is most severe in the morning due to nocturnal hypercarbia causing vasodilatation and supine posture [5]. However, this dogma has been challenged, and some report that morning headache occurs in a minority of patients presenting with increased ICP [6]. Other presenting symptoms of elevated intracranial pressure include vomiting, diplopia from abducens nerve palsy, and papilledema. When unchecked, elevated intracranial pressure may result in brainstem compression manifested by Cushing's triad of hypertension, bradycardia, and irregular breathing, which heralds impending herniation.

With imminent herniation, patients with elevated ICP often become stuporous; therefore management often starts with securing an airway. Sedation and intubation have the added benefit of being means of lowering elevated ICP. Sedation lowers intracranial pressure, though at the expense of a reliable neurologic examination. Intubation allows for hyperventilation to a pCO2 of 26–30 mm Hg which causes vasoconstriction and decreased cerebral blood flow quickly albeit transiently [7].

Following these short-term interventions, osmotherapy is the mainstay of medical treatment of increased ICP. Hyperosmolar agents such as hypertonic saline and mannitol are used to create an osmotic gradient across the blood-brain barrier and shift fluid out of the brain thereby lowering ICP [8, 9]. Neither of these agents can be continued indefinitely as repeated doses without time for clearance between doses can lead to a rebound increase in ICP. Additionally, corticosteroids, specifically dexamethasone, play a critical role in alleviating vasogenic edema associated with brain tumors, by decreasing vascular permeability of the blood-brain barrier, leading to decreased ICP. Finally, following these temporizing interventions, one

must quickly determine if surgical interventions are necessary and/or appropriate for management of hydrocephalus, particularly in the case of obstructive hydrocephalus. Neurosurgical interventions include insertion of an extraventricular drain to alleviate pressure, endoscopic third ventriculostomy, or insertion of a ventriculoperitoneal shunt.

## Seizures/Status Epilepticus

Another complication of primary brain tumors are seizures. Brain tumors are structural abnormalities that can cause cortical irritability and subsequent seizures. Prophylaxis with antiepileptic drugs is not commonly recommended, as a subset of patients with brain tumors never experience seizures [10]. Tumors located in epileptogenic areas such as the cortex, mesial temporal lobe, and insula are more likely to cause seizures. Low-grade gliomas are more epileptogenic than high-grade gliomas [11]. Of patients with low-grade gliomas, those with oligodendroglioma are more likely to develop seizures than those with astrocytoma likely owing to their cortical location and white matter involvement [12, 13].

Specific seizure semiology often reflects the tumor's location. Brain tumor patients generally have localization-related epilepsy with subtypes including simple partial seizures, complex partial seizures, and focal seizures with secondary generalization [13]. Status epilepticus can occur at any stage of a tumor's course – at presentation, progression, or during periods of stability [14]. In addition to seizure location, seizures can be triggered in those with CNS tumors as a complication of treatment whether due to electrolyte abnormalities, treatment-related posterior reversible encephalopathy, or by medications, which lower the seizure threshold commonly used as supportive care in cancer patients.

After recognition of status epilepticus, treatment according to standard management algorithms is vital. First-line treatment of status epilepticus starts with prompt administration of a benzodiazepine (IV lorazepam or IM midazolam if IV access cannot be obtained) followed by phenytoin if needed. Third-line treatments include phenobarbital, valproic acid, lacosamide, and levetiracetam [15]. Choosing ongoing antiepileptic drug therapy in children with brain tumors are challenging due in large part to the potential interactions between antiepileptic drugs and chemotherapy. Levetiracetam is often recommended as initial maintenance monotherapy given its efficacy, tolerability, and pharmacokinetic properties when used in combination with chemotherapy [16].

## Spinal Cord Compression

Spinal cord compression from an epidural mass is a somewhat common complication in specific pediatric cancers such as soft tissue sarcoma, neuroblastoma, medulloblastoma, atypical teratoid rhabdoid tumors (AT/RT), and lymphoma [17, 18]. It constitutes a neuro-oncologic emergency as favorable neurologic outcome depends on early recognition and management.

Prior to spinal cord compression, those with spinal tumors may report pain, particularly in the case of extradural masses arising from the bone. Another source of pain is Lhermitte's sign, an electrical sensation spreading from the spine to the arms or legs following neck flexion. This pain is due to irritation or compression of the dorsal columns. While Lhermitte's sign suggests cord dysfunction, other classic signs include weakness, loss of sensation, and bowel or bladder dysfunction. If compression occurs in the cervical or high thoracic region, patients can develop autonomic dysreflexia with bradycardia and hypertension, which can be triggered by constipation or an excessively full bladder.

A bolus of dexamethasone is the first-line treatment when cord compression is recognized. Steroids should be continued at a maintenance dosing schedule until definitive treatment can be achieved. Definitive treatment may include surgery, radiation therapy, or both. Small studies in adult patients have shown that those patients with acute onset (<48 h) of paraplegia and radiographically proven cord compression were more likely to regain the ability to walk and had improved pain control with treated with surgery followed by radiation compared to radiation alone [19]. Surgery can be avoided in patients with radiosensitive/chemosensitive tumors. Thus, multidisciplinary evaluation by neurosurgery, radiation oncology, and oncology is vital in the management of acute spinal cord compression.

## Encephalopathy with Chemotherapy

Certain cytotoxic and biologic agents can produce neurotoxicity (Table 3.1). The severity depends on the treatment dose, duration, and concomitant use of other neurotoxic therapies.

Within days of administration, high-dose methotrexate, ifosfamide, high-dose cytarabine, and procarbazine can all cause acute encephalopathy including confusion, hallucination, drowsiness, and seizures. Additionally, high doses of cytarabine can cause cerebellar syndromes including progressive and potentially permanent ataxia [20, 21]. Intrathecal chemotherapies including methotrexate or cytarabine can cause aseptic meningitis with symptoms including neck pain, headache, fever, nausea, and vomiting. These intrathecal agents can also cause transverse myelopathy with paraplegia, leg pain, sensory level, and even neurogenic bladder dysfunction [22]. Unfortunately, treatment for most of these neurotoxic side effects is drug cessation and supportive care, with the exception of ifosfamide encephalopathy, which responds to treatment with methylene blue. (50 mg Q4 hours until resolution of symptoms or 1 mg/kg for children under 50 kg.)

Newer biologic agents can cause neurologic side effects as well. Bevacizumab, an anti-VEGF monoclonal antibody, can be associated with thromboembolic stroke, intracranial hemorrhage, and has been associated with PRES. Cessation of therapy and supportive care are the mainstays of treatment with bevacizumab toxicity. Ipilimumab, an anti-CTLA-4 monoclonal antibody, has been associated with acute inflammatory reaction including myopathy, aseptic meningitis, temporal arteritis,

**Table 3.1** Chemotherapy neurologic toxicities and their treatments

| Complication | Agents | Treatment |
|---|---|---|
| Encephalopathy | Ifosfamide,<br>HD-MTX, HD-cytarabine, procarbazine, vincristine | Methylene blue (for Ifosfamide induced only), discontinue drugs |
| Aseptic meningitis | IT-MTX, cytarabine<br>Cetuximab<br>Ipilimumab | Discontinue/reduce drugs<br>Discontinue drug<br>Discontinue drug, IV corticosteroids, IVIG, plasmapheresis |
| Cerebellar syndromes | HD-cytarabine | Discontinue drugs |
| Seizures | Cisplatin, cytarabine, cyclophosphamide, ifosfamide, vincristine | Discontinue drugs |
| Stroke | Bevacizumab | Discontinue drugs |
| PRES | Cisplatin, cyclophosphamide, gemcitabine, bevacizumab | Discontinue drugs |
| Myelopathy | IT-MTX and cytarabine | Discontinue drugs |
| Guillen-Barre syndrome | Ipilimumab | Discontinue drugs, IV corticosteroids, IVIG, plasmapheresis |
| Acute sensory dysesthesia | Ifosfamide, cytarabine (rare) | Discontinue/reduce drugs, anti-epileptics (carbamazepine, lamotrigine, gabapentin), tricyclic antidepressants, SSRIs |

and Guillain-Barre syndrome. These neurologic complications are often immune mediated and therefore are treated with immune modulating therapies such as corticosteroids or IVIG.

## Endocrinopathies

Endocrine dysfunction and disruption of water regulation are common findings of patients with intracranial neoplasms, particularly those arising from the sella and parasellar regions. Tumors that commonly arise in this area include craniopharyngioma, germ-cell tumors, astrocytomas, or pituitary adenomas and may present with endocrinopathies. Additionally, endocrinopathies and disordered water metabolism may result from surgical resection or manipulation of these lesions.

Disordered water regulation can be associated with anatomic injury to the hypothalamus, pituitary stalk, or posterior pituitary gland before or during surgery for sella or parasellar neoplasms. This damage changes water metabolism controlled by the antidiuretic hormone (ADH). ADH is produced by neurons of the paraventricular and supraoptic nuclei. It is then transported along the axons of the hypothalamic neurons and stored in the posterior pituitary. ADH is then released in response to two major stimuli: a raise in plasma osmolality and a decrease in blood pressure/circulating blood volume. After ADH is released, it acts on the kidneys and blood

vessels resulting in water reabsorption at the renal collecting duct and stimulating vasoconstriction respectively [23]. Disorders of water metabolism can occur due to a decrease in ADH release resulting in central diabetes insipidus, or excess ADH release resulting in water retention, and the syndrome of inappropriate ADH secretion (SIADH). Additionally, an ADH-independent condition, cerebral salt wasting syndrome (CSWS) can occur after neurosurgical interventions.

Diabetes insipidus (DI) is defined as the presence of inappropriate hypotonic polyuria in the presence of high or normal serum sodium [24]. While the presence of serum hyperosmolality and hypernatremia are suggestive of DI, these findings may be absent if the patient is conscious, with an intact thirst mechanism and access to free water. Thus, to screen for potential development of postoperative DI, close measurement of urine output and fluid intake, urine specific gravity, and serum sodium are vital. Treatment includes replacement of urine/fluid losses as well as administration and titration of vasopressin or desmopressin (the former having a shorter duration of action and thus easier to titrate if water metabolism continues to evolve). While DI can be transient or permanent, the risk of permanent DI is higher in younger patients, males, those with large intrasellar masses [25], in those with a preoperative diagnosis of DI, and following surgery for craniopharyngioma [26].

While DI is the predominate process resulting in hypernatremia, intracranial neoplasms and their treatment can also result in hyponatremia. In fact, hyponatremia occurs in 10–15% of pediatric patients following intracranial tumor surgery [27, 28]. Postoperative hyponatremia is commonly associated with two conditions: the syndrome of inappropriate antidiuretic hormone (SIADH) and CSWS. Unfortunately, clinical distinction between the two can be challenging; however, it is vitally important as their treatment is divergent (Table 3.2).

SIADH is a syndrome of hypoosmolar hyponatremic euvolemia. It is characterized by an even fluid balance/euvolemia, hyponatremia, hypoosmolality, increased urine osmolality, and elevated urine sodium concentration in an individual with normal salt and water intake [29]. These symptoms are a result of excessive ADH release and therefore increased water reabsorption from the glomerular filtrate at the distal nephron. This produces inappropriately concentrated urine despite serum hypoosmolality. The key feature distinguishing SIADH from CSWS is volume status as SIADH is a state of euvolemia, while CSWS is one of hypovolemia. Thus, patients with SIADH will be unlikely to have changes in blood pressure, body weight, heart rate, or other signs associated with volume loss. Once the diagnosis of SIADH has been established, it is treated with fluid restriction and possible administration of diuretics such as furosemide.

On the other hand, CSWS is a syndrome marked by hypovolemia and/or net negative fluid balance, hyponatremia and serum hypoosmolality, and an elevated urine osmolality and elevated urine sodium [29]. CSWS is caused by excessive renal sodium and water excretion and is often associated with an increase in urine output [30]. The sodium excretion is higher than that of water, and therefore the urine is inappropriately concentrated. Again, accurate assessment of volume status

**Table 3.2** Differentiation of sodium abnormalities

| | DI: Diabetes insipidus | SIADH: Syndrome of inappropriate antidiuretic hormone | CSW: Cerebral salt wasting |
|---|---|---|---|
| **Disorder** | ADH Deficit<br>Decreased reabsorption of water by the distal tubules of the kidney<br>Loss of free water in the urine | ADH Excess<br>Inappropriate secretion of ADH<br>Increased permeability of renal distal tubules and increased water reabsorption | Renal sodium loss<br>Decreased renal sodium reabsorption<br>Free water loss |
| **Volume status** | Decreased, hypovolemia | Increased; fluid overload | Decreased, hypovolemia |
| **CVP** | Decreased | Normal or increased | Decreased |
| **Weight** | Decreased | Normal or increased | Decreased |
| **Salt balance** | Variable | Variable | Negative |
| **Serum sodium** | Increased | Decreased | Decreased |
| **Urine sodium** | Decreased or normal | Increased | Markedly increased |
| **Serum osmolality** | Increased | Decreased | Increased or normal |
| **Urine osmolality** | Decreased | Increased | Increased |
| **Urine spec gravity** | Decreased | Increased | Normal or slightly increased |
| **Signs/ symptoms** | Polyuria, hypoosmolar urine (clear), hyperosmolar plasma, hypernatremia, thirst, polydipsia, dehydration, shock, fatigue, mental status changes, seizure, irritability, lethargy, tachycardia, poor perfusion | Decreased concentrated urine, hyponatremia, hypertension, mental status changes, seizures, lethargy, nausea, vomiting | Differentiate from SIADH with confirmed hypovolemia<br>Anorexia, nausea, vomiting, weakness, hypotension, tachycardia, poor skin turgor, syncope |
| **Treatment** | Evaluate and replace fluid/ urine loss frequently<br>Administer and titrate vasopression (IV or DDAVP) for UO M 2 mL/ kg/h.<br>Prevent overtreatment, hypernatremia correction should be about 2 mEq/L/h | Restrict fluids and consider giving furosemide<br>Correct hyponatremia with 3% NaCL infusion for goal sodium of >/= 125 mEq/L. Replaced deficit over 24–48 h. Observe for water intoxication and cerebral edema due to rapid overcorrection of hypernatremia | Isotonic saline volume loss replacement<br>Enteral sodium replacement<br>Use of 3% saline is restricted to sodium levels <125 mEq/L and is done over 24 h |

is vital to distinguishing SIADH from CSWS. Classic signs of hypovolemia include hypotension, weight loss, increased heart rate, increased capillary refill time, and loss of skin turgor. Once the diagnosis of CSWS has been established, the mainstay of treatment includes the replacement of the sodium and water lost as a result of pathologic natriuresis and diuresis. Initial management includes administration of isotonic fluids (often normal saline) with the goal of restoring intravascular volume. Once euvolemia is achieved, if hyponatremia persists, management can then be directed at correcting hyponatremia. This can be achieved through oral sodium replacements, hypertonic saline administration, or mineralocorticoid use [29]. Generally speaking, the serum sodium concentration should be corrected slowly with an average increase no more than 0.5 mEq/L/h [31].

Not only do intracranial neoplasms and their treatments cause abnormalities in water metabolism, they can also be associated with endocrinopathies. Such hormone deficiencies are often due to injury of the hypothalamus and/or pituitary (either through direct surgical injury or a delayed effect of radiation therapy). Such injuries can cause partial or total hypopituitarism. The risk of postoperative hypopituitarism varies according to case series and tumor type; however, it peaks at 75% for craniopharyngioma [32]. Pituitary hormone deficiencies can include decreased levels of ACTH, TSH, GH, LH, and FSH.

Adrenal insufficiency (AI) is a potentially life-threatening endocrinopathy. It can present as central AI following neurosurgical intervention (oftentimes pituitary surgery) or as secondary AI due to persistent corticosteroid use. In either case, it must be promptly recognized and treated with glucocorticoid replacement. Additionally, it is vital that patients and families understand the importance of recognizing an adrenal crisis and receive instruction on steroid replacement in times of stress, such as with surgeries or acute illnesses.

Additional endocrinopathies may not be readily apparent postoperatively or immediately following treatment of brain tumors but rather may develop over time. Their deficiencies are often not life-threatening or urgent; however, their normalization can significantly alter a patient's quality of life. One can monitor TSH/T4 for thyroid axis function. Sex hormone monitoring can be done with morning serum testosterone in males or with LH, FSH, and menses history in premenopausal females. The growth hormone axis can be monitored by serum insulin-like growth factor-1 (IGF-1) though if low is often confirmed with a GH stimulation test.

## Radiation Injury and Radiation Necrosis

The nervous system is vulnerable to the effects of radiation, and thus its use in the treatment of brain tumors can be associated with tissue injury at various time points during and after radiation therapy. Acute injury (during or less than 1 month after radiation therapy) is associated with capillary injury with associated leak and edema. Neurologic symptoms can include somnolence, headache, nausea, vomiting, and exacerbation of baseline neurologic deficits and are often responsive to

corticosteroids. Early-delayed injury (1–6 months post radiation therapy) complications are often due to edema and demyelination. Patients may present with somnolence syndrome (increased drowsiness, fatigue, anorexia, irritability), and MRI may demonstrate increased edema and contrast enhancement concerning tumor progression, termed pseudo-progression. Again, symptoms are often responsive to corticosteroids. Late injury (more than 6 months after radiation therapy) is hypothesized to be due to small- to medium-sized vessel injury as well as demyelination and is often referred to as radiation necrosis.

Radiation necrosis is a well-characterized toxicity of brain tumor treatment, which refers to necrotic degradation of brain tissue following intracranial radiation. MRI findings include white matter contrast enhancement, soap-bubble/swiss-cheese enhancement, along with edema and mass effect early followed by volume loss later [33]. These imaging findings may or may not be associated with new neurologic findings such as confusion, seizures, or focal neurologic deficits. Retrospective studies of children report widely varying rates of radiation necrosis of 3–26%. Radiation necrosis poses a challenge as it can occur at any time during and after radiation therapy – from acute (during and immediately after radiation therapy) to late-delayed (months to years after radiation therapy) though most often is a late stage complication of radiation therapy. One meta-analysis found that children treated with proton radiation therapy who presented with radiation necrosis were younger and had shorter time to development of radiation necrosis [34]. Additionally, they found that younger children tended to present with ataxia and older children with headache when diagnosed with radiation necrosis, though this may be due to tumor location (infratentorial vs. supratentorial) in the two age groups. Thus, when a child who has received radiation therapy in the past presents with new MRI changes and/or new neurologic findings, one must consider radiation necrosis as a potential etiology.

Radiation necrosis is thought to occur as a result of cerebral vascular injury. It begins as acute cellular injury with endothelial cell death; this causes platelet aggregation, thrombus formation, and occlusion of microvasculature [35]. Vascular endothelial growth factor (VEGF) is released by the dysfunctional endothelial cells, which results in capillary leakage, brain edema, neuronal demyelination, and damage of the blood-brain barrier. It is hypothesized that radiation leads to cellular injury and vascular damage, which in turn leads to tissues hypoxia. This results in degradation of collagen, disruption of the blood-brain barrier [36], release of VEGF, capillary leakage [37], perivascular inflammation, and edema. This process can occur throughout the white matter or focally. Total radiation dose, volume of irradiated area, as well as fractionation regimen are predictive of risk of radiation necrosis [38].

Once recognized, there are typically three modalities of treatment for radiation necrosis – corticosteroids, bevacizumab, and hyperbaric oxygen therapy. These can be used alone or in combination [34]. While corticosteroids are often the mainstay of early treatment of radiation necrosis due to their potent anti-inflammatory effects, they are associated with a significant adverse effect profile, making them less likely to be used long term. Bevacizumab is humanized monoclonal antibody that blocks

VEGF, an important mediator of capillary leakage and brain edema [38]. Hyperbaric oxygen is thought to improve tissue oxygenation, which leads to a reduction of inflammation and neovascularization.

## CNS Infection

Central nervous system (CNS) infections are an important cause of neurologic morbidity and mortality in patients with cancer. While the risk of general CNS infections is greatest in those patients with significant and prolonged immunosuppression, patients with CNS tumors pose a unique risk group. Having disrupted the blood-brain barrier with cranial surgery, frequent need for ventricular shunt placement, and skin breakdown from radiation therapy, patients with brain tumors are at risk for cutaneous skin flora infections. Such pathogens include *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Propionibacterium acnes*, and *Candida* species [39, 40]. These patients may or may not manifest typical signs/symptoms of CNS infection, such as fever, headache, nuchal rigidity, if in the midst of chemotherapy, and therefore immunodeficiency [41]. Instead, altered mental status may be the only indication of a CNS infection. Early recognition and diagnosis of CNS infections with prompt initiation of antimicrobials is vital.

## Conclusions

Children with CNS tumors are at risk for a variety of life-threatening and/or neurologic function compromising complications due to their tumors, treatment of their tumors, or indirect effects of their tumors. Prompt recognition and management of these complications has the potential to preserve neurologic function already at risk.

## References

1. Ostrom QT, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2009–2013. Neuro-Oncology. 2016;18(suppl_5):v1–v75.
2. Ostrom QT, et al. Alex's lemonade stand foundation infant and childhood primary brain and central nervous system tumors diagnosed in the United States in 2007–2011. Neuro-Oncology. 2015;16(Suppl 10):x1–x36.
3. de Blank PM, et al. Years of life lived with disease and years of potential life lost in children who die of cancer in the United States, 2009. Cancer Med. 2015;4(4):608–19.
4. Smith ER, Madsen JR. Cerebral pathophysiology and critical care neurology: basic hemodynamic principles, cerebral perfusion, and intracranial pressure. Semin Pediatr Neurol. 2004;11(2):89–104.

5. Lin AL, Avila EK. Neurologic emergencies in the patients with cancer. J Intensive Care Med. 2017;32(2):99–115.
6. Forsyth PA, Posner JB. Headaches in patients with brain tumors: a study of 111 patients. Neurology. 1993;43(9):1678–83.
7. Stocchetti N, et al. Hyperventilation in head injury: a review. Chest. 2005;127(5):1812–27.
8. Damek DM. Cerebral edema, altered mental status, seizures, acute stroke, leptomeningeal metastases, and paraneoplastic syndrome. Emerg Med Clin North Am. 2009;27(2):209–29.
9. Pater K, Puskulluoglu M, Zygulska AL. Oncological emergencies: increased intracranial pressure in solid tumours' metastatic brain disease. Przegl Lek. 2014;71(2):91–4.
10. Glantz MJ, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the quality standards subcommittee of the American Academy of Neurology. Neurology. 2000;54(10):1886–93.
11. Kerkhof M, Vecht CJ. Seizure characteristics and prognostic factors of gliomas. Epilepsia. 2013;54(Suppl 9):12–7.
12. Ruda R, et al. Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments. Neuro-Oncology. 2012;14(Suppl 4):iv55–64.
13. Vecht CJ, Kerkhof M, Duran-Pena A. Seizure prognosis in brain tumors: new insights and evidence-based management. Oncologist. 2014;19(7):751–9.
14. Cavaliere R, Farace E, Schiff D. Clinical implications of status epilepticus in patients with neoplasms. Arch Neurol. 2006;63(12):1746–9.
15. Brophy GM, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17(1):3–23.
16. Rossetti AO, et al. Levetiracetam and pregabalin for antiepileptic monotherapy in patients with primary brain tumors. A phase II randomized study. Neuro-Oncology. 2014;16(4):584–8.
17. Pollono D, et al. Spinal cord compression: a review of 70 pediatric patients. Pediatr Hematol Oncol. 2003;20(6):457–66.
18. Lewis DW, et al. Incidence, presentation, and outcome of spinal cord disease in children with systemic cancer. Pediatrics. 1986;78(3):438–43.
19. Patchell RA, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet. 2005;366(9486):643–8.
20. Sylvester RK, Fisher AJ, Lobell M. Cytarabine-induced cerebellar syndrome: case report and literature review. Drug Intell Clin Pharm. 1987;21(2):177–80.
21. Herzig RH, et al. Cerebellar toxicity with high-dose cytosine arabinoside. J Clin Oncol. 1987;5(6):927–32.
22. Kwong YL, Yeung DY, Chan JC. Intrathecal chemotherapy for hematologic malignancies: drugs and toxicities. Ann Hematol. 2009;88(3):193–201.
23. Prete A, Corsello SM, Salvatori R. Current best practice in the management of patients after pituitary surgery. Ther Adv Endocrinol Metab. 2017;8(3):33–48.
24. Fenske W, Allolio B. Clinical review: current state and future perspectives in the diagnosis of diabetes insipidus: a clinical review. J Clin Endocrinol Metab. 2012;97(10):3426–37.
25. Loh JA, Verbalis JG. Diabetes insipidus as a complication after pituitary surgery. Nat Clin Pract Endocrinol Metab. 2007;3(6):489–94.
26. Mortini P, et al. Neurosurgical treatment of craniopharyngioma in adults and children: early and long-term results in a large case series. J Neurosurg. 2011;114(5):1350–9.
27. Williams C, et al. Hyponatremia with intracranial malignant tumor resection in children. J Neurosurg Pediatr. 2012;9(5):524–9.
28. Williams CN, et al. The incidence of postoperative hyponatremia and associated neurological sequelae in children with intracranial neoplasms. J Neurosurg Pediatr. 2014;13(3):283–90.
29. Yee AH, Burns JD, Wijdicks EF. Cerebral salt wasting: pathophysiology, diagnosis, and treatment. Neurosurg Clin N Am. 2010;21(2):339–52.
30. Hardesty DA, Kilbaugh TJ, Storm PB. Cerebral salt wasting syndrome in post-operative pediatric brain tumor patients. Neurocrit Care. 2012;17(3):382–7.
31. Adrogue HJ, Madias NE. Hyponatremia. N Engl J Med. 2000;342(21):1581–9.

32. Lo AC, et al. Long-term outcomes and complications in patients with craniopharyngioma: the British Columbia Cancer Agency experience. Int J Radiat Oncol Biol Phys. 2014;88(5):1011–8.
33. Rogers LR, et al. Morphologic magnetic resonance imaging features of therapy-induced cerebral necrosis. J Neuro-Oncol. 2011;101(1):25–32.
34. Drezner N, et al. Treatment of pediatric cerebral radiation necrosis: a systematic review. J Neuro-Oncol. 2016;130(1):141–8.
35. Sundgren PC, Cao Y. Brain irradiation: effects on normal brain parenchyma and radiation injury. Neuroimaging Clin N Am. 2009;19(4):657–68.
36. Greene-Schloesser D, et al. Radiation-induced brain injury: a review. Front Oncol. 2012;2:73.
37. Sadraei NH, et al. Treatment of cerebral radiation necrosis with bevacizumab: the cleveland clinic experience. Am J Clin Oncol. 2015;38(3):304–10.
38. Delishaj D, et al. Bevacizumab for the treatment of radiation-induced cerebral necrosis: a systematic review of the literature. J Clin Med Res. 2017;9(4):273–80.
39. Pruitt AA. Central nervous system infections in cancer patients. Semin Neurol. 2004;24(4):435–52.
40. Pruitt AA. CNS infections in patients with cancer. Continuum (Minneap Minn). 2012;18(2):384–405.
41. Baldwin KJ, Zivkovic SA, Lieberman FS. Neurologic emergencies in patients who have cancer: diagnosis and management. Neurol Clin. 2012;30(1):101–28. viii