Central Nervous System Tumors in Children

Katherine C. Pehlivan, MD,* Megan R. Paul, MD,† and John R. Crawford, MD, MS†,‡

*Department of Pediatrics, Division of Hematology-Oncology, New York Medical College, Valhalla, NY
†Department of Pediatrics, Division of Hematology-Oncology, University of California San Diego and Rady Children’s Hospital, San Diego, CA
‡Department of Neurosciences, University of California and Rady Children’s Hospital, San Diego, CA

EDUCATION GAP

The role of the pediatrician is crucial in both the diagnosis and management of pediatric brain tumors, the most common solid tumor of childhood. Awareness of the presenting signs and symptoms of brain tumors can lead to timely diagnosis, and understanding the late effects of brain tumor treatment improves long-term management of childhood brain tumor survivors.

OBJECTIVES After completing this article, readers should be able to:

1. Recognize the presenting symptoms and physical examination findings suggestive of a childhood brain tumor and how these findings depend on tumor location.
2. Review common brain tumor pathologies affecting children.
3. Understand how molecular genetics plays a role in the diagnosis and treatment of childhood brain tumors.
4. Recognize the late affects associated with the treatment of childhood brain tumors.

INTRODUCTION

Brain tumors are the most common solid malignancy in children and represent the leading cause of pediatric cancer-related deaths. Five thousand new brain tumors are diagnosed yearly in the United States in children ages 0 to 19 years, with an incidence of approximately 6 per 100,000 children. (1) Childhood brain tumors, more than half of which are malignant, vary in terms of biology, prognosis and treatment. Presenting signs and symptoms depend on tumor location, growth rate, and presence of obstructive hydrocephalus. Making the initial diagnosis of a brain tumor can be difficult because early symptoms, such as headaches or vomiting, are nonspecific to brain tumors and more frequently are associated with other etiologies, leading to delays in diagnosis. The pediatrician plays a crucial role in the timely diagnosis of patients with brain tumors as well

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ABBREVIATIONS

ATRT atypical teratoid rhabdoid tumor
CNS central nervous system
CN cranial nerve
CSF cerebrospinal fluid
CT computed tomography
HGG high-grade glioma
ICP intracranial pressure
LGG low-grade glioma
MRI magnetic resonance imaging
NF neurofibromatosis
NGGCT nongerminomatous germ cell tumor
OS overall survival
WHO World Health Organization
as recognizing late effects resulting from tumor therapies. This review summarizes the presenting features on history and physical examination, tumor classification of common tumor types, genetic brain tumor predisposition syndromes, general management strategy, and late effects of therapy.

**PRESENTATION OF BRAIN TUMORS IN CHILDREN**

Signs and symptoms of a pediatric brain tumor can be nonspecific, insidious, intermittent, and dependent on location within the central nervous system (CNS) and the anatomical pathways affected. Although headache is the most common presenting complaint overall, it is present in only approximately one-third of the children presenting with brain tumors, and, in the absence of other symptoms or physical examination findings, is not in itself predictive of a brain tumor. Elevated intracranial pressure (ICP) is present in approximately half of all children with brain tumors. In addition to headache, it can cause nausea/vomiting, abnormalities of gait and coordination, and papilledema. Vital sign abnormalities associated with increased ICP, known as the Cushing triad (bradycardia, hypertension, abnormal respirations), are late signs of acutely increased ICP but can be absent in those with chronically elevated ICP. In young children with an open fontanelle, macrocephaly, especially when progressive, can be suggestive of hydrocephalus and a potential mass-occupying lesion. (2)

Presenting symptoms depend on tumor location (Fig 1), and certain constellations of symptoms can point to specific lesion locations. Table 1 lists commonly overlooked signs and symptoms that can lead to a delayed diagnosis. Wilne et al analyzed presenting features of more than 4,000 childhood brain tumors and found that for posterior fossa tumors, three-quarters presented with nausea and vomiting, two-thirds with headache, three-fifths with abnormal gait and coordination, and one-third with papilledema. (2) In contrast, headache, nausea, and vomiting were rare in patients presenting with supratentorial tumors. Instead, seizures were present in one-third of patients, along with focal neurologic deficits such as weakness or sensory deficits on the contralateral side if there is involvement of the cortical motor or sensory regions, respectively. (2) In cases of brainstem tumors, children can present with crossed findings of ipsilateral facial weakness and contralateral hemiparesis. More than 75% of patients with brainstem tumors present with abnormal gait and coordination, whereas cranial nerve (CN) palsies are present in more than half. Headache, however, is not common in patients with brainstem tumors and is present in less than one-quarter at the time of diagnosis. Thalamic tumors can cause coordination and motor difficulties or hemiplegia. (2)

Patients with pituitary tumors or optic pathway tumors often present with visual deficits. It is not uncommon for even severe visual deficits in children to go unrecognized by the patient, parents, or pediatrician. (3) Because patients with neurofibromatosis (NF) type 1 are at increased risk for optic pathway glioma, they should have yearly ophthalmology evaluations. Children with pituitary or hypothalamic tumors often present with endocrine abnormalities, such as failure to thrive, excess thirst, or central obesity.

![Figure 1. Presenting features of childhood brain tumors based on tumor location. The presenting symptoms in the child with a brain tumor differ based on the anatomical location of the tumor. Here, various anatomical regions of the brain are highlighted and correlated to common constellations of presenting symptoms suggestive of a lesion in that region of the brain.](image)

**Table 1. Initial Presenting Signs and Symptoms Leading to Diagnosis of Brain Tumors in Various Locations**

<table>
<thead>
<tr>
<th>SIGNS AND SYMPTOMS</th>
<th>TUMOR LOCATION</th>
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<tbody>
<tr>
<td>Early-morning vomiting, recurrent vomiting, enlarging head circumference</td>
<td>Posterior fossa, ventricular system</td>
</tr>
<tr>
<td>Failure to thrive, anorexia</td>
<td>Suprasellar region, hypothalamic</td>
</tr>
<tr>
<td>Visual complaints, abnormal eye movements</td>
<td>Optic pathway, suprasellar region, brain stem, posterior fossa</td>
</tr>
<tr>
<td>Tics, tremors, movement disorder</td>
<td>Basal ganglia, thalamus, midbrain</td>
</tr>
<tr>
<td>Early handedness</td>
<td>Cortex, subcortical, brain stem, spinal cord</td>
</tr>
<tr>
<td>Facial nerve palsy</td>
<td>Brain stem, cerebellar pontine angle</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>Cerebellar pontine angle</td>
</tr>
<tr>
<td>Precocious puberty, nocturnal enuresis</td>
<td>Suprasellar region</td>
</tr>
<tr>
<td>Head tilt, torticollis</td>
<td>Cerebellar pontine angle, cervicomедullary junction</td>
</tr>
</tbody>
</table>

Children with spinal cord tumors most commonly present with back pain, present at diagnosis in approximately two-thirds of cases. Spinal cord tumors may occur in extradural, intramedullary, and extramedullary intradural locations. Although some children may present with scoliosis, most will not. Spinal cord compression causes signs such as gait and coordination abnormalities, focal weakness, or bowel and bladder dysfunction. (2)

**ROLE OF THE NEUROLOGIC EXAMINATION**

A comprehensive neurologic examination (summarized in Table 2) is crucial to identify abnormalities that might be suggestive of a CNS tumor. A normal neurologic examination does not exclude the diagnosis of a brain or spinal cord tumor and must be correlated with symptoms.

**Mental Status**

Patients with acute hydrocephalus can display dramatic changes in their mental status, with increased sleepiness, decreased energy, and decreased responsiveness. However, those with chronic hydrocephalus might show only subtle signs, such as slowly declining school performance.

**Cranial Nerves**

A fundoscopic examination of the optic nerve, CN II, is crucial to assess for papilledema and optic nerve pallor, which can reveal information about hydrocephalus or tumors along the optic pathways. A fundoscopic examination can be difficult in young or uncooperative children, warranting referral to ophthalmology for a dilated examination. Vision should be assessed by confrontation in the 4 quadrants of each eye because different patterns of visual field deficits will suggest varying tumor locations. In younger children, assessment of visual fields can be performed using a colorful object for central fixation and introducing a second object in the periphery and watching for the eyes to track to that object.

Eye movements are controlled by CNs III, IV, and VI. The nuclei of CNs III and IV are located in the midbrain, whereas the nucleus of CN VI is in the pons, and brainstem tumors can lead to abnormalities of extraocular movements. Large pineal tumors can cause Parinaud syndrome, characterized by upgaze palsy, convergence-retraction nystagmus, and poorly reactive pupils due to compression of the rostral midbrain. Nystagmus can also be seen in patients with cerebellar tumors or optic pathway tumors.

CN V, the trigeminal nerve, has 3 divisions that give sensation to the face. The trigeminal nucleus is located in the pons, as is the nucleus of CN VII (the facial nerve), which controls facial movement. Facial asymmetry or decreased facial sensation should raise concern for a mass in this region. Hearing in each ear should be assessed to look for CN VIII dysfunction.

The lower CNs (CNs IX, X, XII) exit from the medulla and are involved in phonation, swallowing, and tongue movements.

**Table 2.** Key Components of the Neurologic Examination in a Child with Suspected Central Nervous System Tumor

<table>
<thead>
<tr>
<th>EXAMINATION</th>
<th>PERTINENT FINDINGS SUGGESTIVE OF TUMOR</th>
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<tbody>
<tr>
<td>Mental status (alertness, speech)</td>
<td>Encephalopathy, progressive neurocognitive decline</td>
</tr>
<tr>
<td>Cranial nerve II (visual fields, fundoscopic examination)</td>
<td>Visual field deficit, papilledema, optic nerve pallor</td>
</tr>
<tr>
<td>Cranial nerves III, IV, VI (extraocular movements, efferent pupillary function)</td>
<td>Nystagmus (upgaze in particular), gaze paralysis in any direction, mid-position, poorly reactive pupils</td>
</tr>
<tr>
<td>Cranial nerve V (facial sensation)</td>
<td>Asymmetry or change in facial sensation in anatomical distribution of V1, V2, V3</td>
</tr>
<tr>
<td>Cranial nerve VI (facial symmetry, movement)</td>
<td>Facial weakness (upper vs lower motor neuron distribution)</td>
</tr>
<tr>
<td>Cranial nerve VII (hearing, balance)</td>
<td>Decreased hearing to finger rub (unilateral or bilateral), vertigo</td>
</tr>
<tr>
<td>Cranial nerves IX, X, XII (palate elevation, swallowing, tongue movements)</td>
<td>Drooling, dysphagia, asymmetrical palate</td>
</tr>
<tr>
<td>Motor examination (bulk, tone, proximal and distal strength)</td>
<td>Early handedness, delayed motor milestones, pronator drift, focal changes in tone with associated atrophy</td>
</tr>
<tr>
<td>Sensory examination</td>
<td>Sensory deficits in a focal anatomical distribution</td>
</tr>
<tr>
<td>Reflexes (biceps, triceps, brachioradialis, patellar, Achilles)</td>
<td>Hyperreflexia with Babinski sign</td>
</tr>
<tr>
<td>Coordination (finger to nose testing, mirror testing, rapid finger and/or toe tapping)</td>
<td>Dysemetria, overshoot on mirror testing, marked asymmetry of finger and/or toe tapping (must be differentiated from weakness)</td>
</tr>
<tr>
<td>Gait (heel, toe, tandem straight line)</td>
<td>Wide-based unsteady gait, inability to perform straight-line test, circumduction of gait</td>
</tr>
</tbody>
</table>

A thorough neurologic examination includes assessment of mental status, cranial nerves, motor and sensory function, reflexes, coordination, and gait. Examples of abnormal findings according to each examination component that might suggest a central nervous system mass or lesion are listed. These abnormalities should be interpreted within the clinical context but can suggest a need for imaging or further evaluation.

movement. Palatal asymmetry, change in voice quality, or unilateral glossal atrophy raises suspicion for a medullary lesion. CN XI, the accessory nerve, has the most distal nucleus, also in the medulla, and innervates the trapezius and sternocleidomastoid musculature.

Motor Function, Sensation, Reflexes
Motor function, sensation, and reflexes should be assessed with special attention to comparison with the contralateral findings. Asymmetry can indicate a lesion affecting corticospinal tracts (motor), spinotectal tract (temperature, pain, light touch), or dorsal columns ( proprioception, vibratory sense). Asymmetrical hyporeflexia can indicate lower motor neuron injury, whereas hyperreflexia and the presence of a Babinski reflex are indicative of upper motor neuron dysfunction. In acute upper motor neuron injury, reflexes may be absent.

Gait and Coordination
Patients with cerebellar tumors can present with a wide-based ataxic gait and difficulty with tandem gait. A hemiparetic gait can suggest a tumor involving cortical motor areas, the thalamus, or the brain stem. Patients with cerebellar or brainstem tumors may exhibit abnormal coordination, elicited by testing rapid alternating movements, finger to nose testing, or finger (pointer to thumb) and toe tapping (on the floor) or asking a child to mirror the examiner’s finger as the examiner moves the finger laterally and/or vertically.

Skin Examination
Although not technically part of the neurologic examination, a skin examination is important to assess for dermatologic manifestations of underlying tumor predispositions such as NF type 1 ( predisposed to low-grade gliomas [LGGs], especially in optic pathways), NF type 2 ( predisposed to acoustic schwannomas and meningiomas), tuberous sclerosis complex ( predisposed to subependymal giant cell tumors), or, more rarely, constitutional mismatch repair deficiency syndrome. Patients with constitutional mismatch repair deficiency syndrome have a genetic defect in genes responsible for repairing a specific type of DNA damage known as mismatch repair. Abnormalities in these genes (MLH1, MSH2, MSH5, PMS2) make it more difficult for the body to repair normally occurring DNA damage, leading to mutations and predisposing these patients to many types of cancers at an early age, including brain tumors, most commonly high-grade gliomas (HGGs).

ACUTE MANAGEMENT
The child with a suspected brain tumor might require urgent interventions. Those with unstable vital signs, altered mental status, or concern for increased ICP warrant expedited evaluation, best managed initially in the emergency department. Although magnetic resonance imaging (MRI) with and without contrast is the gold standard imaging technique for optimal visualization for brain tumors and is often needed for neurosurgical planning, in the unstable child, a computed tomographic (CT) scan may be the best initial imaging choice. CT scans can provide information regarding acute hydrocephalus, impending herniation, or acute hemorrhage, all of which represent neurosurgical emergencies. They can also show the anatomical location of a mass, lesion size, presence of hydrocephalus, and whether the mass is compressing other brain structures, thereby helping to triage and plan a timeline for MRI, surgery, or other sedated procedures. When choosing the optimal initial imaging study for a young child who would require anesthesia to complete an MRI, the relative risks of anesthesia compared with the risk of exposure to ionizing radiation from a CT scan, which could be completed without sedation, must be weighed while taking into account the degree of suspicion for an abnormality and individual risk factors specific to that patient.

MRI with and without contrast is generally the preferred imaging modality for diagnosis and follow-up of brain tumors. MRI allows for more detailed characterization of the tumor itself and the surrounding anatomy, with more specialized sequences for visualization of edema, relationship to CNs, blood vessels, and perfusion. Furthermore, MRI does not expose children to ionizing radiation so is preferred over CT for repeated studies, as would be needed to follow a brain tumor. Most patients with a brain tumor require a spinal MRI to evaluate for evidence of leptomeningeal disease.

When a diagnosis of a brain tumor is made based on imaging, in the absence of a neurosurgical emergency, patients should be managed in concert with neuro-oncology teams preoperatively. Early neuro-oncology consultation allows for additional baseline neurologic examination, can help inform surgical planning based on the working differential diagnosis and postoperative treatment options, and facilitates an opportunity for clinical trial enrollment where presurgical consent may be required.

TREATMENT OVERVIEW OF PEDIATRIC BRAIN TUMORS
The care of the pediatric neuro-oncology patient requires a multidisciplinary team–based approach. In addition to an excellent primary care pediatrician, this team includes
neuro-oncology, neuro-surgery, neurology, neuro-radiology, radiation oncology, genetics, endocrinology, ophthalmology, audiology, neuropsychology, physical medicine and rehabilitation, palliative care, and social work.

Upfront treatment of pediatric brain tumors generally includes surgery, radiotherapy, chemotherapy, or a combination of these modalities. For most tumor types, maximal safe surgical resection is pursued to obtain diagnosis and as the first step in definitive treatment. Some notable exceptions to this include tumors in eloquent locations where resection would result in significant morbidity or mortality. These locations include the brain stem, optic pathways, thalamus, internal capsule, sensory and motor cortices, visual cortex, or Broca and Wernicke areas, which are important for receptive and expressive language. In some cases, a small needle biopsy of these areas can be performed to obtain tissue for diagnostic purposes. For germ cell tumors, tumor needle biopsy of these areas can be performed to obtain tissue for diagnostic purposes. For germ cell tumors, tumor markers can be diagnostic, obviating the need for upfront surgery. Some patients with low-grade–appearing lesions are followed with observation alone.

Although some low-grade tumors can be treated with resection only, many low-grade and most high-grade tumors require additional postsurgical treatment. The standard of care for postsurgical management of pediatric brain tumors is constantly evolving based on emerging preclinical and clinical data. In many cases, enrollment in an open clinical trial is considered the standard of care. There are a variety of clinical trial consortia and cooperative groups with open protocols focused on pediatric brain tumors. A complete list of open clinical trials can be found on clinicaltrials.gov.

CLASSIFICATION AND TREATMENT OF PEDIATRIC BRAIN TUMORS

There are more than 30 unique pathologies of CNS tumors in children. MRI characteristics of some common childhood brain tumors are shown in Fig 2. The advent of molecular genetics has enhanced our understanding of the biologic behavior of brain tumors, has changed tumor classification systems, and has had treatment implications.

Medulloblastoma

Medulloblastoma is the most common malignant brain tumor in children and is of embryonal origin. It generally presents as a posterior fossa mass and, due to its location, is often associated with obstructive hydrocephalus. Staging includes an MRI of the spine and a lumbar puncture looking for malignant cells in the cerebrospinal fluid (CSF). Histologically it is classified as classic, large cell anaplastic, or nodular desmoplastic. Overall, medulloblastoma has 5-year overall survival (OS) of approximately 70%. (6)

Treatment depends on age at presentation, extent of resection, and presence of metastatic disease. Recent trials are accounting for molecular subtype in treatment decisions. Generally, treatment involves maximal tumor resection, craniospinal radiotherapy, and chemotherapy. Young patients undergo high-dose chemotherapy with autologous stem cell rescue to avoid or delay irradiation.

Figure 2. Magnetic resonance imaging (MRI) features of pediatric brain tumors with associated clinical presentation. A. MRI with contrast reveals a heterogeneously enhancing mass of the posterior fossa. The patient presented with several days of early-morning vomiting. Examination demonstrated papilledema, ataxia, and dysmetria. Diagnosis: medulloblastoma. B. Fluid-attenuated inversion recovery MRI sequence demonstrates a rightsided, posterior, cortically based tumor. The patient presented with a new onset focal seizure. Neurologic examination was normal. Diagnosis: dysembrioplastic neuroepithelial tumor. C. MRI with contrast demonstrates an enhancing mass involving the optic chiasm and tracts. The patient presented with several months of blunted vision. Examination revealed multiple café au lait macules, axillary freckling, bilateral pale optic nerves, and poor visual acuity. Diagnosis: optic pathway glioma, neurofibromatosis type 1. D. Noncontrast MRI reveals a large hypointense mass involving the pons. The patient presented with several weeks of double vision, facial weakness, and poor coordination. Examination revealed bilateral sixth and seventh nerve palsies, bilateral dysmetria, and diffuse hypereflexia with clonus. Diagnosis: diffuse intrinsic pontine glioma. E. Postcontrast MRI reveals a large supratel lar tumor and hydrocephalus. The patient presented with several months of headaches, double vision, and increasing difficulty seeing objects on the television. Examination revealed bitemporal hemianopsia and papilledema. Diagnosis: craniopharyngioma. F. T2-weighted MRI reveals a large right frontotemporal mass with mass effect. The patient presented with 2 weeks of headache and left-sided weakness. Examination demonstrated left hemiparesis and acute encephalopathy. Diagnosis: high-grade glioma.
Medulloblastoma has been classified into 4 principle molecular subgroups: WNT (wingless), SHH (sonic hedgehog), group 3, and group 4 (Table 3). (7) WNT-driven medulloblastomas are rarely metastatic and have the best overall prognosis, with greater than 90% OS. Current clinical trials are focused on reducing therapy in this subtype. SHH-driven tumors have a bimodal distribution presenting most commonly in infants or adolescents and young adults. They have an intermediate prognosis, although association with p53 mutations portends a poor prognosis. (9) Group 3 and group 4 tumors are known as non-WNT, non-SHH medulloblastoma subtypes. Although immunohistochemical studies can differentiate WNT and SHH medulloblastoma from the non-WNT and non-SHH medulloblastoma subtypes, other molecular methods, such as methylation studies, are needed to distinguish group 3 from group 4 tumors. Group 3 tumors can present in very young children, often have MYC amplification, are commonly metastatic at presentation, and have the poorest outcomes overall of any subgroup. Recent data suggest that group 3 tumors might benefit from intensified chemotherapy concurrent with radiotherapy. Group 4 tumors are the most common subgroup overall, presenting in children and adults and, similar to group 3 tumors, more commonly present in males than in females. (7) Group 4 tumors have an intermediate prognosis.

Atypical Teratoid Rhabdoid Tumor

Atypical teratoid rhabdoid tumors (ATRTs) are also embryonal tumors but can present in the posterior fossa or supratentorial region. These tumors have a very poor prognosis, with 3-year OS of approximately 25%. Survival trends improve with older age at diagnosis, with those older than 3 years faring better than younger patients. (10) Histologically, the loss of INI1, encoded by SMARCB1, is pathognomonic. Up to 35% of patients with ATRT have a germline mutation in SMARCB1 (or rarely SMARCA4), which predisposes them to the development of malignant rhabdoid tumors in other locations, most commonly the kidneys. Germline variants are more common in younger patients, and approximately two-thirds are sporadic. (11)

Staging includes MRI of the brain and spine and lumbar puncture for CSF cytology. Treatment involves surgical resection, radiotherapy, and chemotherapy, with or without triple tandem autologous stem cell transplant. Recent clinical trial data showed improved survival outcomes compared with historical controls achieved with a regimen including radiotherapy for patients as young as 6 months and 3 cycles of high-dose chemotherapy with autologous stem cell rescue for all patients. (12) A meta-analysis including 130 patients with ATRT saw that survival correlated most strongly when patients were treated with regimens that included high-dose chemotherapy with autologous stem cell rescue. Treatment modalities of radiotherapy and intrathecal chemotherapy also lead to a statistically significant improvement in OS in this cohort. (10)

ATRT tumors have also been classified based on molecular characteristics into 3 subgroups: ATRT–tyrosine (ATRT-TYR), ATRT–sonic hedgehog (ATRT-SHH), and ATRT–myelocytomatosis oncogene (ATRT-MYC), but further research is needed to delineate the prognostic and clinical implications of these subgroups. (13)

Ependymoma

Ependymoma represents the third most common brain tumor in children and arises from the ependymal cells lining the ventricles or the central canal of the spinal cord. Two-thirds of ependymomas present in the posterior fossa, with the remainder in the supratentorial region or spinal cord. For pediatric ependymoma as a whole, OS at 10 years is approximately 64%, but cases achieving gross total resection followed by radiotherapy fare significantly better. Molecular subtype and gain of chromosome 1q has important prognostic implications as well. (14)

Ependymoma is treated with maximal surgical resection followed by focal radiotherapy, except for spinal disease, in which gross total resection without adjuvant

### Table 3. The Four Major Consensus Molecular Subgroups of Medulloblastoma

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>WNT</th>
<th>SHH</th>
<th>GROUP 3</th>
<th>GROUP 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>10%</td>
<td>30%</td>
<td>25%</td>
<td>35%</td>
</tr>
<tr>
<td>5-y overall survival</td>
<td>~95%</td>
<td>~75%</td>
<td>~50%</td>
<td>~75%</td>
</tr>
<tr>
<td>Rate of metastases</td>
<td>5%–10%</td>
<td>10%–15%</td>
<td>40%–45%</td>
<td>30%–50%</td>
</tr>
<tr>
<td>Age group</td>
<td>Children</td>
<td>Infants, adults</td>
<td>Infants, children</td>
<td>Children, adults</td>
</tr>
</tbody>
</table>

Medulloblastoma is divided into 4 major molecular subgroups with clinical and prognostic implications. These subgroups are beginning to be integrated into clinical trial designs to impact risk stratification and treatment considerations. However, there is molecular and clinical heterogeneity even within these subgroups. (7)(8)
radiotherapy can be curative. The role of chemotherapy in ependymoma remains under clinical investigation. Studies have also explored the use of postoperative chemotherapy to delay or omit radiotherapy in patients younger than 3 years, but outcomes were inferior to regimens involving radiotherapy for children older than 12 months. (15)

Ependymoma has been divided into 9 molecular subgroups, with 3 subgroups for each anatomical location: spinal, supratentorial, and posterior fossa. Only 6 of the molecular subtypes generally affect children. Pediatric ependymoma of the spine is divided into the SP-MPE subtype (myxopapillary, usually World Health Organization [WHO] grade I) and the SP-EPN subtype (anaplastic, WHO grade II/III). Both spinal subtypes have a relatively good prognosis. In the posterior fossa, patients with PF-EPN-A have a worse prognosis than those with PF-EPN-B, and in the supratentorial compartment, those with RELA fusion-driven disease (ST-EPN-RELA) have poorer OS than those with YAP1 fusion-positive disease (ST-EPN-YAP1). Both PF-EPN-A and ST-EPN-RELA are associated with 10-year OS less than 50% and 10-year progression-free survival of approximately 20%. (14)

Low-Grade Gliomas

Pediatric LGGs are a heterogenous group of tumors that encompass several distinct WHO histologies, including astrocytic tumors (juvenile pilocytic astrocytoma being the most common), oligodendrogial tumors (such as oligodendroglioma), and mixed glioneuronal tumors (including dysembryoblastic neuro-epithelial tumors). When grouped together, LGGs represent the most common brain tumor in children and can present in many anatomical locations. LGGs are less likely to metastasize to other parts of the CNS axis than their malignant counterparts, and in some cases gross total resection can be curative. However, resection is not always possible in certain anatomical locations, such as in the brain stem or with optic pathway gliomas, common in patients with NF type 1. LGGs have a relatively favorable prognosis, with OS of 92.5% and progression-free survival of 67% reported in a study of 1,000 LGGs with median follow-up of 15.9 years. (16)

Classically, when medical therapy is needed for LGGs, the first-line regimen consists of traditional chemotherapy with either carboplatin/vincristine or procarbazine, lomustine, vincristine, and thioguanine, although other chemotherapy regimens have demonstrated responses as well. (17) Radiotherapy is not routinely used in the upfront management of LGG due to concerns for late effects. Study of the molecular landscape of LGGs has demonstrated that most are driven by alterations in the mitogen-activated protein kinase pathway, most commonly KIAA1459-BRAF fusions (33%), BRAF V600E single-nucleotide variants (17%), and NF type 1 alterations (17%). (16) MEK inhibitors have shown activity against mitogen-activated protein kinase–activated pediatric LGGs, and BRAF inhibitors have shown promise in BRAF V600E–altered tumors. (18)(19)

High-Grade Gliomas

In contrast to LGGs, pediatric HGGs have a dismal prognosis. HGGs include hemispheric high-grade tumors (anaplastic pleomorphic xanthoastrocytoma, glioblastoma), brainstem tumors (diffuse intrinsic pontine glioma), and nonbrainstem diffuse midline gliomas.

Treatment of pediatric HGGs is challenging. Hemispheric tumors may be amenable to surgical resection. Resection is typically followed by radiotherapy and chemotherapy for these tumors, as a Children’s Cancer Group study showed improved survival when chemotherapy was added to radiotherapy compared with radiotherapy alone. Nonetheless, no specific chemotherapy regimen has emerged as a clearly superior standard of care for upfront pediatric HGGs. (20) In contrast, for midline tumors such as diffuse intrinsic pontine glioma, adding chemotherapy to radiotherapy has not been shown to prolong survival beyond the median 9- to 12-month OS and the 10% two-year OS achieved with radiotherapy alone. Several open molecularly based and immunotherapy-driven clinical trials are currently accruing patients, hoping to improve outcomes for these patients. (21)(22)

Molecular studies in pediatric HGGs demonstrate that the biology of pediatric HGGs differs from that of adult glioblastomas. Histone mutations H3.1K27M and H3.3 K27M in midline tumors, and H3.3G34R.V in hemispheric tumors, highlight the influence of epigenetics in pediatric HGGs and portend a poor prognosis. Infant HGGs are biologically distinct from HGGs in older children, with significantly improved survival. NTRK fusions are more common in children younger than 1 year, and TRK inhibitors under investigation are showing promising results. (23)(24)

Germ Cell Tumors

CNS germ cell tumors represent approximately 1% of pediatric brain tumors and are categorized as pure germinomas and nongerminomatous germ cell tumors (NGGCTs). They most commonly arise in the pineal region but can also present in the suprasellar region, fourth ventricle, thalamus, or basal ganglia. NGGCTs secrete α-fetoprotein (yolk sac) or human chorionic gonadotropin
(choriocarcinoma) or both (immature teratomas or mixed), which can be detected in peripheral blood and/or CSF. Pure germinomas can cause modest elevation of human chorionic gonadotropin in the CSF but do not secrete \( \alpha \)-fetoprotein. In some cases, diagnosis can be made based on CSF and serum tumor markers, whereas biopsy is required when tumor markers are inconclusive. Germinomas have a better overall prognosis, with OS greater than 90% compared with 60% to 70% for NGGCTs. Accordingly, germinomas are commonly treated with 4 cycles of chemotherapy (carboplatin/etoposide) followed by radiotherapy to the tumor bed and whole ventricles, whereas NGGCTs are generally treated with 6 cycles of chemotherapy (carboplatin/etoposide alternating with ifosfamide/etoposide) and craniospinal radiotherapy in many cases, although studies are examining whether radiotherapy can be reduced in select patients with NGGCTs to minimize toxicity associated with craniospinal radiotherapy. (25)(26)

Craniopharyngioma

A craniopharyngioma is a suprasellar tumor arising from the remnants of the Rathke pouch containing cystic and solid components. Histologically, they are classified as benign tumors and are divided into adenomatous and papillary subtypes. Due to their location they can severely impair visual, hormonal, and cognitive function. Optimal treatment strategy for craniopharyngioma is controversial; some centers perform a more aggressive primarily neurosurgical approach in an attempt to avoid radiotherapy, and others perform an initial subtotal resection followed by upfront radiotherapy. (27)

TUMOR PREDISPOSITION SYNDROMES

There are several germline mutations that predispose children to specific types of childhood brain tumors in the context of tumor predisposition syndromes. Knowledge of these syndromes is important to the primary care physicians who follow these patients longitudinally. In the child who presents with a brain tumor, especially in the context of other personal history of tumors, family history of tumors at a young age, or characteristic dermatologic findings, it is important to consider further evaluation for these cancer predisposition syndromes. Children with a known family history of cancer predisposition syndromes might require genetic screening for the presence of these syndromes, and specific tumor surveillance if found to harbor one of these mutations. Furthermore, the presence of certain underlying syndromes may alter the choice of therapy for the management of a brain tumor. (28)(29)

Table 4 summarizes selected germline syndromes associated with specific brain tumor types.

**ACUTE AND EARLY EFFECTS OF TREATMENT**

Although the treatment of different tumor types varies significantly, each of the commonly used treatment modalities confers their own risks and acute toxicities.

Major risks of neurosurgery include bleeding, stroke, infection, and damage to nearby structures, as well as morbidity dependent on tumor location. For example, posterior fossa syndrome affects an estimated 8% to 30% of patients who undergo resection of large posterior fossa tumors. Posterior fossa syndrome is characterized by a combination of mutism or significant language impairment, with emotional lability and irritability or motor dysfunction occurring within 2 weeks of cerebellar injury. Signs and symptoms can take months to resolve, and unfortunately many are left with residual deficits. (37)(38) Patients with supratentorial tumors are at greater risk for postoperative seizures and are often started on prophylactic antiepileptic medications. Children with suprasellar tumors are at increased risk for postoperative visual deficits and hormone dysfunction.

Radiotherapy treats tumors by directing high-energy protons or photons at a tumor target to damage DNA. Radiation is fractionated over several weeks to achieve a total dose to the target. Photons are waves without mass, meaning that when concentrated at a point to a certain dose, they also deliver radiation “scatter” at a lower dose on both the entrance and exit side of the wave. Photons have mass, so the radiation is designed to “stop” within the target tissue, releasing the highest amount of energy at that point, minimizing the scatter that exits beyond the target. Acute adverse effects of radiotherapy are mostly due to the radiation absorbed in off-target tissues. With both proton and photon radiotherapy, patients can develop local skin reactions, which generally worsen over the treatment period. Patients receiving intracranial radiotherapy often experience headache or nausea. Craniospinal radiotherapy can cause myelosuppression due to the dose received by the vertebral body bone marrow and can harm the growth plates of the vertebral bodies, resulting in loss of adult height (worse in younger children). Proton radiotherapy is becoming increasingly preferred over photon radiotherapy, particularly for patients who require craniospinal radiotherapy, because it avoids scatter to several important anterior midline organs, such as the esophagus, mediastinum, heart, breast tissue, and intestines. For
**Table 4. Selected Tumor Predisposition Syndromes Associated with Childhood Brain Tumors**

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>GENES KNOWN TO BE INVOLVED</th>
<th>BRAIN TUMORS ASSOCIATED</th>
<th>OTHER ASSOCIATED TUMOR TYPES</th>
<th>BRAIN TUMOR SURVEILLANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdoid tumor predisposition</td>
<td>SMARCB1, SMARCA4</td>
<td>Atypical teratoid rhabdoid tumor</td>
<td>Extracranial malignant rhabdoid tumor</td>
<td>Consider screening if age &lt;5 y or symptomatic (30)</td>
</tr>
<tr>
<td>Gorlin</td>
<td>PTCH1, SUFU</td>
<td>Medulloblastoma (sonic hedgehog subgroup)</td>
<td>Basal cell carcinomas</td>
<td>PTC1H: Screen if symptomatic SUFU: Consider screening if age &lt;5 y or symptomatic (30)</td>
</tr>
<tr>
<td>Familial adenomatous polyposis (Tuscot type 2)</td>
<td>APC</td>
<td>Medulloblastoma, astrocytoma, ependymoma</td>
<td>Colon cancer, osteomas, fibromatosis, others</td>
<td>Screen if symptomatic (28)</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>TP53</td>
<td>Glioma, medulloblastoma, choroid plexus carcinoma</td>
<td>Sarcomas, adrenocortical carcinoma, breast cancer, others</td>
<td>Annual screening from birth (31)</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>NF1</td>
<td>Low-grade glioma, optic glioma, astrocytoma</td>
<td>Malignant peripheral nerve sheath tumor, neurofibroma, leukemia</td>
<td>Yearly clinical assessment and ophthalmology; screen if vision loss or other symptoms of brain tumor (32)</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>NF2</td>
<td>Schwannoma, meningioma, astrocytoma, ependymoma</td>
<td>Malignant peripheral nerve sheath tumor, neurofibroma</td>
<td>Screen brain every 1–2 y and spine every 2–3 y if age &gt;10 y or symptomatic (33)</td>
</tr>
<tr>
<td>Schwannomatosis</td>
<td>SMARCB1 (mosaic or hypomorphic)</td>
<td>Schwannoma, meningioma</td>
<td>SMARCB1: malignant peripheral nerve sheath tumors, rarely other rhabdoid tumors LZTR1: other tumors uncommon</td>
<td>SMARCB1: screen brain/spine at diagnosis, every 2–3 y after age 10 y LzTR1: screen brain/spine at diagnosis, every 2–3 y after age 15–19 y (33)</td>
</tr>
<tr>
<td>Germline retinoblastoma</td>
<td>Rb</td>
<td>Pineoblastoma, primitive neuroectodermal tumor</td>
<td>Retinoblastoma, osteosarcoma, others</td>
<td>Periodic brain MRI until age 5 y (34)</td>
</tr>
<tr>
<td>Simpson-Golabi-Behmel syndrome</td>
<td>GPC3, GPC4</td>
<td>Medulloblastoma</td>
<td>Wilms tumor, hepatoblastoma, neuroblastoma, gonadoblastoma</td>
<td>No established guidelines, screen if clinically indicated</td>
</tr>
<tr>
<td>Constitutional mismatch repair deficiency, Lynch syndrome (Tuscot type 1)</td>
<td>MLH1, MSH2, PMS2, MSH6</td>
<td>Astrocytoma, glioblastoma, ganglioglioma, meningioma, medulloblastoma, hemangioblastoma</td>
<td>Leukemia, gastrointestinal tumors, others</td>
<td>Brain MRI every 6 mo from time of diagnosis (4)</td>
</tr>
<tr>
<td>Tuberous sclerosis complex</td>
<td>TSC1, TSC2</td>
<td>Subependymal giant cell astrocytoma</td>
<td>Renal angiomyolipoma, cardiac rhabdomyoma, fibroma, hamartoma</td>
<td>Surveillance brain MRI every 1–3 y until age 25 y (35)</td>
</tr>
<tr>
<td>Von Hippel Lindau</td>
<td>VHL</td>
<td>Hemangioblastoma</td>
<td>Pheochromocytoma, paraganglioma, renal cell carcinoma</td>
<td>Screen brain/spine every 2 y after age 8 y or if symptomatic (36)</td>
</tr>
</tbody>
</table>

Brain tumor surveillance recommendations are created by consensus groups and change over time. The imaging modality of surveillance is typically brain MRI with and without contrast. Many syndromes also include guidelines for screening for extra–central nervous system tumors, not reviewed here. It is strongly recommended to refer to the most up-to-date guidelines when caring for a patient with a cancer disposition syndrome and to refer families for genetic counseling when available. MRI=magnetic resonance imaging.

Patients receiving focal radiotherapy, proton therapy may spare irradiation to important structures or result in a significantly smaller overall radiation field, depending on tumor location. Comparison plans showing the radiation field and dose for a proton plan versus a photon plan can be helpful to evaluate relative advantages of proton over photon based on the brain structures that would receive a given dose with each plan. Primary limitations to the use of proton therapy are the restricted number of proton radiotherapy centers, requiring some patients to travel long distances for therapy, as well as the relative cost of treatment compared with photon radiotherapy.

A small percentage of patients might experience radiation necrosis, especially in areas treated to high total doses of radiation or that have been irradiated again. In some cases, radiation necrosis is discovered based solely on imaging findings, but symptomatic patients may require medical management with corticosteroids or bevacinumab, or further intervention such as surgery. Research is ongoing into other strategies for treatment of radiation necrosis, such as the use of laser interstitial thermal therapy. (39)

By targeting rapidly dividing cells, chemotherapy medicines kill fast-growing tumor cells but also have off-target effects on other cell types with high turnover rates, such...
as hair, gastrointestinal tract, and bone marrow. Alopecia, although not painful or medically toxic, can be psychologically difficult for patients and parents. Nausea and vomiting affect most patients and, especially when combined with mucositis, contribute to poor appetite and weight loss during therapy. Myelosuppression leads to anemia, thrombocytopenia, and leukopenia. Children are supported with red blood cell and platelet transfusions. Leukopenia causes immunocompromise, making children more prone to opportunistic infections. Patients are maintained on pneumocystis prophylaxis (trimethoprim-sulfamethoxazole is first line) throughout treatment and for at least 6 months after chemotherapy. Fever in the oncology patient is a medical emergency, and neutropenic patients with fever are admitted to the hospital for broad spectrum antibiotic therapy due to the risk of life-threatening infection. Vaccine response is impaired during chemotherapy and shortly after, so routine vaccinations should be deferred during chemotherapy because development of antibodies may be inadequate and live virus vaccines are strictly contraindicated. However, immunocompromised children should still receive yearly influenza vaccination.

In addition to the shared toxicities of chemotherapy medicines, individual chemotherapies carry drug-specific adverse effects. Some commonly used chemotherapy medicines in patients with pediatric brain tumor include vincristine (associated with constipation, peripheral neuropathies, hyporeflexia, and jaw pain), cisplatin and carboplatin (associated with renal toxicity and ototoxicity), and cyclophosphamide (associated with hemorrhagic cystitis).

Novel targeted therapies have distinct mechanisms of action from traditional chemotherapy and thus different adverse effects. MEK inhibitors, for example, are known to cause frequent dermatologic toxicity and gastrointestinal adverse effects and also carry a risk of cardiac toxicity, prompting frequent cardiac surveillance for patients receiving therapy. TRK inhibitors, on the other hand, carry an increased risk of weight gain and long bone fractures.

Immunotherapy medicines such as PD-1/PD-L1 inhibitors activate the patient’s immune system to better recognize and attack tumor cells and thus present a different array of toxicities. Patients taking immunotherapy medicines are at increased risk for development of autoimmune disease and should be closely monitored for autoimmune-mediated processes, including dermatitis, thyroiditis, pancreatitis, and colitis.

**FOLLOW-UP AND LATE EFFECTS**

As advancements in treatment have improved the survival rates of patients with pediatric brain tumors, pediatricians are caring for more survivors with late effects of cancer therapy. Figure 3 shows the multitude of late effects that can impact patients treated for pediatric brain tumors. The number and severity of late effects depend on many factors, including tumor location, age at treatment, treatment modalities, and intensity of treatment.

Survivors of childhood brain tumors, especially those who have received radiotherapy, are at high risk for neurocognitive impairment. Studies have shown a decreased IQ of approximately 10 to 15 points, with radiotherapy at a younger age correlating to worse deficits. The domains most affected are executive function, processing, and working memory.

Cranial radiotherapy also significantly increases the risk of cerebrovascular disease, including stroke, moyamoya syndrome, cavernomas, and aneurysms, which often manifest years after therapy. The Childhood Cancer Survivor Study showed that survivors of CNS malignancy had a 30x increased risk of stroke compared with a sibling control group. Stroke risk correlated with radiation dose and increased over time from completion of therapy, with a cumulative incidence greater than 1% in survivors of brain tumors 10 years after treatment. The imaging findings of radiation-induced vascular infarction can overlap with those of tumor recurrence, so the cumulative risk over time is important to consider when interpreting follow-up imagining in survivors of brain tumor.
hypertension and diabetes significantly further increased stroke risk, underscoring the importance of screening for, and treating, these comorbidities in childhood cancer survivors. (42)

Patients who have had surgery or radiotherapy involving the hypothalamic-pituitary axis can experience endocrinopathies, including growth hormone deficiencies, hypothyroidism, adrenal insufficiency, and sex hormone deficiencies. Certain chemotherapy medications also contribute to risk of infertility in survivors of cancer. Those with hypothalamic injury from tumor, surgery, or radiotherapy are at risk for hypothalamic obesity. (40)

Many survivors of childhood brain tumor experience high-frequency sensorineural hearing loss as well. Although it can occur in the acute phase of therapy, it can also manifest as a late effect in children who have received cisplatin chemotherapy or radiotherapy to structures in the inner ear or auditory nerve. Otoprotective agents may be used in select patients to decrease the risks of certain patients receiving platin-based chemotherapy. Many of these children require hearing aids and other accommodations long-term.

Unfortunately, even after surviving brain cancer, children are at increased risk for a secondary malignancy. Certain chemotherapy agents, such as alkylating agents (eg, cyclophosphamide, lomustine, temozolomide) and topoisomerase inhibitors (eg, etoposide) are known to predispose patients to secondary leukemia later in life. Radiotherapy is also a risk factor for the development of a secondary malignancy within the radiation field. Underlying genetic disorders, such as congenital mismatch repair deficiency of p53 mutations, can further increase this risk. In a study of more than 34,000 survivors of childhood cancer with median follow-up of 21 years, approximately 2% of survivors died of secondary malignancies, accounting for nearly 20% of late mortality in this cohort. However, all-cause late mortality and rate of secondary malignancy in cancer survivors has decreased over time due to efforts to decrease the toxicity of therapy and improve survivorship care. (43)

Brain tumor treatment also takes a toll on the psychological health of survivors, who report higher rates of depression and lower rates of life satisfaction than their peers. In addition, they are less likely to report having close friends, being married, attending college, and being employed. Even compared with other childhood cancer survivors, survivors of childhood brain tumors have significantly poorer psychosocial outcomes. It is imperative for providers to be aware of these disparities and refer appropriately for mental health services, educational assistance, and psychosocial support. (40)

**FUTURE DIRECTIONS IN PEDIATRIC NEURO-Oncology**

Recent advances in pediatric neuro-oncology have enhanced understanding of tumor biology and molecular determinants of disease. Molecularly based clinical trials will promote even greater knowledge regarding molecular predictors of disease severity, response to therapy, and molecularly based treatment strategies, helping to define the role of novel targeted agents in pediatric neuro-oncology (eg, MEK inhibitors, TRK inhibitors, SHH inhibitors).

Unanswered questions remain, such as whether these are most effective as single agents, in combination with one another, or in combination with cytotoxic chemotherapy.

Duration of treatment and duration of response once treatment is suspended also remain to be determined, as well as long-term adverse effects of their use in children.

Immunotherapy is another area of active research. Immunotherapy approaches such as bivalent mab and chimeric antigen receptor T cells drastically improved survival in relapsed acute lymphoblastic leukemia, and the addition of antibody therapy in high-risk neuroblastoma significantly improved survival in this population. Researchers hope that similar gains in survival might be seen with the integration of immunotherapy in the treatment of childhood brain tumors. Several different agents are currently under investigation to enhance immune cell activation and function against brain tumors, including agents such as PD-1 and PD-L1 inhibitors or CD47 inhibitors. Chimeric antigen receptor T cells are also in clinical trials for certain pediatric CNS malignancies expressing specific targets. Vaccine studies for CNS tumors are also being investigated.

Research is also ongoing to minimize morbidity associated with diagnosis and treatment of pediatric brain tumors. Some studies are looking to decrease chemotherapy and radiotherapy in tumor types with excellent survival outcomes, such as WNT-driven medulloblastoma and CNS germ cell tumors. Research is also ongoing to investigate the utility of liquid biopsy as a minimally invasive technique that might be used not only to make a diagnosis, but also to monitor response to therapy or detect early relapse. (44) Liquid biopsy involves the isolation of circulating tumor DNA or proteins from body fluids such as CSF, blood, or plasma, which could potentially decrease the need for surgical interventions.

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CONCLUSIONS

Although pediatric neuro-oncology is a specialized and rapidly evolving field, patients often initially present to their primary care pediatricians. It is essential for pediatricians to be familiar with presenting signs and symptoms, relevant physical examination findings, and acute management of pediatric brain tumors. Knowledge of common tumor types and their treatments, as well as acute and late effects of therapy, is also important as pediatricians continue to follow these medically complex patients during therapy and beyond as essential members of the neuro-oncology team.

Summary

- Based on strong evidence, brain tumors are the most common solid tumors in children and the most common cause of childhood cancer death.
- Based on strong research evidence, patterns of symptoms and physical examination findings at presentation in a child with a brain tumor vary with tumor location.
- Based on research evidence and consensus, brain tumors are managed by a combination of surgery, chemotherapy, or radiotherapy, depending on tumor type, location, dissemination, and age.
- Based on research evidence as well as consensus, the morbidity and mortality associated with childhood brain tumors are determined by many factors, including tumor pathology, tumor genetics, anatomical location, and treatment.

- Based on strong evidence, treatment of childhood brain tumors with radiotherapy and chemotherapy places survivors at increased risk for neurocognitive deficits, neurovascular complications, endocrine dysfunction, secondary malignancies, impaired psychosocial functioning, and other late effects.

Acknowledgment

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To view teaching slides that accompany this article, visit 10.1542/pir.2020-004499.
1. An 8-year-old boy presents with early-morning vomiting, headache, and increased clumsiness. On physical examination, vision and extraocular movements are normal and there is no facial asymmetry or hemiparesis. The physician wants to rule out a brain tumor. Based on his signs and symptoms, which of the following is the most likely location of a brain tumor in this patient?
   A. Brain stem.
   B. Pituitary gland.
   C. Posterior fossa.
   D. Spinal cord.
   E. Suprasellar region.

2. A 10-year-old girl presents with abnormal gait and coordination. She denies headache, back pain, nausea, or vomiting. On physical examination she has left-sided facial palsy and right-sided hemiparesis. She is diagnosed as having a brain tumor. Which of the following is the most likely location of the brain tumor in this patient?
   A. Brain stem.
   B. Pituitary gland.
   C. Posterior fossa.
   D. Spinal cord.
   E. Suprasellar region.

3. A 6-year-old boy is found on physical examination to have numerous café-au-lait spots on his trunk and axillary freckling. His gait and balance are steady. This patient is at greatest risk for which of the following tumors?
   A. Acoustic schwannomas.
   B. High-grade gliomas.
   C. Meningiomas.
   D. Optic pathway gliomas.
   E. Subependymal giant cell tumors.

4. A 2-year-old girl, who was diagnosed as having choroid plexus carcinoma, has a family history of her father with osteosarcoma as a teenager, a paternal aunt with breast cancer at 30 years of age, and a paternal grandmother with adrenocortical carcinoma at 40 years of age. This family is most likely to have which of the following associated conditions?
   A. Familial adenomatous polyposis.
   B. Li-Fraumeni syndrome.
   C. Neurofibromatosis type 1.
   D. Neurofibromatosis type 2.
   E. Tuberous sclerosis.

5. A 15-year-old boy completed treatment for medulloblastoma with surgical resection, craniospinal radiotherapy, and chemotherapy 5 years ago. At this time, he is most at risk for which of the following conditions?
   A. Bleeding.
   B. Hyperthyroidism.
   C. Immune suppression.
   D. Neurocognitive dysfunction.
   E. Visual defects.