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Neurological complications of pediatric cancer

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Abstract
Both the onset of various malignancies as well as the treatment of cancer can lead to neurologic symptoms which can be difficult to diagnose. In this review, we highlight the varied ways in which neurologic sequelae of cancer and its treatment manifest in children. Initial neurologic presentation may be secondary to mass effect or to immune-mediated paraneoplastic syndromes. Treatment effects on the nervous system may arise from surgery, chemotherapy, radiation, or bone marrow transplantation. In addition, the rapidly expanding field of immunotherapies for cancer has generated numerous new approaches to eradicating cancer including monoclonal antibodies, checkpoint inhibitors, and chimeric antigen receptor T cells (CAR-T cells), which have neurologic side effects mediated by immune responses that are also being recognized. Here we review common consult questions to the neurologist and our general approach to these scenarios including altered mental status, headaches, seizures, and sensorimotor complaints, considering the multifactorial nature of each.

Keywords Childhood cancer · Neurology · Chemotherapy · Immunotherapy

1 Introduction

The fields of both neurology and oncology are rapidly advancing with new treatment strategies and new understandings of pathophysiology of disease. Neurologic symptoms may herald the presence of an underlying oncologic diagnosis, and they may also arise in oncology patients as complications of the cancer or its treatments. As such, in this review, we will explore the common intersections of the two specialties, including neurologic presentations of cancer or cancer recurrence, paraneoplastic syndromes, and neurological complications of cancer treatments. We will also explore the neurologist's approach to common consult questions from oncology.

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2 Neurologic symptoms caused by tumor mass effect or tumor invasion of the nervous system

2.1 Brain tumors

In children, the most common symptoms of primary or metastatic central nervous system (CNS) tumors include headache, nausea/vomiting, seizures, head tilt, diplopia or squinting, ataxia, and behavioral changes [1, 2]. Focal neurologic findings depend on the eloquent functions of the brain area involved and can include hemiparesis, unilateral sensory changes, speech changes, hyperreflexia, spasticity, ataxia, cranial nerve abnormalities, stridor, vision changes, and endocrine abnormalities [3]. Suprasellar tumors can cause proptosis, hydrocephalus, and diencephalic syndrome (consisting of vision abnormalities, headaches, pallor, vomiting, and failure to thrive), though initial symptoms are often endocrine in nature with delayed puberty, obesity, diabetes insipidus (DI), growth failure, or panhypopituitarism [4–6]. More rarely, brain tumors, metastases, and hematologic cancers can present with unusual neurologic symptoms such as subacute meningitis, subdural collections, and psychiatric symptoms including psychosis, anxiety, and behavioral changes [5–9].

2.2 Spinal cord

Spinal cord tumors are uncommon in children, representing < 10% of all CNS tumors in this population [10]. Tumors of the spine, including spinal presentations of hematologic malignancies, typically present first with pain followed by weakness and sensory changes. Cord compression and cauda equina syndrome cause urinary and fecal incontinence or retention symptoms as well as sexual dysfunction [7, 8].

2.3 Meninges, nerve roots, plexuses, and peripheral nerves

Multiple primary tumors can spread along the meninges, including ependymoma, pineoblastoma, medulloblastoma, leukemia, lymphoma, and neuroblastoma [3, 9]. This process can cause increased intracranial pressure (ICP), encephalopathy, and focal neurologic symptoms. When nerve roots are involved, multiple cranial or peripheral neuropathies may be observed.

3 Paraneoplastic autoimmune complications

Paraneoplastic disorders are defined as remote effects of cancer not attributable to metastases, treatments or other illnesses [11]. They are caused by immunologic cross-reactivity between tumor antigens and neuronal tissue which can lead to immune destruction of any part of the nervous system. In pediatrics, the most common paraneoplastic syndromes include opsoclonus myoclonus syndrome and limbic encephalitis, particularly a subclass of limbic encephalitis called NMDA-receptor (NMDA-R) encephalitis. Myasthenia gravis can also be a paraneoplastic syndrome, as it can present along with thymoma in 15–20% of adults and can be seen in children with thymomas [12, 13]. Other clinical syndromes are associated with paraneoplastic antibodies as well and are discussed below. See criteria for paraneoplastic syndromes in Table 1.

The incidence of paraneoplastic syndromes in children is unknown, but they are rare, occurring in < 1% of adult cancers. Cancers composed of neuroendocrine cells, affecting immunoregulatory organs, or containing neuronal tissue (i.e., B cell and plasma cell cancers, small cell lung cancer (SCLC), neuroblastoma, thymoma) are most likely to present with paraneoplastic syndromes [13]. Paraneoplastic syndromes are thought to arise due to antigen-driven clonal expansions of T cells. However, some syndromes such as opsoclonus-myoclonus-ataxia syndrome (OMAS) may involve both B and T cells [13, 14]. In autoimmune non-paraneoplastic versions of these diseases, B cell therapies such as rituximab are often effective for management of refractory cases. This suggests that there is heterogeneity in mechanism among different antibodies and targets [16, 17].

Table 1 Criteria for diagnosis of paraneoplastic syndrome [14, 15]

Definite:
1) Classic syndrome[a] with cancer diagnosed within 5 years of symptom onset
2) Non-classic syndrome that resolves or improves with cancer treatment without immunotherapy (provided that the syndrome is not susceptible to spontaneous remission)
3) Non-classic syndrome with cancer diagnosed within 5 years of symptom onset and positive for antineuronal antibodies
4) Neurologic syndrome with or without cancer, with well-characterized onconeuronal antibodies (Hu, Ri, Yo, CRMP5/CV2, Ma-2, or amphiphysin)
Possible:
1) Classic syndrome[a] with high risk of cancer (e.g. a genetic or syndromic diagnosis with predisposition) without antineuronal antibodies
2) Neurologic syndrome with or without cancer, with partially characterized antineuronal antibodies
3) Non-classic syndrome without antineuronal antibodies, with cancer diagnosed within 2 years of neurologic symptom development

[a] Classic syndromes were originally defined as encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus myoclonus syndrome, subacute sensory neuronopathy, chronic gastrointestinal pseudo-obstruction and Lambert-Eaton myasthenic syndrome [11]

In children, the criteria for diagnosis of paraneoplastic syndrome remain the same as for adults (Table 1). However, a modification to decrease the maximal interval between neurologic symptom presentation and diagnosis of tumor has been proposed, since the more common types of tumors in children (e.g., neuroblastoma, teratoma, and lymphoma) tend to present more quickly than common tumors in adults [13]. In addition, the sensitivity and specificity of antibody panels are not yet known in children, while 70–80% of adults with initial presentation of paraneoplastic syndromes will have a positive antibody screen [15]. Further complicating the picture, the same clinical syndromes can be present with autoimmune non-paraneoplastic antibodies. This is particularly true for children. For example, approximately 10% of children with NMDA-R antibodies have an underlying tumor, while in adults, a tumor is found in up to 60% of cases. Furthermore, there are also case reports of classically paraneoplastic antibodies such as anti-Hu (antineuronal nuclear antibody-1 or ANNA-1) occurring without tumors in children, but not adults [18–21]. Similarly, voltage-gated potassium channel (VGKC) complexes (which include proteins called CASPR2—contactin associated protein-like 2—and LGI1—leucine-rich glioma-inactivated 1) have been seen in adult patients with paraneoplastic disorders such as limbic encephalitis. However, in a recent review of 37 studies of children with VGKC antibodies, none of the children with CASPR2- or

LGI1-associated encephalitis had underlying tumors [11, 22–24].

When evaluating for paraneoplastic disorders, symptoms should first be fully characterized and antibodies sought from serum (Table 2). Additional CSF studies may show oligoclonal bands, elevated IgG index, and moderate leukocytosis [11]. There are no guidelines outlining the need for screening for tumors in children given the lower incidence of underlying tumor in this population. However, screening in cases thought to be paraneoplastic may start with ultrasound of the abdomen and pelvis including the testes in boys [15]. If suspicion is high, magnetic resonance imaging (MRI) or computed tomography (CT) scan should be pursued if ultrasound is negative. In cases of classic paraneoplastic syndromes with high suspicion of underlying malignancy, for example in the setting of classically paraneoplastic antibodies, a fluorodeoxyglucose positron emission tomography (FDG-PET) scan or another specialized nuclear study may be considered if other modalities are all negative. Imaging can be repeated over time if symptoms do not remit with treatment. In a study of 20 adults with paraneoplastic neurological syndromes, sensitivity of FDG-PET for detecting malignancy was > 83%, while another study found sensitivity of CT in antibody-positive adults was only 30% [13, 28, 29].

Once diagnosed, treatment modalities for paraneoplastic syndromes include prompt removal of tumors and initiation of cancer treatment; immunosuppression with corticosteroids, intravenous immunoglobulin (IVIg), plasma exchange (PLEX); and when refractory to initial management, chemotherapeutic agents such as cyclophosphamide and rituximab. Generally, patients with antibodies to membrane proteins seem to respond better to immunosuppressive therapies than those with antibodies to intracellular proteins, although there are some reports of improvement in children with immunotherapies despite the presence of intracellularly directed antibodies such as anti-Hu [30–32]. Speech, physical, behavioral, and occupational therapy are also important for functional recovery even after treatment of both the malignancy and the paraneoplastic syndrome [13].

3.1 Opsoclonus myoclonus ataxia syndrome (OMAS)

OMAS requires three of four key features for diagnosis: (1) abnormal eye movements called opsoclonus, (2) ataxia and/or myoclonic jerks, (3) behavior or sleep changes (e.g. emotional lability, drooling, hypotonia, speech changes), and (4) diagnosis of neuroblastoma [11, 13, 33]. The syndrome is thought to be due to autoantibodies against cerebellar targets and is rare, but when it occurs, up to 50% of children will have an underlying neuroblastoma (while on the other hand, only 2–3% of children with neuroblastoma will have OMAS) [34]. Most cases in both children and adults have negative antibody screening, although there have been case reports of antibodies to Hu being associated with OMAS in children with neuroblastoma [18, 31, 35, 36]. Other reported antibodies seen associated with OMAS and neuroblastoma or ganglioneuroblastoma include neuroleukin, gliadin, Ri (antineuronal nuclear antibody-2 or ANNA-2), and Zic2 (zinc finger associated protein 2) [11]. In addition, OMAS has also been seen with other tumors including hepatoblastoma and ganglioglioma [11, 37].

In cases of OMAS, screening for tumors with CT may be more sensitive in the abdomen than MRI due to better ability to detect small calcifications, while MRI is favored for thoracic tumors. Workup should also include urine catecholamine metabolites (vanillymandelic acid and homovanillic acid) and potentially a nuclear metaiodobenzylguanidine (MIBG) scan, although the latter should be interpreted with caution in patients on adrenocorticotropic hormone (ACTH). These tests, when positive, are supportive of a diagnosis of neuroblastoma, though sensitivity of urine catecholamines scans may be as low as 24% [11, 14, 38–40]. While immunomodulatory therapy improves symptoms in children more consistently than adults, there is a high incidence of residual motor, speech, behavioral, and sleep disorders, and symptoms frequently relapse during illnesses [13, 14].

3.2 Limbic encephalitis

Limbic encephalitis is characterized by personality changes, irritability, decreased speech, depression, hallucinations, memory loss, seizures, autonomic instability, and cognitive dysfunction. In children, movement disorders are a common initial symptom and can include dyskinesias, stereotypies, chorea, ataxia, athetosis, gait disturbance, or dystonia [41–43]. Initial cases in adults, described in 2007, were associated with ovarian teratomas expressing NMDA receptors, and subsequent reports of hundreds of cases of both paraneoplastic and non-paraneoplastic anti-NMDA receptor (NMDA-R) encephalitis have emerged [19, 44–46]. Tumors are less commonly found in children with limbic encephalitis compared with adults, but ovarian teratomas, neuroblastoma, germ cell tumors, testicular tumors, thymomas, and Hodgkin's lymphoma have all been found in association with limbic encephalitis in children [11, 13, 20].

In addition to NMDA-R antibodies, other antibodies found in children presenting with paraneoplastic limbic encephalitis include those against Hu, Ma-2 (Ta), SOX-1 (SRY-box 1), PCA-2 (Purkinjie cell cytoplasmic antibody 2), glycine receptor, mGluR5 (metabotropic glutamate receptor 5), CRMP5/CV2 (collapsin response mediator protein 5), and amphiphysin [11, 18, 47–49]. Anti-GAD65 (glutamic acid decarboxylase 65) antibodies are nonspecific but have been associated with limbic encephalitis in children, with more specific prognostic information obtained by adding $GABA_A$ and $GABA_B$ receptor antibody testing [50]. Antibodies

Table 2 Known pediatric paraneoplastic syndromes and antibodies

Paraneoplastic syndrome	Symptoms	Associated malignancies	Associated antibodies
Opsoclonus Myoclonus Ataxia Syndrome (OMAS)	- Opsoclonus - Ataxia - Myoclonic jerks, - Emotional lability - Drooling - Hypotonia - Speech, sleep difficulties	- Neuroblastoma (in up to 50% of cases) - Ganglioblastoma - Ganglioglioma - Hepatoblastoma - In adults: breast, ovarian, SCLC	- Usually antibody negative - Hu, neuroleukin, gliadin, Zic2 - In adults: Ri, CRMP5/CV2, Yo, Ma-2
Limbic encephalitis (including NMDA-R, anti Ma-2, Ophelia syndrome subtypes)	- Personality changes - Irritability - Depression - Hallucinations - Seizures - Memory loss - Cognitive dysfunction - Autonomic dysfunction +/− medial temporal lobe lesions - Movement disorders in NMDA-R encephalitis	- Hodgkin lymphoma - Ovarian teratoma or carcinoma - Testicular tumors - Germ cell tumors - Thymoma - Neuroblastoma - In adults: SCLC	- NMDA-R, Ma-2, mGluR-5, Hu, GAD65, $GABA_A$ receptor, $GABA_B$ - receptor, glycine receptor, VGKC (CASPR2 & LGI1), CRMP5/CV2, amphiphysin, SOX-1, PCA-2 - In adults: Ri, AMPA receptor, DPPX
Subacute cerebellar degeneration	- Vestibular symptoms - Dizziness, ataxia - Psychiatric symptoms - Parkinsonism - Motor tics - Dystonia - Sleep disturbances	- Hodgkin and non-Hodgkin lymphoma - Langerhans cell histiocytosis - Neuroblastoma - In adults: SCLC, gynecologic cancer, breast cancer, thymoma	- Tr, mGluR-1, mGluR-2 - In adults: dopamine 2 receptor, Yo, PCA-2, Hu, Ri, ANNA-3, GAD65, CRMP5/CV2, Zic4, VGCC, amphiphysin
Necrotizing myelopathy	- Usually thoracic ascending sensory deficits - Autonomic dysfunction - Flaccid or spastic paraplegia - Enhancing spinal cord lesions - Elevated CSF protein	- Leukemia - Melanoma	- In adults: CRMP5/CV2, amphiphysin, AQP4, Hu
Subacute sensory neuronopathy	- Asymmetric pain and paresthesias with sensory ataxia, +/− encephalitis	- Hodgkin's and non-Hodgkin's lymphoma - In adults: SCLC, plasma cell cancer, breast cancer	- Hu, CRMP5/CV2, amphiphysin, MAG
Subacute motor neuronopathy	- Painless asymmetric flaccid weakness [25, 26]	- Hodgkin and non-Hodgkin lymphoma - In adults: SCLC, breast cancer	- Hu, GM1, Gd1b
Myasthenia gravis	- Fatigable weakness affecting skeletal muscles	- Thymoma	- AChRs (usually), MuSK
Lambert Eaton myasthenic syndrome (LEMS)	- Weakness on waking, improves with exercise - Autonomic dysfunction	- Neuroblastoma - In adults: SCLC	- VGCC P/Q type - In adults: Hu, Sox-1
Chronic intestinal pseudoobstruction	- Recurrent episodes of apparent obstruction of the small intestine +/− other areas of the GI tract without physical obstruction [27]	- Neuroblastoma - In adults: SCLC, carcinoid, thymoma	- Hu, antibodies targeting enteric nervous system - In adults: VGKC

ANNA = antineuronal nuclear antibody, AQP4 = aquaporin 4, CASPR2 = contactin associated protein-like 2, CRMP5/CV2 = collapsin response mediator protein 5, DPPX = dipeptidyl aminopeptidase-like protein 6, GAD65 = glutamic acid decarboxylase 65, GM1 = ganglioside GM1, Gd1b = ganglioside Gd1b, Hu = ANNA-1, LGI1 = leucine-rich glioma-inactivated 1, MAG = myelin associated glycoprotein, mGluR = metabotropic glutamate receptor, NMDA-R = NMDA receptor, PCA-2 = Purkinjie cell cytoplasmic antibody 2, Ri = ANNA-2, SCLC = small cell lung cancer, SOX-1 = SRY-box 1, Tr = Purkinjie cell cytoplasmic antibody Trotter antigen, VGCC = voltage gated calcium channels, VGKC = voltage gated potassium channels, Yo = PCA1, Zic = zinc finger associated protein

against Ma-2 cause a unique syndrome of isolated or combined limbic, diencephalic, or brainstem dysfunction often with eye movement abnormalities and more frequent MRI abnormalities including nodular enhancement that can mimic tumor [11]. Limbic encephalitis associated with mGluR5 receptor antibodies presents with primarily psychiatric, cognitive, and memory impairments, sometimes known as Ophelia syndrome, and has been reported in children with Hodgkin lymphoma [49].

Evaluation for limbic encephalitis requires CSF antibody analysis, which is more sensitive for detection of NMDA-R antibodies than serum analysis [51]. Supportive features for limbic encephalitis include moderate CSF pleocytosis (lymphocyte-predominant, present in 80% of cases), elevated protein (30% of cases), oligoclonal bands (50–60% of cases), or positive IgG index; electroencephalogram (EEG) with slowing or epileptiform activity; and contrast enhancement or FLAIR changes on MRI in limbic areas, cortex, deep gray structures, cerebellum, or brainstem [11, 52]. None of these features is always present, particularly early in the course.

3.3 Subacute cerebellar degeneration (SCD)

SCD presents with vestibular symptoms, dizziness, ataxia, dysarthria, diplopia, psychiatric symptoms, parkinsonism, tics, dystonia, and sleep disturbances developing in a subacute fashion secondary to destruction of cerebellar Purkinje cells [53]. Progressive cerebellar degeneration is found on MRI, sometimes with enhancement, and FDG-PET scan demonstrates hypermetabolism of the cerebellum followed by hypometabolism later in the course [14].

In children, SCD has been best described in association with Hodgkin lymphoma and antibodies against Tr (Purkinje cell cytoplasmic antibody Trotter antigen) and mGluR-1 (metabotropic glutamate receptor 1), though it can be seen in non-Hodgkin lymphoma as well. A case of SCD with ataxia and speech difficulty associated with antibodies to GluR-2 (glutamate receptor 2) has also been seen in Langerhans cell histiocytosis [54]. In adults, the classic antibody, anti-Yo (Purkinje cell cytoplasmic antibody 1 or PCA-1), is usually related to breast or gynecologic cancer, and SCLC can produce any of a number of antibodies that have been associated with SCD [14, 55].

If not treated early in the course, irreversible damage to cells can occur. Clonazepam may provide symptomatic treatment in some cases. In addition to typical immunomodulatory therapy, tacrolimus plus prednisone, mycophenolate, and rituximab have been reported to have benefit in case reports and series, but no controlled trials have been performed [53, 56].

3.4 Necrotizing myelopathy

Necrotizing myelopathy is a rare paraneoplastic syndrome, but it has been described in older children with leukemia and skin cancer [25, 57]. Symptoms typically begin in the thoracic spine with flaccid or spastic paralysis, ascending sensory deficits, and autonomic dysfunction that progresses over days to weeks and can lead to respiratory failure. Imaging can show longitudinally extensive lesions which can enhance with contrast, and CSF can have elevated protein without pleocytosis. It has been hypothesized that some cases may be secondary to neuromyeltis optica (NMO) associated antibodies to aquaporin 4 (AQP4), which have been seen in the setting of breast, cervical, lung, thyroid, pituitary, and B cell malignancies in adults as young as 18 years, though it remains unclear if this antibody is specific enough to be considered paraneoplastic [25, 58].

3.5 Subacute sensory neuronopathy

Subacute sensory neuronopathy presents with vibratory and proprioception loss followed by pain and temperature loss with sensory ataxia, hyporeflexia, and a non-length dependent decrease in sensory action potentials. About 20% of all cases (most in adults) are paraneoplastic, most commonly associated with SCLC and Hu antibodies. This syndrome has also been seen in children with Hodgkin lymphoma [13].

3.6 Myasthenia gravis

Myasthenia Gravis presents with fatigable weakness of proximal limb muscles, ocular muscles, and/or bulbar muscles. The characteristic pattern of decrement with repetitive stimulation and jitter on electromyography (EMG) can confirm the diagnosis [11]. It is caused by antibodies to acetylcholine receptors (AChRs) or muscle-specific tyrosine kinase (MuSK). Paraneoplastic causes of myasthenia gravis tend to present with more classic generalized weakness, rather than isolated ocular symptoms, and they also tend to have positive serum AChR antibodies or striated muscle antibodies, as opposed to MuSK or a seronegative status [26]. Thymic lymphoid hyperplasia is found in a majority of adults with myasthenia gravis, though the percentage of children with this finding is unknown. Treatment is with thymectomy (if AChR antibodies are present), symptomatic treatment with cholinesterase inhibitors, and immunotherapy, though steroids must be used with caution in this population [11].

3.7 Lambert Eaton myasthenic syndrome (LEMS)

LEMS is characterized by episodic muscle weakness, hyporeflexia, autonomic dysfunction, and a characteristic EMG pattern of decremental response to low-frequency repetitive stimulation and facilitation with high-frequency stimulation or exercise. It is more often paraneoplastic than autoimmune. In adults, it is most often seen with SCLC but in children, it can be secondary to neuroblastoma [13, 59].

Antibodies against the P/Q type calcium channels (VGCC) and Sox-1 have been reported in association with LEMS [26].

4 Treatment-related neurologic effects

Neurologic side effects of cancer treatments are common, and understanding the causes, prognosis, and treatments of these symptoms may help avoid unnecessary adjustments in the treatment regimen to less effective alternatives. Here, we review the most common neurologic complications of cancer treatment.

4.1 Lumbar punctures

Frequent lumbar punctures for both monitoring of disease as well as for delivery of intrathecal medications can lead to CSF leaks and low-pressure headaches. Low-pressure headache should be suspected when headache is predominantly present when standing and relieved with laying down. In most cases, it can be treated with conservative measures such as lying flat and increasing fluid intake. In addition, administration of chemotherapy intrathecally can cause chemical meningitis and arachnoiditis [60].

4.2 Surgery

Surgery involving the brain, spine, or areas around peripheral nerves can cause direct physical injury to the nervous system. When surgery is performed in the brain, vascular injury at the time of surgery can lead to hemorrhage as well as ischemic stroke. Hemorrhage predisposes to seizures and all surgical patients are at the highest risk for seizures in the immediate postoperative period [3]. CSF leaks after dural opening can occur and may be difficult to identify and repair.

One unique entity seen after surgery in the posterior fossa is known as posterior fossa syndrome or cerebellar mutism. Of children undergoing posterior fossa surgery, 25% develop this syndrome beginning 6 to 48 h after surgery. The syndrome is characterized by mutism, supranuclear gaze palsy, high pitched crying, cerebellar dysfunction, and emotional lability. Symptoms often resolve in days to months but can persist in about 50% of cases [4, 60, 61]. In these cases, treatment is supportive and most children should be referred for speech therapy.

4.3 Chemotherapy

Many chemotherapeutic agents have neurologic side effects, particularly when given at high doses or administered intrathecally (IT). Neurologic toxicity can at times require reduction in dose or even switching to alternative therapies if side effects cannot be mitigated [60, 62]. Here we discuss the neurologic side effects of chemotherapeutic agents, which are summarized in Table 3.

Asparaginase causes depletion of antithrombin-III (AT-III) and decreases production of coagulation and thrombolytic proteins. This predisposes to both hemorrhage and thrombosis [63]. Up to 40% of children develop thrombosis after asparaginase administration during induction chemotherapy for leukemia, and this reaches clinical significance in about 5% of cases [60, 77, 78]. In more than half of cases of symptomatic thrombosis, the CNS is affected most commonly as cerebral sinovenous thrombosis (CSVT) [79]. The risk of venous thrombosis is so high with the use of asparaginase during induction chemotherapy for acute lymphocytic leukemia (ALL) that recent studies suggest that the use of prophylactic anticoagulation with enoxaparin or AT-III maintenance should be considered during induction [78, 80]. In a patient with prior venous thrombosis with asparaginase, heparin prophylaxis can be used to allow reintroduction of this agent [81].

Ifosfamide causes an encephalopathy, including confusion, agitation, hallucinations, psychosis, muscle twitching, and incontinence, in about 30% of patients receiving it. These effects usually begin 12 h to several days after infusion and resolve within 3 days of cessation, though prolonged symptoms and even death have been reported [60, 82]. EEG changes include triphasic waves, diffuse slowing, or even nonconvulsive status epilepticus. Because of the risk of seizures, continuous EEG monitoring is recommended in children with altered mental status after ifosfamide infusion [82, 83]. Methylene blue and thiamine have been suggested to prevent or treat neurotoxicity, but in the absence of randomized, controlled trials, the efficacy of these agents is unknown because the encephalopathy typically remits spontaneously. For children who experience this toxicity, slower infusion or lower dose of ifosfamide on reintroduction, or switching to cyclophosphamide, can be considered [60].

Methotrexate has a well-known side effect of leukoencephalopathy. Symptoms consist of encephalopathy, stroke-like symptoms, seizures, and headaches that develop within 2 weeks of administration and typically resolve over weeks, although chronic cases have been reported as well [60, 84]. While only 3–4% of children receiving IT methotrexate are symptomatic, 20% have been found to have T2/FLAIR hyperintensities and diffusion restriction on MRI, sometimes preceding symptom development [60, 84]. The diffusion restriction usually resolves with symptomatic improvement, while changes on T2-weighted images can persist [85]. In a longitudinal analysis of 190 survivors of childhood ALL, children with acute leukoencephalopathy were found to have significantly more long term neurobehavioral dysfunction than those without leukoencephalopathy [86]. Chronic leukoencephalopathy can present with progressive learning disorders, memory loss, gait abnormalities, and incontinence 6 months or more after exposure. Toxicity may be enhanced

Table 3 Neurologic side effects of common chemotherapeutic agents

Chemotherapy	Reported neurologic side effects [60, 63–67]	Timeline
L-Asparaginase	- Encephalopathy, seizures, coma, focal deficits, hyperammonemia, headache, coagulopathy / venous sinus thrombosis	- Encephalopathy begins within 24 h after administration, improves within a few days after discontinuation
Bleomycin	- Seizures, encephalopathy, and visual dysfunction - *Typically occurs when used with other drugs*	–
Blinatumomab	- Seizures, acute or chronic encephalopathy, transient ataxia, tremors, somnolence, speech & coordination dysfunction	- Side effects can resolve with discontinuation
Bortezomib	- Acute encephalopathy, headache, insomnia, PRES, cerebellar syndrome, painful length-dependent small fiber neuropathy, severe poly-radiculopathy or demyelinating neuropathy (rare) - *Reduced risk with subcutaneous administration*	- Peripheral neuropathy usually begins within first 2 months of treatment - Worsens with continued use - Resolves 3–4 months after discontinuation
Brentuximab	- Peripheral neuropathy, PML, chronic encephalopathy [68]	- 80% show improvement in symptoms after discontinuation
Busulfan	- Seizure, headaches, dizziness	- Seizures typically occur within 48 h of administration
Calcineurin inhibitors (cyclosporine, tacrolimus)	- Seizure, PRES, headache, leukoencephalopathy, psychosis, catatonia, akinetic mutism, dysarthria, postural tremor, coma, endothelial injury and vascular complications, peripheral neuropathy	- Symptoms usually occur after drug initiation but can occur months or years later
CAR-T cells	- Encephalopathy (in 40%), headache, seizures (at times intractable), focal neurologic deficits, cerebral edema, strokes	- Inflammatory response within days to weeks - Longer-term neurotoxicity over months
Checkpoint inhibitors (pembrolizumab, nivolumab, ipilimumab, tremelimumab, pidilizumab, durvalumab)	- Hypophysitis, myositis retinopathy, fatigue, headache, CNS vasculitis, PRES, immune-mediated disorders (e.g. aseptic meningitis, AIDP, CIDP, enteric neuropathy, vascular neuropathies, cranial neuropathies, polyradiculopathies, inflammatory myopathies, myasthenia gravis, autoimmune encephalitis, cerebellar degeneration, worsening of existing demyelinating disease)	- Symptoms are usually acutely progressive, arising in days to weeks after starting treatment (sometimes months from treatment)
Chlorambucil	- Seizures, delirium, myoclonus, neuropathy, retinopathy (reported with high doses only)	- Hours to days after exposure [69]
Cladribine	- Headache, generalized weakness, rare myelopathy & Guillain Barre-like syndrome (reported with high doses only)	- Myelopathy 1–3 months after exposure [69]
Corticosteroids	- PRES, proximal muscle weakness	- Myopathy onset within 1 month of initiation
Cyclophosphamide	- Encephalopathy with dizziness, blurred vision, confusion, seizures, RCVS [63, 70] (rare)	- Symptoms are typically mild, reversible
Cytarabine (Ara-C)	- Seizures, PRES, RCVS, headache, subacute cerebellar syndrome, encephalopathy, transverse myelitis, peripheral neuropathy, chemical meningitis, arachnoiditis, cauda equina abnormalities [71]	- Most symptoms occur within hours to days of infusion - Cerebellar syndrome 6–8 days after therapy - Transverse myelitis 48 h - 2 weeks after intrathecal (IT) administration
Dinutuximab	- Pain, sensory neuropathy, PRES, reversible internal ophthalmoplegia manifesting as mydriasis/loss of accommodation, rare transverse myelitis [72]	- Onset during or immediately after exposure - Reversible
Doxorubicin	- Intra-arterial administration: hemorrhagic necrosis and cerebral infarcts - Inadvertent IT administration leads to ascending myelopathy/encephalopathy which can be fatal	- Limited to time of administration
Etoposide	- Severe headache, seizures, encephalopathy	- During or after high-dose IV infusions
Fludarabine	Deterioration of vision (either optic neuritis or cortical blindness), seizures, ataxia, tremor, demyelinating T2 lesions in brain & spine, PML	- Onset typically during treatment with resolution but can be delayed 21–60 days after administration and progressive
5-Fluorouracil	- Acute cerebellar syndrome (2–4%), headache, seizures,encephalopathy, optic neuropathy, extrapyramidal disorders, leukoencephalopathy	- Typically begin during infusion and resolve within weeks [73]
Gemcitabine	- Headache, seizures, PRES (rare)	- During or immediately after exposure
Ifosfamide	- Encephalopathy, delirium, seizures, focal motor deficits, facial nerve palsy, aphasia, mutism, visual hallucinations, incontinence, myoclonus, rare sensory neuropathy	- During or immediately after infusion to several days after infusion - Typically resolves within 3 days of cessation
Imatinib	- Seizures, headaches, muscle cramping & myalgias, intracranial bleeding	- Symptoms resolve with discontinuation
Interferons	- Headache, acute encephalopathy, somnolence, cognitive slowing, personality changes, depression, mania, movement disorders, visual dysfunction	- Symptoms typically arise during course of treatment - Resolve slowly with discontinuation
Interleukins	- Fatigue, headache, Increased permeability of blood brain barrier, increased ICP, cerebral edema, focal neurologic deficits, neuropsychiatric symptoms	- Onset 2–22 days after initiation of treatment - Resolve over weeks

Table 3 (continued)

Chemotherapy	Reported neurologic side effects [60, 63–67]	Timeline
Irinotecan	- Dizziness, insomnia, occasional episodes of dysarthria	- Resolve completely with discontinuation
Methotrexate	- Seizures, headache, transient focal neurologic deficits, PRES, leukoencephalopathy, transverse myelitis, chemical meningitis, transient cytotoxic edema, rare ascending para or tetraparesis, chronic progressive learning disorders, memory loss, gait abnormalities, and incontinence	- Transverse myelitis 48 h–2 weeks after IT administration - Leukoencephalopathy usually within 2 weeks of administration (can take months) - Chronic leukoencephalopathy after 6 months
Nelarabine	- Headache, encephalopathy, tremors, seizures, myelopathy and Guillain Barre-like demyelinating neuropathy (rare) [65]	- Symptoms can arise months after exposure and have slow resolution [74]
Nilotinib	- Demyelinating disease (peripheral or central), prothrombotic state, stroke	- Symptoms arise during treatment, may respond to discontinuation [75]
Nitrosureas (carmustine > lomustine)	- Disorientation, lethargy, ataxia, dysarthria, seizures, coma, focal weakness, stroke, optic neuropathy, rare but sometimes fatal necrotizing leukoencephalopathy	- Onset of symptoms can be delayed after administration by up to 6 months
Platinum-based (cisplatin ≫ carboplatin, oxaliplatin)	- Sensory ganglionopathy, hypomagnesemia, muscle weakness, SIADH, cranial neuropathies (ototoxicity, ageusia), ataxia, Lhermitte's phenomenon, urinary retention, acute musculoskeletal pain - Cisplatin: Seizures, stroke, encephalopathy, focal motor deficits, retinopathy, rarely cerebral edema with excess hydration - Oxaliplatin: acute cold allodynia (associated with neuromyotonia)	- Usually, peripheral neuropathy begins within first 2–6 months of treatment - Worsens with continued use - Can worsen for several months after discontinuation (coasting), - Incomplete resolution over 6–8 months after discontinuation
Procarbazine	- Somnolence, depression, headache, obtundation, psychosis, hypertensive encephalopathy	- Arises during treatment course and resolves with discontinuation [69]
Rituximab	- Cerebellar syndrome, PRES, myositis, PML	- Headache, dizziness onset during infusion that resolves after infusion
Retinoids	- Headache (50–80%), elevated ICP, abnormal color vision, rare oculogyric crisis, ataxia	- Resolve with discontinuation
Selumetinib	- CK elevation, proximal arm weakness, pain, cramps, head drop [76]	- Symptoms arise during treatment course
Taxanes (paclitaxel > docetaxel, cabalitaxel)	- Sensory neuropathy (occasionally sensorimotor or proximal motor neuropathy), autonomic and optic neuropathies, scintillating scotomas, rare encephalopathy and seizures	- Peripheral neuropathy begins in first 2 months of treatment, resolves with dis-continuation
Temozolomide	- Increased blood-brain-barrier permeability, increased contrast enhancement on MRI, headache, exacerbation of focal tumor-associated symptoms	- Transient at onset of therapy
Thiotepa	- Seizures, tremors, headache, blurred vision, dizziness, confusion, encephalopathy, chemical meningitis, myelopathy	- Median onset of 2 days after administration
Topotecan	- Headache	- During treatment
VEGF inhibitors (Bevacizumab, Sorafenib, Sunitinib)	- Chronic and hypertensive encephalopathies, PRES, extrapyramidal syndrome, cognitive impairment, rare intracerebral hemorrhage (bevacizumab)	- Rapidly reversible on discontinuation
Vinca alkyloids (vincristine, vinblastine, vindesine, vinorelbine)	- Ataxia, visual hallucinations, tremor, parkinsonism, length dependent sensorimotor neuropathy, mononeuropathies, autonomic and cranial neuropathies (ageusia, optic neuropathy), SIADH, rare encephalopathy, seizures, transient cortical blindness	- Peripheral neuropathy onset in first 2 months of treatment - Worsens with continued use - Can exhibit coasting phenomenon - Effects can be long lasting or have late onset in children

Abbreviations: *PRES* posterior reversible encephalopathy syndrome, *PML* progressive multifocal leukoencephalopathy, *AIDP* acute inflammatory demyelinating polyneuropathy or Guillain Barre syndrome, *CIDP* chronic inflammatory demyelinating polyneuropathy, *RCVS* reversible cerebral vasoconstriction syndrome, *SIADH* syndrome of inappropriate antidiuretic hormone

by prior radiation exposure. In addition, rarely, an ascending para or tetraparesis that can lead to locked-in syndrome or even death has been described, and overdoses can be fatal [63]. In one series of three children with IT methotrexate-associated progressive paraparesis, gadolinium enhancement of ventral lumbosacral spinal nerve roots was seen on MRI in all cases [87].

Tacrolimus can cause tremor, dysarthria, cortical blindness, psychosis, posterior reversible encephalopathy syndrome (PRES), refractory status epilepticus, and prolonged coma. Endothelial cell injury can lead to blood brain barrier breakdown as well as vascular complications including hemorrhage and stroke. On MRI, leukoencephalopathy that can include the brainstem can be seen and may lag behind clinical symptoms [70, 88].

4.3.1 Common side effects of multiple chemotherapeutic agents

Chemotherapy-induced peripheral neuropathy (CIPN) is a common complication of many chemotherapeutic regimens. Vinca alkyloids, platinum-based chemotherapy, taxanes,

bortezomib, and thalidomide are well-known culprits. Symptoms typically begin within the first 2 months of treatment and worsen with ongoing administration of the offending agent. After completion of chemotherapy, symptoms typically stabilize, except in the case of platinum-containing compounds, vinca alkyloids, and thalidomide, in which the symptoms can worsen for several months before stabilization, known as the 'coasting' phenomenon [60, 64, 65, 89].

Posterior reversible encephalopathy syndrome (PRES) has been seen in conjunction with a number of chemotherapeutic agents and suspicion for this entity should be high in children undergoing chemotherapy who develop hypertension, mental status changes, seizures, and focal neurologic symptoms including vision changes. Imaging demonstrates vasogenic edema with T2/FLAIR lesions that may restrict diffusion. Treatment includes normalization of blood pressure, treatment of seizures, and avoidance of metabolic derangements such as hypomagnesemia. Prompt recognition is important because PRES can be complicated by status epilepticus, hemorrhage, or even cerebral edema which can lead to herniation. After prompt treatment, induction chemotherapy can usually continue [90]. Symptoms typically remit over days to weeks, and radiographic lesions usually resolve over 1–2 months; however, in 10% of children with cancer, lesions and symptoms can persist longer [60].

A related condition called reversible cerebrovascular vasoconstriction syndrome (RCVS) typically presents as recurrent thunderclap headaches which can be precipitated or exacerbated by chemotherapies, such as cyclophosphamide, IT cytarabine, or steroids [60, 71]. Imaging demonstrates segmental vasoconstriction that may be subtle early in the course but can persist for up to 12 weeks. In severe cases, RCVS can lead to stroke and intraparenchymal or subarachnoid hemorrhage. Calcium channel blockade with verapamil or nimodipine is often used for treatment of RCVS, though there are no high-quality studies supporting this strategy.

Acute cerebellar syndrome can be seen after IT cytarabine administration as well as with 5-fluorouracil, bortezomib, and rituximab and consists of dysarthria, ataxia, nystagmus, dysmetria, and other cerebellar signs days after administration. It typically resolves within several days to weeks, although persistent symptoms have been seen as well [60, 63, 66].

Progressive multifocal leukoencephalopathy (PML) is caused by reactivation of JC virus and can be seen with brentuximab, efalizumab, infliximab, fludarabine, natalizumab, and rituximab. PML presents with rapidly progressive neurologic symptoms including aphasia, abnormal gait, memory loss, hemiparesis, and vision changes which progress to death over the course of months. Reversal of immunosuppression may be life-saving but can also cause immune reconstitution inflammatory syndrome (IRIS) in which the rapid CNS infiltration of T cells causes additional symptoms [67].

4.4 Immunotherapy

Neurologic side effects of immunotherapies, including monoclonal antibodies, tumor vaccines, checkpoint inhibitors, and CAR-T cells, are common [91]. In addition to agent-specific side effects, neurologic reactions frequently arise due to release of cytokines which can disrupt the function of the blood brain barrier [66]. Monoclonal antibodies and immunoconjugates can cause neurologic effects in up to 50% of patients, likely due to cytokine release [66, 91].

4.5 Checkpoint inhibitors

While most checkpoint inhibitors remain in clinical trials in pediatrics, pembrolizumab, a PD-1 inhibitor, has FDA approval for Hodgkin lymphoma in children [92–94]. Acute neurologic side effects of checkpoint inhibitors are generally inflammatory and can consist of hypophysitis, fatigue, headache, aseptic meningitis, myositis, PRES, plexitis, enteric neuritis, cranial neuropathies, and large vessel CNS vasculitis [66, 95]. Acute or chronic inflammatory demyelinating neuropathies (AIDP or CIDP) or vasculitic neuropathies have been seen in up to 3% of patients. In about 1% of adults receiving checkpoint inhibitors, severe autoimmune neurologic diseases including autoimmune encephalitis, cerebellar ataxia, and myasthenia gravis can be uncovered, and known demyelinating disorders can also be exacerbated [96, 97]. Distinguishing paraneoplastic versus autoimmune presentations is important since it affects treatment options. In general, paraneoplastic autoimmune disease has a more subacute progressive course compared with the faster onset for autoimmune cases triggered by checkpoint inhibitor use. Treatment for checkpoint inhibitor-induced autoimmune neurologic disease typically consists of steroids, IVIg, and PLEX as first line while rituximab, mycophenolate, cyclophosphamide, and methotrexate can also be considered as second-line [97, 98]. The risks and benefits of use or continuation of checkpoint inhibitors in cases of existing autoimmunity or new autoimmune disease are typically discussed on a case-by-case basis.

4.6 Chimeric antigen receptor T (CAR-T) cells

Cytokine release syndrome (CRS), a common toxicity occurring in the first 2 weeks after CAR-T cell administration, is a systemic inflammatory response that typically manifests as fevers, tachycardia, hypotension, and multiorgan dysfunction [99, 100]. CAR-T cell neurotoxicity, which is closely related to but separate from CRS, occurs 2–11 days after CAR-T cell administration and may include acute encephalopathy, ataxia, and speech disturbance, and in severe cases focal neurological

deficits, seizures, myoclonus, cerebral edema, or obtundation [66, 99, 101, 102]. EEG typically reveals diffuse slowing but may also reveal rhythmic activity or seizures [100, 103]. CSF analysis may demonstrate a lymphocytic pleocytosis or increased protein, and CAR-T cells are often but not always found in the CSF, though they can also be found in the CSF of patients without neurotoxicity [104]. Neuroimaging is normal in mild cases, but in severe cases, MRI may reveal patchy increased T2 signal in the white matter and deep gray nuclei, sometimes associated with microhemorrhages or diffusion restriction [102, 104]. Tocilizumab, which blocks interleukin-6 (IL-6) to decrease cytokine response, is FDA-approved for the treatment of severe CRS [105]; however, it may not impact neurotoxicity, perhaps due to its inability to cross the blood-brain barrier [99]. As corticosteroids may decrease the antineoplastic effect of CAR-T cells, they are typically reserved for severe symptoms refractory to tocilizumab; however, some experts advocate for their use as first-line agents for severe neurotoxicity [99, 101]. While there are no high-quality data to support the use of seizure prophylaxis in children after CAR-T cell administration, some centers routinely use levetiracetam in this population.

4.7 Radiation

Cranial radiation therapy (CRT) is necessary for many CNS tumors as well as some hematologic malignancies despite known significant neurologic side effects. Neurotoxicity is one of the main side effects limiting its use.

Post-radiation somnolence syndrome occurs 3–12 weeks after CRT in children and consists of somnolence, fever, anorexia, nausea, vomiting, dysphagia, cerebellar ataxia, and EEG slowing. This syndrome typically lasts 3–14 days before spontaneously resolving [70].

Post-radiation arteriopathy, one type of moyamoya syndrome, typically occurs years after radiation. It is characterized by steno-occlusive disease of the distal internal carotid arteries and proximal middle and anterior cerebral arteries, increasing the risk of stroke [60]. It is particularly problematic in patients with neurofibromatosis type 1 (NF1), in whom radiation is also often avoided due to higher risk of malignant transformation of tumors, due to pre-existing risk for moyamoya syndrome in this population. Children receiving radiation near the circle of Willis are at highest risk for a moyamoya-like vasculopathy and strokes [60]. This risk is present even with the use of newer proton-beam radiation [106]. In high-risk patients, surveillance imaging can be pursued so that surgical revascularization can be considered.

Cognitive dysfunction is a well-known complication of CRT that is usually recognized years after treatment. Young age at the time of treatment is a risk factor for the development of CRT-associated cognitive dysfunction [60, 107]. Annual neuropsychologic testing is therefore recommended for children who have undergone CRT.

Vascular malformations can also occur after radiation, though there is debate as to the pathophysiological basis of these findings [108]. Cerebral cavernous malformations occur commonly, with retrospective studies reporting a cumulative incidence of 3–4% at 10 years after CRT [109, 110]. However, the incidence has been reported to be significantly higher in those who received CRT for medulloblastoma [111]. They typically present with either seizures or hemorrhage, with symptoms developing an average of 8–12 years after CRT. Cerebral aneurysms are less common. They most frequently present with aneurysmal subarachnoid hemorrhage with a mean latency of 10.6 years [112].

Stroke-like migraine attacks after radiation therapy (SMART) syndrome is a late complication of CRT, occurring 2–10 years after radiation. It presents as recurrent episodes of migrainous headaches, focal neurological deficits, and/or seizures lasting days to weeks. While the pathophysiology of SMART syndrome is poorly understood, subclinical seizures are common on EEG monitoring and hemispheric hypoperfusion and cerebrovascular abnormalities have been described in imaging studies [60, 113, 114].

Peripheral nervous system or spine involvement can be seen when radiation is directed at or traverses the spine or peripheral nerves. Myelopathy that presents early is typically reversible while late-onset symptoms tend to be progressive. Radiation-induced peripheral nerve injury can appear within weeks or be delayed by years, and the rate of progression is variable [115]. Generally, symptoms consist of pain, sensory loss, and/or weakness. The autonomic nervous system can also be involved.

Focal myopathy can occur at the site of radiation causing weakness and muscle spasm. Histology can show nemaline rods [115]. Fibrosis and sclerosis can occur over time in areas of direct injury and can result in contractures.

Late secondary malignancies can also occur secondary to radiation and are most commonly high-grade gliomas or meningiomas although sarcomas, histiosarcomas, and chondrosarcomas have also been reported [60]. The dose of radiation correlates with risk for secondary malignancy [60, 116]. Tumors typically appear in adulthood, on average 20 years after treatment with high-dose and 32 years after low-dose radiation [108].

4.8 Transplant

The rate of neurologic complications in hematopoietic stem cell transplantation (HSCT) is high, ranging from 10 to 60%, highest in unrelated allogenic transplants followed by related allogenic and then autologous transplants [60, 70]. Side effects of transplant medications, particularly calcineurin inhibitors, busulfan, and thiotepa are common, both during

preparation for and after hematopoietic stem cell transplant (HSCT) (see Table 3) [70]. In addition, the cryopreservative for stem cells, dimethyl sulfoxide (DMSO), can cause transient blindness, RCVS, PRES, seizures, strokes, and transient amnesia [70].

After transplant, infections are the most common neurologic complication (Table 4). Because of the lack of immune response, symptoms of even serious infections such as meningitis and encephalitis can initially be subtle [67]. Amphotericin, which may be used in treating fungal infections, can cause parkinsonism as a side effect [70]. Prion diseases have also been reported rarely in the setting of HSCT in children [70].

Numerous other neurologic complications of HSCT have been reported. Transplant-associated thrombotic microangiopathy can cause confusion, drowsiness, hallucinations, headaches, PRES, and seizures. Most cases resolve with time and treatment with eculizumab; however, persistent severe altered mental status after resolution of microangiopathic complications in other organ systems has occurred [118]. Inflammatory disorders have been seen after HSCT rarely and include acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS), and NMO. These are generally treated as they would be outside of the setting of HSCT. Vascular complications include stroke, intracranial hemorrhage, venous sinus thrombosis, and vasculitis [70]. In addition, development of epilepsy partialis continua affecting mainly the motor region has been reported, sometimes associated with Rasmussen encephalitis [70]. Finally, metabolic disturbances such as electrolyte abnormalities or hepatic or renal failure in the setting of HSCT can predispose to altered mental status and seizures. The syndrome of inappropriate antidiuretic hormone (SIADH) and hyponatremia are commonly seen in children under 4 years of age after transplant [70].

5 A neurologist's approach to the most common neurology consults in cancer patients

When evaluating neurologic complaints, it is important to evaluate all aspects of patient care, including the initial location and type of primary cancer, treatment modalities (surgery, chemotherapy agents, and radiation) as well as current disease status, specific time course of the current concern, associated symptoms, current and past medical comorbidities (including inflammatory, bone, endocrine, and genetic conditions), and a

Table 4 Infectious complications secondary to HSCT

Infection [67, 70, 117]		Unique neurologic sequelae
Bacterial	Nocardia	- Brain abscesses - Indolent meningitis
Viral	EBV	- Meningoencephalitis - Post-transplant CNS lymphoproliferative disorder
	VZV	- Meningitis - CNS vasculopathy, strokes
	HSV	- Encephalitis
	CMV	- Chorioretinitis - Myeloradiculitis, encephalitis, and ventriculitis with ependymal enhancement and debris seen in the ventricles on MRI (risk enhanced with graft versus host disease (GVHD))
	Enterovirus	- Meningoencephalitis
	HHV-6	- Limbic encephalitis including temporal lobe seizures - Insomnia - Confluent non-enhancing limbic and basal ganglia lesions on MRI - Symmetric necrotizing encephalopathy that can also involve thalamus and brainstem (rare, increased risk with GVHD)
	HHV-7	- Fatal encephalitis
	JCV	- Progressive multifocal leukoencephalopathy (PML)
Fungal	Aspergillus	- Predilection for invasion of blood vessels which can predispose to mycotic aneurysms, hemorrhage, vasculitis, or arterial infarction - Abscesses later in course with ring enhancing lesions
	Candida	- Multiple ring enhancing micro-abscesses at the gray-white junction, cerebellum, and basal ganglia
Parasitic	Toxoplasma	- Encephalitis largely seen as reactivation of latent infection after HSCT (highest risk 2–6 months after transplant) - Focal brain lesions characterized by ring enhancing lesions on MRI with elevated lipid/lactate peak on MR spectroscopy (lack of FDG-PET avidity can help differentiate lesions from those of lymphoma)
	Amoeba	- Brain abscess

detailed timeline of recent medications. Often, numerous predisposing factors are found for neurologic symptoms.

5.1 Altered mental status (AMS)

The time course of the mental status change is one of the most helpful pieces of information and should be ascertained immediately. Changes that occurred acutely over minutes should raise concern for vascular events (ischemic stroke and intracranial hemorrhage) and seizures. Changes in level of consciousness in patients with cerebral edema can indicate brain herniation. For acute changes, urgent imaging should be obtained to rule out these possibilities. Though CT scans are quick, widely available, and sensitive for blood products, MRI may be preferable if available to avoid radiation exposure and evaluate for other etiologies, such as ischemic stroke, which would not be apparent on head CT in the acute setting. Limited MRI sequences (diffusion sequences to evaluate for ischemia, susceptibility-weighted imaging to identify hemorrhage, and T2 weighted HASTE sequences to look at ventricular and cisternal size) can usually be obtained without sedation [119, 120]. Any changes in mental status that are episodic should prompt concern for seizures and continuous EEG monitoring can be helpful to resolve the question of delirium versus seizures.

In cases of persistent altered mental status arising over hours to days, medication effects are common culprits. Both intoxication as well as withdrawal effects of all medications given in the preceding 7 days should be considered in addition to chemotherapeutic agents given throughout the treatment course [121]. Procedural sedation, if performed prior to the change in mental status, can also cause persistent alteration in consciousness in patients with decreased neurologic reserve. Other diffuse metabolic causes for altered mental status include electrolyte derangements, hyperammonemia, hypercalcemia, hypomagnesemia, hypothyroidism, adrenal insufficiency, lactic acidosis, uremia, hypoxemia, dehydration, and hypotension. Wernicke's encephalopathy, with typical presentation including encephalopathy, vertigo, ataxia, headache, ophthalmopathy, and nystagmus, can be seen in children with prolonged parenteral nutrition needs and should be considered in all cases of encephalopathy [70]. It should be treated promptly with thiamine and correction of other vitamin deficiencies. PRES should be considered in all patients receiving chemotherapy. The possibility of CNS infection and sepsis should remain on the differential even in the absence of clear fever or vital sign changes, given that immunosuppressed patients may not mount a normal inflammatory response to infections. Increased intracranial pressure or intracranial tumor progression or metastasis should also be considered. Leptomeningeal spread of malignancy can cause alteration in consciousness which can be intermittent or continuous. Post-radiation somnolence syndrome should be considered if radiation to the CNS has occurred in the preceding 3 months.

For diagnostic evaluation of subacute or chronic altered mental status, MRI is preferred since CT scans entail radiation and are notoriously poor at imaging the posterior fossa, recognizing that MRI may require exposure to anesthesia in children who cannot remain still for an MRI [119]. A spot EEG can be helpful to confirm the presence of encephalopathy by demonstrating slowing or triphasic waves or to raise concern for nonconvulsive status epilepticus which can also present with persistent alteration in consciousness. Metabolic/infectious evaluation should include a metabolic panel with both renal and liver function tests, ammonia, lactate, magnesium, thyroid studies, complete blood count, vitamins B1, B2, B12, blood and urine cultures, and urine toxicology if needed. If indicated, CSF should be obtained for cell counts, glucose, protein, and bacterial and viral studies with consideration for fungal studies, cytology, oligoclonal bands, IgG index, and paraneoplastic panel.

5.2 Seizures

In patients with primary brain tumors, 15–25% will first present with seizures and these patients are more likely to require long term treatment with anti-seizure medications (ASMs) [122, 123]. For children with known CNS tumors, approximately half develop epilepsy, and even in the absence of a structural lesion (as in hematologic cancers), 8–10% of children develop seizures and 1/3 of those develop lasting epilepsy [3, 62, 122]. Low-grade tumors such as ganglioglioma, oligodendroglioma, pleomorphic xanthoastrocytoma, and dysembryoplastic neuroepithelial tumor (DNET) are particularly likely to present with seizures. Tumors that are supratentorial (compared with infratentorial), have hemorrhagic components, are incompletely resectable, or are located in superficial areas of cortex (compared to deep structures) are more likely to cause seizures [3]. Despite the high risk for seizures in patients with CNS malignancies, seizure prophylaxis is typically not indicated in patients with without a history of seizures [3, 124]. Retrospective data suggest that perioperative seizure prophylaxis may not be indicated in children with brain tumors older than 2 years of age with normal sodium levels, but the utility of perioperative prophylactic ASMs in children under 2 years of age deserves further study [125]. Other settings in which temporary prophylactic ASMs may be indicated include radiation therapy or high-risk chemotherapy.

Infants with any focal brain lesion, including CNS tumors, are at high risk for a type of seizure called infantile spasms, most commonly seen from age 4 months to 1 year but at times seen in younger infants or in children up to 2 years of age. When suspected, urgent neurologic evaluation is needed, since developmental outcomes depend on prompt treatment. First-line treatment for infantile spasms depends on the

clinical scenario but is typically high dose steroids (either ACTH or prednisolone) or vigabatrin.

In children with known systemic or CNS cancer, new seizures or a change in seizure semiology often heralds CNS progression or recurrence or can be the first sign of a stroke or PRES, and thus imaging should be obtained on an urgent basis in these patients. In patients with known CNS tumors and seizures who present with seizures of typical semiology, screening for electrolyte derangements, infection, missed medications or medication changes, sleep deprivation, head injury, and other potential provoking factors is indicated. If a recent seizure threshold-lowering chemotherapeutic agent has been introduced, an increase in or addition of another ASM may be needed at least temporarily to prevent further seizures. Frequently, if a provoking factor is identified, a temporary taper of additional medication (often benzodiazepines) during the period of provocation can be sufficient to manage breakthrough seizures in this setting.

In patients with CNS tumors, choice of ASM is important because any medication that affects cytochrome p450 can influence the efficacy or toxicity of chemotherapy [3]. Liver enzyme CYP450-inducing ASMs include carbamazepine, oxcarbazepine, phenobarbital, and phenytoin, while valproate is a CYP450 inhibitor. Levetiracetam is frequently selected as the first line ASM due to low incidence of side effects, primarily renal clearance, and lack of interaction with chemotherapeutic agents. The main side effect, irritability, presents in about 13% of children and of these, 30% resolve with the addition of vitamin B6 [126]. When needed acutely for seizures, compared with other benzodiazepines, lorazepam has more renal clearance and fewer medication interactions than others.

5.3 Headaches

Of patients presenting with brain tumors, 41% will have concurrent headaches and up to 2/3 of patients with brain tumors will complain of headaches during their clinical course [3, 127]. In addition to headaches secondary to malignancy, primary headache disorders such as migraines can be exacerbated in the setting of cancer. In children with alarm signs such as early morning headaches that wake the patient from sleep, a positional component, pain worsened by Valsalva, vision changes, tinnitus, persistent nausea/vomiting, or progressively worsening symptoms, secondary causes of headache such as new tumors, seizures, CSVT, vascular malformations, and Chiari malformations should be considered. Headaches in cancer patients are often multifactorial and can be exacerbated by anemia, electrolyte disturbances such as hypocalcemia or hypomagnesemia, and dehydration, as well as these additional factors.

Surgical procedures can cause persistent pain due to manipulation of vascular or dural structures. Posterior fossa craniotomies are more likely to lead to headache than supratentorial craniotomies [128]. Intraventricular hardware such as a shunts or Ommaya reservoirs predispose to infection and malfunction that can cause headache. In patients with intracranial hardware and new headache, imaging to evaluate ventricle size and CSF studies to evaluate for infection should be considered.

Increased intracranial pressure (ICP) can present with headaches and may be due to hardware malfunction, reduced CSF clearance through arachnoid granulations (following meningitis, hemorrhage, or when malignant cells are found in the CSF), adhesions obstructing CSF flow, or intracranial mass. Vision loss, difficulty abducting the eyes (due to pressure on cranial nerve VI), tinnitus, and positional complaints are common in cases of increased ICP. Parinaud syndrome, which consists of impaired upgaze, convergence-retraction nystagmus, light-near dissociation, and lid retraction (Collier's sign), can be seen due to midbrain compression by increased ICP or mass effect. Depending on the etiology, corticosteroids and surgical intervention are the primary treatments, and in some cases, palliative radiotherapy can alleviate headache [128].

Low-pressure headaches and CSF leaks can be seen after lumbar punctures (LPs) and surgical procedures that disrupt the dura. Initial management includes lying flat, intravenous hydration, and caffeine [60]. Epidural blood patches are contraindicated in children with hematologic malignancies due to concerns about the low but significant risk of seeding the CSF space with circulating neoplastic cells [60, 129]. Therefore, prevention is paramount, using techniques such as atraumatic LP needles and reinsertion of the stylet prior to removal of the needle to prevent CSF leaks from occurring [130, 131].

Chemotherapy often causes headache as a primary side effect (Table 3), and both chemotherapeutic medications as well as cancer itself can predispose to more concerning CNS pathology such as PRES and RCVS (see chemotherapy section above). Blood pressure should be monitored and controlled during chemotherapy and these entities should be considered in patients with new-onset headaches after receiving chemotherapy.

Cerebral sinovenous thrombosis (CSVT) can cause increased intracranial pressure, headache, and venous infarction and hemorrhage. Children with cancer are at high risk for CSVT due to a hypercoagulable state related to underlying malignancy, chemotherapeutic agents (such as asparaginase), immobility related to procedures, and indwelling catheters [60]. MR venography should, therefore, be considered for patients with new headaches or signs of increased ICP [60]. When present, treatment of CSVT consists of anticoagulation, typically for 3–6 months or until asparaginase therapy is complete and the clot has resolved [60].

Radiation is a frequent independent cause of headaches that are often unresponsive to traditional headache treatments. In

one study of 265 pediatric brain tumor patients, in children who had undergone radiation treatment without tumor progression, infection, or shunt malfunction, severe recurrent headache reported on more than two outpatient visits was a predictor of post-radiation ischemic complications [132]. Therefore, surveillance for post-radiation vasculopathy may be indicated in patients with severe headache after history of cranial radiation. Radiation can also lead to SMART syndrome (see Radiation section above) which may be most closely associated with subclinical seizures and therefore an EEG is warranted to rule out seizure in such cases [113, 133].

Once the above causes are ruled out or treatment has been initiated, headaches can be treated symptomatically with cocktails consisting of an analgesic (NSAID or Tylenol), an antiemetic (prochlorperazine, metoclopramide, or ondansetron), and hydration followed by addition of magnesium and valproate, unless contraindicated. These cocktails can be repeated every 6 h for up to 72 h until either no further benefit is seen after 2 sequential cocktails or until one cocktail after headache resolution. In some cases, daily prophylactic migraine therapy can be considered when headaches are recurrent.

New onset focal neurologic deficits or new focal seizures should prompt emergent evaluation for ischemic or hemorrhagic stroke. Though not evidence-based in the pediatric population, acute interventions such as IV thrombolysis or endovascular thrombectomy may be considered for some patients with arterial ischemic strokes within a limited time window after onset of symptoms, provided the child is being managed by a team with expertise in pediatric stroke [134–136]. Importantly, children with cancer are more likely to have contraindications to these therapies than children without cancer, and these must be considered in detail. Regardless, emergent evaluation with imaging remains appropriate when stroke is suspected.

There are numerous possible predisposing factors which have been discussed throughout this review, which we consider when approaching a pediatric cancer patient with cerebrovascular complications. Direct compression or invasion of blood vessels by tumor can cause either thrombosis or hemorrhage. Hemorrhage into tumors can cause acute neurologic deficits or even sudden death [137, 138]. Coagulation abnormalities such as disseminated intravascular coagulation (DIC) can predispose to both hemorrhagic and ischemic strokes [139]. Hypercoagulability may lead to thromboembolic ischemic strokes as well as CSVT, which may cause venous infarction and hemorrhage. Numerous chemotherapeutic agents, including asparaginase, tyrosine kinase inhibitors, thalidomide, and cisplatin, can cause hypercoagulability, predisposing to ischemic stroke [140]. Medications that are administered intra-arterially for direct tumor effects can also cause strokes. Chemotherapy has also been reported to cause RCVS, which can lead to arterial ischemic stroke or subarachnoid, subdural, or intraparenchymal hemorrhage. Finally, infections such as VZV and aspergillus can cause cerebral vasculitis and stroke. Patients with remote history of cancer are also at increased risk for stroke due to CRT-associated radiation vasculopathy, which can involve both the large vessels (moyamoya syndrome) and small vessels.

5.4 Sensory symptoms and weakness localizing to the peripheral nervous system

While peripheral nervous system (PNS) complaints in cancer patients are often related to chemotherapy, other causes such as paraneoplastic disorders, direct infiltration of the nerve by neoplastic cells, infections, nutritional deficiencies, GVHD in BMT patients, other immune disorders, diabetes, or critical illness neuropathy should be considered and treatable causes ruled out [60, 66]. In the absence of ongoing chemotherapy, static or improving symptoms suggest direct injury or chemotherapy side effect. Progressive symptoms can be seen after certain chemotherapies even after cessation ('coasting' phenomenon), after radiation, with neoplastic invasion, infection, hypothyroidism, vitamin B1 or B12 deficiency, and paraneoplastic or autoimmune causes.

Localization of the injury (that is, spinal cord, nerve roots, sensory ganglia, nervous plexuses, peripheral nerves, neuromuscular junction, and muscle) must be identified [89]. Episodic symptoms that worsen or improve with exertion raise suspicion for neuromuscular junction disorders (such as myasthenia gravis and Lambert Eaton myasthenic syndrome). On exam, areas of muscle atrophy can assist in identifying muscle groups that are affected. Reflexes can be helpful in localization because injury to a plexus or peripheral nerve will cause diminished reflexes while spinal involvement leads to increased reflexes. Electromyography (EMG), nerve conduction studies (NCS), specialized imaging, and CSF analysis are often important to identify the location of the problem, to rule out cancer spread or recurrence, and to identify inflammatory or infectious causes that might be amenable to treatment [115]. Electrodiagnostic studies should be planned to evaluate the entire field of radiation, if present, and all muscles and nerve roots and plexuses in the area of concern. Mixed myopathic and neuropathic signs are often present in affected areas, particularly after radiation [115]. MRI of the affected nerve roots and plexus with and without contrast can show masses that are adjacent to the area of involvement, enlargement of nerves, contrast enhancement, and sometimes edema. CSF analysis could include a search for paraneoplastic antibodies, viruses, malignant cells, and inflammatory markers in addition to routine studies [89].

Malignant invasion is one of the most feared causes of PNS symptoms. The progressive spread of motor or sensory deficits or pain gradually over a multiradicular distribution is highly suggestive of leptomeningeal disease, especially in the absence of a history of radiation to the

area [89]. Solid tumors as well as ALL and lymphoblastic or Burkitt lymphoma tend to spread along the leptomeninges and may require a meningeal biopsy for diagnosis. Sensitivity of imaging for leptomeningeal disease is estimated at only 20%, and so when there is high suspicion, repeated LPs or meningeal biopsies may be needed to confirm the diagnosis [141, 142].

Neurolymphomatosis is defined as infiltration of peripheral nerves or nerve roots by malignant lymphoma cells and presents with neuropathy that can affect peripheral nerves, cranial nerves, nervous plexuses, or nerve roots. Non-Hodgkin lymphoma is the most common malignancy to cause neurolymphomatosis, but diffuse large B cell lymphoma and primary CNS lymphoma have presented with neurolymphomatosis in children [9, 143]. Clinical presentation is with peripheral mononeuropathy, radiculopathy, cranial neuropathies, or mononeuritis multiplex, and it can be painful or painless [144]. Neurolymphomatosis involving a plexus typically has an insidious onset of unrelenting aching or burning pain in the shoulder or hip with gradual loss of reflexes and amyotrophy [89]. When lesions localize to a plexus, dedicated plexus imaging with MRI is about 70–80% sensitive for malignancy. Sensitivity can be enhanced by adding FDG-PET which detects 80–90% of cases and can be used to direct biopsy which may be required for confirmation since enlargement of nerves is nonspecific [144]. While FDG-PET differentiates malignancy from radiation-induced injury, it is important to note that inflammatory lesions can also be FDG avid on PET scan and also may be steroid-responsive.

Radiation injury to the PNS is transient in the acute phase, but in the chronic phase is progressive, manifesting at least 90 days after treatment completion and frequently delayed by years. Differentiation between radiation-induced injury and recurrence with neoplastic invasion as a cause of PNS dysfunction can be very difficult. Pain can be present in both cases. Unilateral plexus involvement, pain, Horner syndrome, enhancement with MRI contrast, and FDG avidity on PET are more common with neoplastic invasion while bilateral involvement of the entire or upper portion of the plexus, local tissue necrosis, edema, proximal conduction blocks on NCS, and myokymia on EMG are more common in radiation-induced nerve injury [115]. When suspicion is high for neoplastic recurrence in the absence of findings on MRI or FDG-PET, serial imaging (over months) is necessary as imaging is often negative early in the progression of disease [115].

Inflammatory causes typically have a subacute progressive course, are often multifocal, and can be associated with constitutional symptoms [26]. As discussed above and in Table 2, paraneoplastic and autoimmune disorders can present with lower motor neuron disease, distal sensory neuropathy, sensorimotor neuropathy, neuromyotonia, myokymia, mononeuritis multiplex, brachial plexopathy, autonomic neuropathy, and myasthenia gravis [26, 89]. Weakness and sensory symptoms, often in an ascending and progressive pattern, can also be seen in acute or chronic immune-mediated demyelinating polyneuropathy (AIDP or CIDP, which have duration shorter or greater than 8 weeks duration, respectively) and can be seen as part of GVHD in patients who have undergone HSCT [60]. CSF analysis may be normal in inflammatory causes or may show an elevated protein and/or a mild lymphocytic pleocytosis. A paraneoplastic antibody panel should be sent from CSF in addition to serum when symptoms could localize to CNS or proximal nerve roots. Muscle involvement can be seen in paraneoplastic or autoimmune dermatomyositis and polymyositis which present with signs of irritative myopathy [26].

Chemotherapy, as detailed in Table 3, has well-known effects on the PNS. When considering whether peripheral neuropathy is secondary to chemotherapeutic agents, it is helpful to compare the medications and doses to which the patient has been exposed to established doses of chemotherapy which are likely to cause CIPN [64, 145]. The risk of CIPN is higher in older children, with concurrent exposure to antifungal azoles, and with high doses or longer duration of chemotherapy. Patients with underlying disorders such as Charcot-Marie-Tooth or other hereditary disorders predisposing to neuropathies or cytochrome P450 polymorphisms that affect vincristine metabolism are at higher risk of peripheral neuropathy [60]. Symptoms of CIPN can be long-lasting, with increases in motor and sensory latencies demonstrated even 10 years after completion of chemotherapy for childhood ALL [146]. Treatment of CIPN includes mainly cessation or dose reduction of the offending agent.

Thyroid studies, vitamin B1, B6, B12, vitamin E, hemoglobin A1c, and inflammatory markers should be sent to ensure there are no correctible causes that are exacerbating symptoms. Tricyclic and other types of antidepressants, anticonvulsants, gabapentin, pregabalin, and topical capsaicin are frequently used in clinical practice, though randomized data to support these strategies is insufficient [64]. There is some evidence for symptomatic benefit of duloxetine in adults, but there are no randomized controlled trials in children to determine which strategies are most effective [147, 148].

6 Conclusion

Neurologic symptoms are common both as primary presentations of malignancy and complications of cancer and its treatment. The approach to the pediatric oncology patient with neurologic symptoms requires a detailed history and examination and consideration of multiple, sometimes compounding, etiologies. As treatment options for malignancy are rapidly expanding and survivorship is increasing, the

spectrum of both acute and chronic neurologic symptoms that can be attributed to cancer and its treatment is also expected to expand.

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Compliance with ethical standards

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

References

1. Dobrovoljac, M., Hengartner, H., Boltshauser, E., & Grotzer, M. (2002). Delay in the diagnosis of paediatric brain tumours. *Eur J Pediatr, 161*(12), 663–667. https://doi.org/10.1007/s00431-002-1088-4.
2. Reulecke, B. C., Erker, C. G., Fiedler, B. J., Niederstadt, T.-U., & Kurlemann, G. (2008). Brain tumors in children: Initial symptoms and their influence on the time span between symptom onset and diagnosis. *J Child Neurol, 23*(2), 178–183. https://doi.org/10.1177/0883073807308692.
3. Ullrich, N. J. (2009). Neurologic sequelae of brain tumors in children. *J Child Neurol, 24*(11), 1446–1454. https://doi.org/10.1177/0883073809342491.
4. Wells, E. M., & Packer, R. J. (2015). Pediatric brain tumors. *CONTINUUM: Lifelong Learning in Neurology, 21*(2), 373–396. https://doi.org/10.1212/01.CON.0000464176.96311.d1.
5. Malbari, F., Gershon, T. R., Garvin, J. H., Allen, J. C., Khakoo, Y., Levy, A. S., & Dunkel, I. J. (2016). Psychiatric manifestations as initial presentation for pediatric CNS germ cell tumors, a case series. *Childs Nerv Syst, 32*(8), 1359–1362. https://doi.org/10.1007/s00381-016-3145-8.
6. Taylor M, Couto-Silva, A-C, Adan L, Trivin C, Sainte-Rose C, Zerah M, … Brauner R (2012). Hypothalamic-pituitary lesions in pediatric patients: endocrine symptoms often precede neuro-ophthalmic presenting symptoms. J Pediatr, 161(5), 855–63. doi: https://doi.org/10.1016/j.jpeds.2012.05.014.
7. Pretell-Mazzini, J., Chikwava, K. R., & Dormans, J. P. (2012). Low back pain in a child associated with acute onset cauda equina syndrome: a rare presentation of an aggressive vertebral hemangioma: a case report. *J Pediatr Orthop, 32*(3), 271–276. https://doi.org/10.1097/BPO.0b013e318247195a.
8. Mora, J., & Wollner, N. (1999). Primary epidural non-Hodgkin lymphoma: spinal cord compression syndrome as the initial form of presentation in childhood non-Hodgkin lymphoma. *Med Pediatr Oncol, 32*(2), 102–105. https://doi.org/10.1002/(SICI)1096-911X(199902)32:2<102::AID-MPO6>3.0.CO;2-Y.
9. Da Silva, A. N., Lopes, M. B., & Schiff, D. (2006). Rare pathological variants and presentations of primary central nervous system lymphomas. *Neurosurg Focus, 21*(5), E1–E7. https://doi.org/10.3171/foc.2006.21.5.8.
10. Wilson, R. E., Oleszek, J. L., & Clayton, G. H. (2007). Pediatric spinal cord tumors and masses. *J Spinal Cord Med, 30*(sup1), S15–S20. https://doi.org/10.1080/10790268.2007.11753963.
11. Ma, G. M., Chow, J. S., & Taylor, G. A. (2019). Review of paraneoplastic syndromes in children. *Pediatr Radiol, 49*(4), 534–550. https://doi.org/10.1007/s00247-019-04371-y.
12. Nikolic, D. M., Nikolic, A. V., Lavrnic, D. V., Medjo, B. P., & Ivanovski, P. I. (2012). Childhood-onset myasthenia gravis with thymoma. *Pediatr Neurol, 46*(5), 329–331. https://doi.org/10.1016/j.pediatrneurol.2012.02.025.
13. Wells, E. M., & Dalmau, J. (2011). Paraneoplastic neurologic disorders in children. *Curr Neurol Neuroscie Rep, 11*(2), 187–194. https://doi.org/10.1007/s11910-010-0169-4.
14. Dalmau, J., & Rosenfeld, M. R. (2008). Paraneoplastic syndromes of the CNS. *Lancet Neurol, 7*(4), 327–340. https://doi.org/10.1016/S1474-4422(08)70060-7.
15. Graus, F., Delattre, J. Y., Antoine, J. C., Dalmau, J., Giometto, B., Grisold, W., Honnorat, J., Smitt, P. S., Vedeler Ch, Verschuuren, J. J., Vincent, A., & Voltz, R. (2004). Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry, 75*(8), 1135–1140. https://doi.org/10.1136/jnnp.2003.034447.
16. Pranzatelli, M. R., Tate, E. D., Swan, J. A., Travelstead, A. L., Colliver, J. A., Verhulst, S. J., Crosley, C. J., Graf, W. D., Joseph, S. A., Kelfer, H. M., & Raju, G. P. (2010). B cell depletion therapy for new-onset opsoclonus-myoclonus. *Mov Disord, 25*(2), 238–242. https://doi.org/10.1002/mds.22941.
17. Shams'ili, S., de Beukelaar, J., Gratama, J. W., Hooijkaas, H., van den Bent, M., van't Veer, M., & Sillevis Smitt, P. (2006). An uncontrolled trial of rituximab for antibody associated paraneoplastic neurological syndromes. *J Neurol, 253*(1), 16–20. https://doi.org/10.1007/s00415-005-0882-0.
18. Honnorat, J., Didelot, A., Karantoni, E., Ville, D., Ducray, F., Lambert, L., Deiva, K., Garcia, M., Pichit, P., Cavillon, G., Rogemond, V., DeLattre, J., & Tardieu, M. (2013). Autoimmune limbic encephalopathy and anti-Hu antibodies in children without cancer. *Neurology, 80*(24), 2226–2232. https://doi.org/10.1212/WNL.0b013e318296e9c3.
19. Florance-Ryan, N., & Dalmau, J. (2010). Update on anti-N-methyl-D-aspartate receptor encephalitis in children and adolescents. *Curr Opin Pediatr, 22*(6), 739–744. https://doi.org/10.1097/MOP.0b013e3283402d2f.
20. Lebas, A., Husson, B., Didelot, A., Honnorat, J., & Tardieu, M. (2010). Expanding spectrum of encephalitis with NMDA receptor antibodies in young children. *J Child Neurol, 25*(6), 742–745. https://doi.org/10.1177/0883073809343319.
21. Haberlandt, E., Bast, T., Ebner, A., Holthausen, H., Kluger, G., Kravljanac, R., Kröll-Seger, J., Kurlemann, G., Makowski, C., Rostasy, K., Tuschen-Hofstätter, E., Weber, G., Vincent, A., & Bien, C. G. (2011). Limbic encephalitis in children and adolescents. *Arch Dis Child, 96*(2), 186–191. https://doi.org/10.1136/adc.2010.183897.
22. Nosadini M, Toldo I, Tascini B, Bien CG, Parmeggiani L, De Gaspari P, … Sartori S (2019). LGI1 and CASPR2 autoimmunity in children: systematic literature review and report of a young girl with Morvan syndrome. J Neuroimmunol, 335, 577008. doi: https://doi.org/10.1016/J.JNEUROIM.2019.577008.
23. Nikolaus, M., Jackowski-Dohrmann, S., Prüss, H., Schuelke, M., & Knierim, E. (2018). Morvan syndrome associated with CASPR2 and LGI1 antibodies in a child. *Neurology, 90*(4), 183–185. https://doi.org/10.1212/WNL.0000000000004861.
24. Allen, N. M., McKeon, A., O'Rourke, D. J., O'Meara, A., & King, M. D. (2012). Excessive blinking and ataxia in a child with occult neuroblastoma and voltage-gated potassium channel antibodies. *Pediatrics, 129*(5), e1348–e1352. https://doi.org/10.1542/peds.2011-2690.
25. Rosenfeld, M. R. (2018). Paraneoplastic syndromes affecting the spinal cord and dorsal root ganglia. *Up To Date, 12*, 1–12.
26. Sharp, L., & Vernino, S. (2012). Paraneoplastic neuromuscular disorders. *Muscle Nerve, 46*(6), 839–840. https://doi.org/10.1002/mus.23502.

27. Amini, A., Lang, B., Heaney, D., & Irani, S. R. (2016). Multiple sequential antibody-associated syndromes with a recurrent mutated neuroblastoma. *Neurology, 87*(6), 634–636. https://doi.org/10.1212/WNL.0000000000002945.
28. Younes-Mhenni S, Janier MF, Cinotti L, Antoine JC, Tronc F, Cottin V, … Honnorat J (2004). FDG-PET improves tumour detection in patients with paraneoplastic neurological syndromes. Brain, 127(10), 2331–2338. doi:https://doi.org/10.1093/brain/awh247.
29. Linke, R., Schroeder, M., Helmberger, T., & Voltz, R. (2004). Antibody-positive paraneoplastic neurologic syndromes: Value of CT and PET for tumor diagnosis. *Neurology, 63*(2), 282–286. https://doi.org/10.1212/01.WNL.0000129983.06983.4E.
30. Blaes, F., Pike, M. G., & Lang, B. (2008). Autoantibodies in childhood opsoclonus-myoclonus syndrome. *J Neuroimmunol, 201*, 221–226. https://doi.org/10.1016/j.jneuroim.2008.05.033.
31. van Vuurden, D. G., Plötz, F. B., de Jong, M., Bokenkamp, A., & van Wijk, J. A. E. (2005). Therapeutic total plasma exchange in a child with neuroblastoma-related anti-Hu syndrome. *Pediatr Nephrol, 20*(11), 1655–1656. https://doi.org/10.1007/s00467-005-2004-8.
32. Sillevis Smitt, P., Grefkens, J., De Leeuw, B., Van Den Bent, M., Van Putten, W., Hooijkaas, H., & Vecht, C. (2002). Survival and outcome in 73 anti-Hu positive patients with paraneoplastic encephalomyelitis/sensory neuronopathy. *J Neurol, 249*(6), 745–753. https://doi.org/10.1007/s00415-002-0706-4.
33. Chong, C., Soon, D. T. L., & Yeo, L. L. L. (2019). Opsoclonus - myoclonus syndrome. *J Clin Neurosci, 61*, 254–255. https://doi.org/10.1016/j.jocn.2018.10.099.
34. Tate, E. D., Allison, T. J., Pranzatelli, M. R., & Verhulst, S. J. (2005). Neuroepidemiologic trends in 105 US cases of pediatric opsoclonus-myoclonus syndrome. *J Pediatr Oncol Nurs, 22*(1), 8–19. https://doi.org/10.1177/1043454204272560.
35. Morales La Madrid, A., Rubin, C. M., Kohrman, M., Pytel, P., & Cohn, S. L. (2012). Opsoclonus-myoclonus and anti-Hu positive limbic encephalitis in a patient with neuroblastoma. *Pediatr Blood Cancer, 58*(3), 472–474. https://doi.org/10.1002/pbc.23131.
36. Fisher, P. G., Wechsler, D. S., & Singer, H. S. (1994). Anti-Hu antibody in a neuroblastoma-associated paraneoplastic syndrome. *Pediatr Neurol, 10*(4), 309–312. https://doi.org/10.1016/0887-8994(94)90127-9.
37. Wilfong, A. A., Parke, J. T., & McCrary, J. A. (1992). Opsoclonus-myoclonus with Beckwith-Wiedemann syndrome and hepatoblastoma. *Pediatr Neurol, 8*(1), 77–79. https://doi.org/10.1016/0887-8994(92)90060-c.
38. Swart, J. F., De Kraker, J., & Van der Lely, N. (2002). Metaiodobenzylguanidine total-body scintigraphy required for revealing occult neuroblastoma in opsoclonus-myoclonus syndrome. *Eur J Pediatr, 161*(5), 255–258. https://doi.org/10.1007/s00431-002-0934-8.
39. McGarvey, C. K., Applegate, K., Lee, N. D., & Sokol, D. K. (2006). False-positive metaiodobenzylguanidine scan for neuroblastoma in a child with opsoclonus-myoclonus syndrome treated with adrenocorticotropic hormone (ACTH). *J Child Neurol, 21*(7), 606–610. https://doi.org/10.1177/08830738060210070801.
40. Brunklaus, A., Pohl, K., Zuberi, S. M., & De Sousa, C. (2012). Investigating neuroblastoma in childhood opsoclonus-myoclonus syndrome. *Arch Dis Child*. https://doi.org/10.1136/adc.2010.204792.
41. Baizabal-Carvallo, J. F., Stocco, A., Muscal, E., & Jankovic, J. (2013). The spectrum of movement disorders in children with anti-NMDA receptor encephalitis. *Mov Disord, 28*(4), 543–547. https://doi.org/10.1002/mds.25354.
42. Mohammad, S. S., Fung, V. S. C., Grattan-Smith, P., Gill, D., Pillai, S., Ramanathan, S., et al. (2014). Movement disorders in children with anti-NMDAR encephalitis and other autoimmune encephalopathies. *Mov Disord, 29*(12), 1539–1542. https://doi.org/10.1002/mds.25999.
43. Yeshokumar, A. K., Sun, L. R., Klein, J. L., Baranano, K. W., & Pardo, C. A. (2016). Gait disturbance as the presenting symptom in young children with anti-NMDA receptor encephalitis. *Pediatrics, 138*(3), e20160901. https://doi.org/10.1542/peds.2016-0901.
44. Darnell, R. B. (2007). NMDA receptor as a target in paraneoplastic encephalitis. *Ann Neurol, 61*(1), 3–4. https://doi.org/10.1002/ana.21074.
45. Dalmau, J., Tüzün, E., Wu, H., & Masjuan, J. (2007). Paraneoplastic anti–N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol, 61*(1), 25–36.
46. Dalmau, J., Gleichman, A. J., Hughes, E. G., Rossi, J. E., Peng, X., Lai, M., Dessain, S. K., Rosenfeld, M. R., Balice-Gordon, R., & Lynch, D. R. (2008). Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol, 7*(12), 1091–1098. https://doi.org/10.1016/S1474-4422(08)70224-2.
47. Kunstreich, M., Kreth, J. H., Oommen, P. T., Schaper, J., Karenfort, M., Aktas, O., Tibussek, D., Distelmaier, F., Borkhardt, A., & Kuhlen, M. (2017). Paraneoplastic limbic encephalitis with SOX1 and PCA2 antibodies and relapsing neurological symptoms in an adolescent with Hodgkin lymphoma. *Eur J Paediatr Neurol, 21*(4), 661–665. https://doi.org/10.1016/j.ejpn.2017.03.005.
48. Chan, D. W. S., Thomas, T., Lim, M., Ling, S., Woodhall, M., & Vincent, A. (2017). Focal status epilepticus and progressive dyskinesia: a novel phenotype for glycine receptor antibody-mediated neurological disease in children. *Eur J Paediatr Neurol, 21*(2), 414–417. https://doi.org/10.1016/j.ejpn.2016.08.013.
49. Spatola, M., Sabater, L., Planagumà, J., Martínez-Hernandez, E., Armangué, T., Prüss, H., Iizuka, T., Caparó Oblitas, R. L., Antoine, J. C., Li, R., Heaney, N., Tubridy, N., Munteis Olivas, E., Rosenfeld, M. R., Graus, F., & Dalmau, J. (2018). Encephalitis with mGluR5 antibodies: symptoms and antibody effects. *Neurology, 90*(22), e1964–e1972. https://doi.org/10.1212/WNL.0000000000005614.
50. Rudock R, Helis J, & Mar SS (2017). Anti-glutamic acid decarboxylase limbic encephalitis. In Pediatric demyelinating diseases of the central nervous system and their mimics (pp. 67–73). Springer International Publishing. doi:https://doi.org/10.1007/978-3-319-61407-6_9.
51. Gresa-Arribas, N., Titulaer, M. J., Torrents, A., Aguilar, E., McCracken, L., Leypoldt, F., Gleichman, A. J., Balice-Gordon, R., Rosenfeld, M. R., Lynch, D., Graus, F., & Dalmau, J. (2014). Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol, 13*(2), 167–177. https://doi.org/10.1016/S1474-4422(13)70282-5.
52. Rosenfeld, M. R., & Dalmau, J. (2011). Anti-NMDA-receptor encephalitis and other synaptic autoimmune disorders. *Curr Treat Options Neurol, 13*(3), 324–332. https://doi.org/10.1007/s11940-011-0116-y.
53. Gungor, S., Kilic, B., Arslan, M., Ozgen, U., & Dalmau, J. (2017). Hodgkin's lymphoma associated with paraneoplastic cerebellar degeneration in children: a case report and review of the literature. *Childs Nerv Syst, 33*(3), 509–512. https://doi.org/10.1007/s00381-016-3284-y.
54. Nakamura, T., Morimoto, N., Goto, F., Shioda, Y., Hoshino, H., Kubota, M., & Taiji, H. (2012). Langerhans cell histiocytosis with disequilibrium. *Auris Nasus Larynx, 39*(6), 627–630. https://doi.org/10.1016/j.anl.2012.01.003.
55. Emir, S., Tezer Kutluk, M., Göğüş, S., & Büyükpamukçu, M. (2000). Paraneoplastic cerebellar degeneration and horner syndrome: association of two uncommon findings in a child with

hodgkin disease. *Am J Pediatr Hematol/Oncol, 22*(2), 158–161. https://doi.org/10.1097/00043426-200003000-00015.
56. Greenlee, J. E. (2013). Treatment of paraneoplastic cerebellar degeneration. *Curr Treat Options Neurol, 15*(2), 185–200. https://doi.org/10.1007/s11940-012-0215-4.
57. Ojeda, V. J., & Ojeda, V. J. (1984). Necrotizing myelopathy associated with malignancy. a clinicopathologic study of two cases and literature review. *Cancer, 53*(5), 1115–1123. https://doi.org/10.1002/1097-0142(19840301)53:5<1115::aid-cncr2820530517>3.0.co;2-w.
58. Pittock, S. J., & Lennon, V. A. (2008). Aquaporin-4 autoantibodies in a paraneoplastic context. *Arch Neurol, 65*(5), 629–632. https://doi.org/10.1001/archneur.65.5.629.
59. de Buys Roessingh, A. S., Loriot, M. H., Wiesenauer, C., & Lallier, M. (2009). Lambert-Eaton myasthenic syndrome revealing an abdominal neuroblastoma. *J Pediatr Surg, 44*(8), E5–E7. https://doi.org/10.1016/j.jpedsurg.2009.04.023.
60. Sun, L. R., & Cooper, S. (2018). Neurological complications of the treatment of pediatric neoplastic disorders. *Pediatr Neurol, 85*, 33–42. https://doi.org/10.1016/j.pediatrneurol.2018.05.011.
61. Küper, M., & Timmann, D. (2013). Cerebellar mutism. *Brain Lang, 127*(3), 327–333. https://doi.org/10.1016/J.BANDL.2013.01.001.
62. Neil, E. C., Hanmantgad, S., & Khakoo, Y. (2016). Neurological complications of pediatric cancer. *J Child Neurol, 31*(12), 1412–1420. https://doi.org/10.1177/0883073815620673.
63. Newton HB (2012). Neurological complications of chemotherapy to the central nervous system. In Handbook of clinical neurology (Vol. 105, pp. 903–916). Elsevier B.V. doi:https://doi.org/10.1016/B978-0-444-53502-3.00031-8.
64. Staff, N. P, Grisold, A., Grisold, W., & Windebank, A. J. (2017). Chemotherapy-induced peripheral neuropathy: a current review. *Ann Neurol, 81*(6), 772–781. https://doi.org/10.1002/ana.24951.
65. Schiff, D., Wen, P. Y., & van den Bent, M. J. (2009). Neurological adverse effects caused by cytotoxic and targeted therapies. *Nat Rev Clin Oncol, 6*(10), 596–603. https://doi.org/10.1038/nrclinonc.2009.128.
66. Wick, W., Hertenstein, A., & Platten, M. (2016). Neurological sequelae of cancer immunotherapies and targeted therapies. *Lancet Oncol, 17*(12), e529–e541. https://doi.org/10.1016/S1470-2045(16)30571-X.
67. Cordelli, D. M., Masetti, R., Zama, D., Toni, F., Castelli, I., Ricci, E., Franzoni, E., & Pession, A. (2017). Central nervous system complications in children receiving chemotherapy or hematopoietic stem cell transplantation. *Front Pediatr, 5*, 105. https://doi.org/10.3389/fped.2017.00105.
68. Carson KR, Newsome SD, Kim EJ, Wagner-Johnston ND, Von Geldern G, Moskowitz CH, … Bennett CL (2014). Progressive multifocal leukoencephalopathy associated with brentuximab vedotin therapy: a report of 5 cases from the Southern Network on Adverse Reactions (SONAR) project. Cancer, 120(16), 2464–2471. doi:https://doi.org/10.1002/cncr.28712.
69. Toxicology and Environmental Health Information Program (TEHIP). (2019). TOXNET. National Library of Medicine. Retrieved November 26, 2019, from https://toxnet.nlm.nih.gov/index.html Accessed 12/2/2019.
70. Aspesberro, F., Milewski, L. S., & Brogan, T. V. (2014). Acute central nervous system complications in pediatric hematopoietic stem cell patients. *J Pediatr Intensive Care, 3*, 169–181. https://doi.org/10.3233/PIC-14100.
71. Tibussek D, Natesirinilkul R, Sun LR, Wasserman, B. A., Brandao LR, deVeber G, … deVeber G (2016). Severe cerebral vasospasm and childhood arterial ischemic stroke after intrathecal cytarabine. Pediatrics, 137(2), e20152143–e20152143. doi:https://doi.org/10.1542/peds.2015-2143.
72. Sait, S., & Modak, S. (2017). Anti-GD2 immunotherapy for neuroblastoma. *Expert Rev Anticancer Ther, 17*(10), 889–904. https://doi.org/10.1080/14737140.2017.1364995.
73. Han, R., Yang, Y. M., Dietrich, J., Luebke, A., Mayer-Pröschel, M., & Noble, M. (2008). Systemic 5-fluorouracil treatment causes a syndrome of delayed myelin destruction in the central nervous system. *J Biol, 7*(4), 12. https://doi.org/10.1186/jbiol69.
74. Ewins, K., Malone, A., Phelan, E., Webb, D., McHugh, J. C., & Smith, O. (2017). Nelarabine-induced peripheral and central neurotoxicity: can sequential MRI brain imaging help to define its natural history? *Br J Haematol, 179*(2), 294–297. https://doi.org/10.1111/bjh.14921.
75. Judge, C., Moheb, N., & Melinosky, C. (2019). Nilotinib-associated demyelinating disease. *Neurology, 92*(Suppl 15), P2.2–P093.
76. Dombi E, Baldwin A, Marcus LJ, Fisher MJ, Weiss B, Kim A, … Widemann BC (2016). Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. N Eng J Med, 375(26), 2550–2560. doi:https://doi.org/10.1056/NEJMoa1605943.
77. Grace, R. F., Dahlberg, S. E., Neuberg, D., Sallan, S. E., Connors, J. M., Neufeld, E. J., Deangelo, D. J., & Silverman, L. B. (2011). The frequency and management of asparaginase-related thrombosis in paediatric and adult patients with acute lymphoblastic leukaemia treated on Dana-Farber Cancer Institute consortium protocols. *Br J Haematol, 152*(4), 452–459. https://doi.org/10.1111/j.1365-2141.2010.08524.x.
78. Mitchell LG, Andrew M, Abshire T, Halton J, Anderson R, Cherrick I, … Way C (2003). A prospective cohort study determining the prevalence of thrombotic events in children with acute lymphoblastic leukemia and a central venous line who are treated with L-asparaginase: results of the Prophylactic antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) study. Cancer, 97(2), 508–516. doi:https://doi.org/10.1002/cncr.11042.
79. Caruso, V., Iacoviello, L., Di Castelnuovo, A., Storti, S., Mariani, G., De Gaetano, G., & Donati, M. B. (2006). Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients. *Blood*. https://doi.org/10.1182/blood-2006-04-015511.
80. Greiner J, Schrappe M, Claviez A, Zimmermann M, Niemeyer C, Kolb R, … Möricke A (2019). THROMBOTECT – a randomized study comparing low molecular weight heparin, antithrombin and unfractionated heparin for thromboprophylaxis during induction therapy of acute lymphoblastic leukemia in children and adolescents. Haematologica, 104(4), 756–765. doi:https://doi.org/10.3324/haematol.2018.194175.
81. Malhotra, P., Jain, S., & Kapoor, G. (2018). Symptomatic cerebral sinovenous thrombosis associated with L-asparaginase in children with acute lymphoblastic leukemia: a single institution experience over 17 years. *J Pediatr Hematol Oncol, 40*(7), e450–e453. https://doi.org/10.1097/MPH.0000000000001127.
82. Nicolao, P., & Giometto, B. (2003). Neurological toxicity of ifosfamide. *Oncology, 65*(Suppl 2), 11–16. https://doi.org/10.1159/000073352.
83. Taupin, D., Racela, R., & Friedman, D. (2014). Ifosfamide chemotherapy and nonconvulsive status epilepticus: case report and review of the literature. *Clin EEG Neurosci, 45*(3), 222–225. https://doi.org/10.1177/1550059413500777.
84. Bhojwani, D., Sabin, N. D., Pei, D., Yang, J. J., Khan, R. B., Panetta, J. C., Krull, K. R., Inaba, H., Rubnitz, J. E., Metzger, M. L., Howard, S. C., Ribeiro, R. C., Cheng, C., Reddick, W. E., Jeha, S., Sandlund, J. T., Evans, W. E., Pui, C. H., & Relling, M. V. (2014). Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia.

J Clin Oncol, 32(9), 949–959. https://doi.org/10.1200/JCO.2013.53.0808.

85. Inaba, H., Khan, R. B., Laningham, F. H., Crews, K. R., Pui, C. H., & Daw, N. C. (2008). Clinical and radiological characteristics of methotrexate-induced acute encephalopathy in pediatric patients with cancer. *Ann Oncol, 19*(1), 178–184. https://doi.org/10.1093/annonc/mdm466.
86. Cheung, Y. T., Sabin, N. D., Reddick, W. E., Bhojwani, D., Liu, W., Brinkman, T. M., Glass, J. O., Hwang, S. N., Srivastava, D., Pui, C. H., Robison, L. L., Hudson, M. M., & Krull, K. R. (2016). Leukoencephalopathy and long-term neurobehavioural, neurocognitive, and brain imaging outcomes in survivors of childhood acute lymphoblastic leukaemia treated with chemotherapy: a longitudinal analysis. *Lancet Haematol, 3*(10), 456–466. https://doi.org/10.1016/S2352-3026(16)30110-7.
87. Koh, S., Nelson, M. D., Kovanlikaya, A., & Chen, L. S. (1999). Anterior lumbosacral radiculopathy after intrathecal methotrexate treatment. *Pediatr Neurol, 21*(2), 576–578. https://doi.org/10.1016/S0887-8994(99)00040-5.
88. Junna, M. R., & Rabinstein, A. A. (2007). Tacrolimus induced leukoencephalopathy presenting with status epilepticus and prolonged coma. *J Neurol Neurosurg Psychiatry, 78*(12), 1410–1411. https://doi.org/10.1136/jnnp.2007.121806.
89. Antoine, J. C., & Camdessanché, J. P. (2007). Peripheral nervous system involvement in patients with cancer. *Lancet Neurol, 6*(1), 75–86. https://doi.org/10.1016/S1474-4422(06)70679-2.
90. Tang, J.-H., Tian, J.-M., Sheng, M., Hu, S.-Y., Li, Y., Zhang, L.-Y., Gu, Q., & Wang, Q. (2016). Study of posterior reversible encephalopathy syndrome in children with acute lymphoblastic leukemia after induction chemotherapy. *J Child Neurol, 31*(3), 279–284. https://doi.org/10.1177/0883073815589758.
91. Landi, D. B., Thompson, E. M., & Ashley, D. M. (2018). Immunotherapy for pediatric brain tumors. *Neuroimmunol Neuroinflamm, 5*, 29. https://doi.org/10.20517/2347-8659.2018.35.
92. Kabir, T. F., Chauhan, A., Anthony, L., & Hildebrandt, G. C. (2018). Immune checkpoint inhibitors in pediatric solid tumors: status in 2018. *Ochsner J, 18*(4), 370–376. https://doi.org/10.31486/toj.18.0055.
93. AlHarbi M, Mobark NA, AlMubarak L, Aljelaify R, AlSaeed M, Almutairi A, … Abedalthagafi M (2018). Durable response to nivolumab in a pediatric patient with refractory glioblastoma and constitutional biallelic mismatch repair deficiency Saudi human genome project View project medulloblastoma View project, 23(12), 1401–1406. doi:https://doi.org/10.1634/theoncologist.2018-0163.
94. Gorsi H, Malicki DM, Barsan, V, Tumblin M, Yeh-Nayre L, Milburn M, … Crawford JR (2019). Nivolumab in the treatment of recurrent or refractory pediatric brain tumors: a single institutional experience. J Pediatr Hematol/Oncol, 41(4), e235–241. doi: https://doi.org/10.1097/MPH.0000000000001339.
95. Wang, S. S., Bandopadhayay, P., & Jenkins, M. R. (2019). Towards immunotherapy for pediatric brain tumors. *Trends Immunol, 40*(8), 748–761. https://doi.org/10.1016/j.it.2019.05.009.
96. Williams TJ, Benavides DR, Patrice, K A, Dalmau JO, De Ávila AL R, Le DT, … Mowry EM (2016). Association of autoimmune encephalitis with combined immune checkpoint inhibitor treatment for metastatic cancer. JAMA Neurol, 73(8), 928–933. doi: https://doi.org/10.1001/jamaneurol.2016.1399.
97. Zekeridou, A., & Lennon, V. A. (2019). Neurologic autoimmunity in the era of checkpoint inhibitor cancer immunotherapy. *Mayo Clin Proc, 94*(9), 1865–1878. https://doi.org/10.1016/j.mayocp.2019.02.003.
98. Dalakas, M. C. (2018). Neurological complications of immune checkpoint inhibitors: what happens when you 'take the brakes off' the immune system. *Ther Adv Neurol Disord, 11*, 1756286418799864. https://doi.org/10.1177/1756286418799864.
99. Brudno, J. N., & Kochenderfer, J. N. (2019). Recent advances in CAR T-cell toxicity: mechanisms, manifestations and management. *Blood Rev, 34*, 45–55. https://doi.org/10.1016/j.blre.2018.11.002.
100. Gust, J., Hay KA, Hanafi L A, Li D, Myerson D, Gonzalez-Cuyar LF, … Turtle CJ (2017). Endothelial activation and blood–brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. Cancer Discov doi:https://doi.org/10.1158/2159-8290.CD-17-0698.
101. Hay, K. A. (2018). Cytokine release syndrome and neurotoxicity after CD19 chimeric antigen receptor-modified (CAR-) T cell therapy. *Br J Haematol*. https://doi.org/10.1111/bjh.15644.
102. Santomasso BD, Park JH, Salloum D, Riviere, I., Flynn J, Mead E, … Brentjens RJ (2018). Clinical and biological correlates of neurotoxicity associated with car t-cell therapy in patients with B-cell acute lymphoblastic leukemia. Cancer Discov. doi:https://doi.org/10.1158/2159-8290.CD-17-1319.
103. Willis, M. D., & Robertson, N. P. (2019). Neurotoxicity of novel cancer immunotherapies. *J Neurol, 266*, 2087–2089. https://doi.org/10.1007/s00415-019-09444-4.
104. Gust, J., Taraseviciute, A., & Turtle, C. J. (2018). Neurotoxicity associated with CD19-targeted CAR-T cell therapies. *CNS Drugs, 32*(12), 1091–1101. https://doi.org/10.1007/s40263-018-0582-9.
105. Le RQ, Li L, Yuan W, Shord SS, Nie L, Habtemariam BA, … Pazdur R (2018). FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. The Oncologist, 23(8), 943–947. doi:https://doi.org/10.1634/theoncologist.2018-0028.
106. Reynolds, M. R., Haydon, D. H., Caird, J., & Leonard, J. R. (2016). Radiation-induced moyamoya syndrome after proton beam therapy in the pediatric patient: a case series. *Pediatr Neurosurg, 51*(6), 297–301. https://doi.org/10.1159/000446075.
107. Meadows, A. T., Massari, D. J., Fergusson, J., Gordon, J., Littman, P., & Moss, K. (1981). Declines in IQ scores and cognitive dysfunctions in children with acute lymphocytic leukaemia treated with cranial irradiation. *Lancet, 2*(8254), 1015–1018. https://doi.org/10.1016/S0140-6736(81)91216-2.
108. Amirjamshidi, A., & Abbassioun, K. (2000). Radiation-induced tumors of the central nervous system occurring in childhood and adolescence. *Childs Nerv Syst, 16*(7), 390–397. https://doi.org/10.1007/s003819900125.
109. Gastelum, E., Sear, K., Hills, N., Roddy, E., Randazzo, D., Chettout, N., Hess, C., Cotter, J., Haas-Kogan, D. A., Fullerton, H., & Mueller, S. (2015). Rates and characteristics of radiographically detected intracerebral cavernous malformations after cranial radiation therapy in pediatric cancer patients. *J Child Neurol, 30*(7), 842–849. https://doi.org/10.1177/0883073814544364.
110. Strenger, V., Sovinz, P., Lackner, H., Dornbusch, H. J., Lingitz, H., Eder, H. G., Moser, A., & Urban, C. (2008). Intracerebral cavernous hemangioma after cranial irradiation in childhood: incidence and risk factors. *Strahlenther Onkol, 184*(5), 276–280. https://doi.org/10.1007/s00066-008-1817-3.
111. Lew, S. M., Morgan, J. N., Psaty, E., Lefton, D. R., Allen, J. C., & Abbott, R. (2006). Cumulative incidence of radiation-induced cavernomas in long-term survivors of medulloblastoma. *J Neurosurg, 104*(Suppl 2), 103–107. https://doi.org/10.3171/ped.2006.104.2.6.
112. Sciubba, D. M., Gallia, G. L., Recinos, P., Garonzik, I. M., & Clatterbuck, R. E. (2006). Intracranial aneurysm following radiation therapy during childhood for a brain tumor: case report and review of the literature. *J Neurosurg, 105*(2), 134–139. https://doi.org/10.3171/ped.2006.105.2.134.

113. Fan, E. P., Heiber, G., Gerard, E. E., & Schuele, S. (2018). Stroke-like migraine attacks after radiation therapy: a misnomer? *Epilepsia, 59*(1), 259–268. https://doi.org/10.1111/epi.13963.
114. Wai, K., Balabanski, A., Chia, N., & Kleinig, T. (2017). Reversible hemispheric hypoperfusion in two cases of SMART syndrome. *J Clin Neurosci, 43*, 146–148. https://doi.org/10.1016/j.jocn.2017.05.013.
115. Stubblefield, M. D. (2017). Neuromuscular complications of radiation therapy. *Muscle Nerve, 56*(6), 1031–1040. https://doi.org/10.1002/mus.25778.
116. Neglia, J. P., Robison, L. L., Stovall, M., Liu, Y., Packer, R. J., Hammond, S., Yasui, Y., Kasper, C. E., Mertens, A. C., Donaldson, S. S., Meadows, A. T., & Inskip, P. D. (2006). New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the childhood cancer survivor study. *J Natl Cancer Inst, 98*(21), 1528–1537. https://doi.org/10.1093/jnci/djj411.
117. Schmidt-Hieber, M., Silling, G., Schalk, E., Heinz, W., Panse, J., Penack, O., Christopeit, M., Buchheidt, D., Meyding-Lamadé, U., Hähnel, S., Wolf, H. H., Ruhnke, M., Schwartz, S., & Maschmeyer, G. (2016). CNS infections in patients with hematological disorders (including allogeneic stem-cell transplantation)-guidelines of the infectious DiseasesWorking party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). *Ann Oncol, 27*(7), 1207–1225. https://doi.org/10.1093/annonc/mdw155.
118. Schoettler, M., Duncan, C., & Lehmann, L. (2019). Severe, persistent neurotoxicity after transplant-associated thrombotic microangiopathy in a pediatric patient despite treatment with eculizumab. *Pediatr Transplant, 23*(3), e13381. https://doi.org/10.1111/petr.13381.
119. Callahan, M. J., MacDougall, R. D., Bixby, S. D., Voss, S. D., Robertson, R. L., & Cravero, J. P. (2018). Ionizing radiation from computed tomography versus anesthesia for magnetic resonance imaging in infants and children: patient safety considerations. *Pediatr Radiol, 48*(1), 21–30. https://doi.org/10.1007/s00247-017-4023-6.
120. Tekes, A., Senglaub, S. S., Ahn, E. S., Huisman, T. A. G. M., & Jackson, E. M. (2018). Ultrafast brain MRI can be used for indications beyond shunted hydrocephalus in pediatric patients. *Am J Neuroradiol, 39*(8), 1515–1518. https://doi.org/10.3174/ajnr.A5724.
121. Tuma, R., & DeAngelis, L. M. (2000). Altered mental status in patients with cancer. *Arch Neurol, 57*(12), 1727–1731. https://doi.org/10.1001/archneur.57.12.1727.
122. Khan, R. B., Hunt, D. L., Boop, F. A., Sanford, R. A., Merchant, T. E., Gajjar, A., & Kun, L. E. (2005). Seizures in children with primary brain tumors: Incidence and long-term outcome. *Epilepsy Res, 64*(3), 85–91. https://doi.org/10.1016/j.eplepsyres.2005.03.007.
123. Ibrahim, K., & Appleton, R. E. (2004). Seizures as the presenting symptom of brain tumours in children. *Seizure, 13*(2), 108–112. https://doi.org/10.1016/S1059-1311(03)00083-9.
124. Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, … Cairncross JG (2000). Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors: report of the quality standards Subcommittee of the American Academy of neurology. Neurology, 54(10), 1886–1893. doi:https://doi.org/10.1212/WNL.54.10.1886.
125. Hardesty, D. A., Sanborn, M. R., Parker, W. E., & Storm, P. B. (2011). Perioperative seizure incidence and risk factors in 223 pediatric brain tumor patients without prior seizures: clinical article. *J Neurosurg Pediatr*. https://doi.org/10.3171/2011.3.PEDS1120.
126. Patsalos, P. N., & St. Louis, E. K. (2018). *The epilepsy prescriber's guide to antiepileptic drugs* (3rd ed.). Cambridge: Cambridge University Press. https://doi.org/10.1017/9781108669399.
127. The Childhood Brain Tumor Consortium. (1991). The epidemiology of headache among children with brain tumor. Headache in children with brain tumors. *J Neuro-Oncol, 10*(1), 31–46. https://doi.org/10.1007/bf00151245.
128. Kirby, S., & Purdy, R. A. (2007). Headache and brain tumors. *Curr Neurol Neurosci Rep, 7*(2), 110–116. https://doi.org/10.1007/s11910-007-0005-7.
129. Demaree, C. J., Soliz, J. M., & Gebhardt, R. (2016). Cancer seeding risk from an epidural blood patch in patients with leukemia or lymphoma. *Pain Med, 18*(4), 218. https://doi.org/10.1093/pm/pnw218.
130. Rusch, R., Schulta, C., Hughes, L., & Withycombe, J. S. (2014). Evidence-based practice recommendations to prevent/manage post-lumbar puncture headaches in pediatric patients receiving intrathecal chemotherapy. *J Pediatr Oncol Nurs, 31*(4), 230–238. https://doi.org/10.1177/1043454214532026.
131. Lee, L. C.-Y., Sennett, M., & Erickson, J. M. (2007). Prevention and management of post–lumbar puncture headache in pediatric oncology patients. *J Pediatr Oncol Nurs, 24*(4), 200–207. https://doi.org/10.1177/1043454207303884.
132. Kranick, S. M., Campen, C. J., Kasner, S. E., Kessler, S. K., Zimmerman, R. A., Lustig, R. A., Phillips, P. C., Beslow, L. A., Ichord, R., & Fisher, M. J. (2013). Headache as a risk factor for neurovascular events in pediatric brain tumor patients. *Neurology, 80*(16), 1452–1456. https://doi.org/10.1212/WNL.0b013e31828cf81e.
133. Black, D., Bartleson, J., Bell, M., & Lachance, D. (2006). SMART: stroke-like migraine attacks after radiation therapy. *Cephalalgia, 26*(9), 1137–1142. https://doi.org/10.1111/j.1468-2982.2006.01184.x.
134. Sporns PB, Sträter R, Minnerup, J, Wiendl H, Hanning U, Chapot R, … Kemmling A (2019). Feasibility, safety, and outcome of endovascular recanalization in childhood stroke: the Save ChildS Study. JAMA Neurol. doi:https://doi.org/10.1001/jamaneurol.2019.3403.
135. Bigi, S., Dulcey, A., Gralla, J., Bernasconi, C., Melliger, A., Datta, A. N., Arnold, M., Kaesmacher, J., Fluss, J., Hackenberg, A., Maier, O., Weber, J., Poloni, C., Fischer, U., & Steinlin, M. (2018). Feasibility, safety, and outcome of recanalization treatment in childhood stroke. *Ann Neurol, 83*(6), 1125–1132. https://doi.org/10.1002/ana.25242.
136. Amlie-Lefond, C., & Wainwright, M. S. (2019). Organizing for acute arterial ischemic stroke in children. *Stroke, 50*(12), 3662–3668. https://doi.org/10.1161/STROKEAHA.119.025497.
137. Furuhata, M., Aihara, Y., Eguchi, S., Horiba, A., Tanaka, M., Komori, T., & Okada, Y. (2014). Pediatric medulloblastoma presenting as cerebellar hemorrhage: a case report. *No shinkei geka. Neurol Surg, 42*(6), 545–551.
138. Wilson, M. P., Johnson, E. S., Hawkins, C., Atkins, K., Alshaya, W., & Pugh, J. A. (2016). Hemorrhagic presentations of cerebellar pilocytic astrocytomas in children resulting in death: report of 2 cases. *J Neurosurg Pediatr, 17*(4), 446–452. https://doi.org/10.3171/2015.10.PEDS1580.
139. Packer, R. J., Rorke, L. B., Lange, B. J., Siegel, K. R., & Evans, A. E. (1985). Cerebrovascular accidents in children with cancer. *Pediatrics, 76*(2), 194–201.
140. Bajzar, L., Chan, A. K., Massicotte, M. P., & Mitchell, L. G. (2006). Thrombosis in children with malignancy. *Curr Opin Pediatr, 18*(1), 1–9. https://doi.org/10.1097/01.mop.0000193270.09001.ea.
141. Herrlinger, U., Schabet, M., Bitzer, M., Petersen, D., & Krauseneck, P. (1999). Primary central nervous system lymphoma: from clinical presentation to diagnosis. *J Neuro-Oncol, 43*(3), 219–226. https://doi.org/10.1023/A:1006298201101.
142. Bühring, U., Herrlinger, U., Krings, T., Thiex, R., Weller, M., & Küker, W. (2001). MRI features of primary central nervous system

lymphomas at presentation. *Neurology, 57*(3), 393–396. https://doi.org/10.1212/wnl.57.3.393.

143. Bjornard, K. L., Leventaki, V., Nichols, K. E., Sandlund, J. T., Prockop, S., & Ehrhardt, M. J. (2018). Two-year-old female with EBV-positive diffuse large B-cell lymphoma and subsequent CNS involvement with neurolymphomatosis. *Pediatr Blood Cancer, 65*(12), e27415. https://doi.org/10.1002/pbc.27415.
144. Grisariu S, Avni B, Batchelor T T, Bent MJ van den, Bokstein F, Schiff, D, … Siegal T (2010). Neurolymphomatosis: an international primary CNS lymphoma collaborative group report. Blood, 115(24), 5005–5011. doi:https://doi.org/10.1182/BLOOD-2009-12-258210.
145. Grisold, W., Cavaletti, G., & Windebank, A. J. (2012). Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. *Neuro-Oncology, 14*(suppl 4), v45–v54. https://doi.org/10.1093/neuonc/nos203.
146. Ness, K. K., Hudson, M. M., Pui, C. H., Green, D. M., Krull, K. R., Huang, T. T., Robison, L. L., & Morris, E. B. (2012). Neuromuscular impairments in adult survivors of childhood acute lymphoblastic leukemia: associations with physical performance and chemotherapy doses. *Cancer, 118*(3), 828–838. https://doi.org/10.1002/cncr.26337.
147. Chu, S. H., Lee, Y. J., Lee, E. S., Geng, Y., Wang, X. S., & Cleeland, C. S. (2015). Current use of drugs affecting the central nervous system for chemotherapy-induced peripheral neuropathy in cancer patients: A systematic review. *Support Care Cancer, 23*(2), 513–524. https://doi.org/10.1007/s00520-014-2408-8.
148. Hou, S., Huh, B., Kim, H. K., Kim, K. H., & Abdi, S. (2018). Treatment of chemotherapy-induced peripheral neuropathy: systematic review and recommendations. *Pain Physician, 21*(6), 571–592.