Brain Tumors in Children

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Introduction

Tumors of the central nervous system (CNS) (including the brain and spinal cord) are rare in the pediatric population. However, as a group they make up 25% of all childhood neoplasms and represent the most common solid tumor of childhood. Significant advances in surgery, radiation, and chemotherapy have led to better treatment outcomes over the past decades. Although cure rates have been steadily improving for some types of brain tumors, many challenges remain. In this issue of *Current Problems in Pediatric and Adolescent Health Care*, we review the epidemiology, clinical presentation, subtypes, treatment options, and recommended follow-up for children with brain tumors. We hope that this serves as a useful reference for pediatricians, general practitioners, nursing, and oncology trainees for this small but important group of pediatric patients. In this article, the term "brain tumor" is often used interchangeably with "central nervous system tumor," which includes tumors of the spinal cord as well. We limit our discussion to that of primary tumors that arise within the CNS; the number of brain lesions in children representing metastatic disease from extracranial sites is extremely low.[1] This is in contrast to adult patients, where metastatic disease represents a very common type of tumor in the CNS.[2]

Statistics and Epidemiology

In the USA, the largest information data sets on childhood brain tumors are available through the National Cancer Institute's Surveillance Epidemiology End Results Report and through the Central Brain Tumor Registry of the USA (CBTRUS). These 2 organizations publish detailed reports that are available to the public online and provide excellent resources for tracking trends on the incidence and survival by age, geography, race, and tumor type.

According to the latest CBTRUS report (February 2011), the average annual incidence of brain tumors diagnosed in the 0- to 19-year-old age group is 4.84 per 100,000 population. This includes all primary CNS tumors, including those classified as malignant and nonmalignant. Based on these data, approximately 4150 people under the age of 20 are expected to develop a primary brain tumor in the USA in 2010.[3] The prevalence of primary CNS tumors in children 0-19 years old is estimated at 35.4 per 100,000 population, meaning that over 28,000 children are living with this diagnosis in the USA. The Surveillance Epidemiology End Results data report a difference in incidence by race, with primary CNS tumors being more common in whites than blacks (5.02 vs 3.69 per 100,000). A smaller difference was found between males and females, with a slightly higher incidence in males (4.9 vs 4.8 per 100,000).[3]

References occasionally are made in the news media on the "rising incidence" of brain tumors in children, speculating a link with certain environmental hazards or toxic exposures. Epidemiologic evidence to support these theories does not exist,[4] and the actual incidence has not been rising according to the recent CBTRUS analysis.[3] There was a measurable rise in the detection of childhood brain tumors associated with the advent of magnetic resonance imaging (MRI) scanning, presumably because of the dramatic increase in the ability to find CNS tumors. Similarly, the incidence of brain tumors is also reported to be slightly higher in the developed world, most likely accountable to the widespread availability of MRI technology.

When faced with the devastating news that their child has a brain tumor, most parents want to understand why this happened to their child. Most importantly, parents need reassurance that pediatric brain

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Curr Probl Pediatr Adolesc Health Care 2012;42:80-103
1538-5442/$ - see front matter

doi:10.1016/j.cppeds.2011.12.002

tumors occur sporadically, and this diagnosis was not related in any way to their lifestyle or parenting choices. There are only 2 factors linked to an increased risk of developing a primary CNS tumor in childhood: having a history of receiving significant doses of radiation to the CNS, or having been born with certain genetic syndromes. Because early signs and symptoms of a brain tumor will often mimic common complaints, the primary care clinician must have a higher index of suspicion when caring for these 2 groups of patients.

Brain Tumors Associated with Prior Radiation Exposure. Children who have had prior CNS radiation therapy are known to have an increased risk over their lifetime of developing a secondary brain tumor.[5] Although meningiomas and malignant gliomas can occur spontaneously in the general population, they also are known to arise as secondary tumors within a radiation treatment field. It is important to recognize that secondary tumors can occur many years or even decades after initial exposure, which should lower the threshold to obtain imaging in patients with such a history. There has been increasing recognition of the radiation exposure from diagnostic imaging studies, such as computerized tomography (CT) scans and X-rays.[6] Whether the exposure from medical imaging is significant is a difficult question to answer, but is being explored in prospective studies.

Brain Tumors Associated with Genetic Syndromes. There are several genetics syndromes that are associated with an increased risk for the development of CNS tumors. These children deserve closer monitoring and attention to warning signs; it is critical that clinicians who care for these children are aware of the risk, both in terms of the role for surveillance and for the appropriate investigation of new symptoms. Oncologists also need to be aware that many genetic syndromes can be associated with a higher risk for developing secondary malignancies after treatment of the primary tumor, which may influence the choice of chemotherapy or radiation.

Neurofibromatosis Type 1. Neurofibromatosis type 1 (NF-1, previously known as von Recklinghausen's disease) represents 1 of the most common genetic syndromes in the world.[7] It has an autosomal-dominant inheritance pattern and involves a mutation of the gene *neurofibromin* on chromosome 17. Clinical features of NF-1 include café au lait spots, Lisch' nodules (iris hamartomas), neurofibromas, axillary freckling, and bony abnormalities.[7] During their lifetime, approximately 15% of patients with NF-1 will develop a glial tumor of their optic tract (optic pathway glioma).[8,9] These are typically low-grade brain tumors that warrant close observation; the most important method of following these patients is by measuring their visual fields and acuity. Up to 10% of these tumors will become symptomatic, but an optic glioma in a NF-1 patient will usually have a more benign course and may even regress spontaneously.[9-11] Treatment options should aim to spare neurocognitive function, because baseline deficits are not uncommon in NF-1 patients. These patients also have an increased risk of developing secondary malignancies, as well as radiation-induced vasculopathies, such as moya-moya syndrome.[12,13] Aside from optic pathway gliomas, NF-1 patients have an increased chance of developing other tumors throughout the CNS. Brain MRIs for patients with NF-1 will often show multiple small T2 bright, nonenhancing areas called "unidentified bright objects"; these are not tumors and do not require biopsy or treatment.[14]

Familial Cancer Predisposition Syndromes. Familial cancer predisposition syndromes are defined by germ line mutations in specific genes that normally function to protect us against the development of cancer. There are now dozens of known inheritable mutations that may increase the risk of cancer in offspring who carry that specific gene. The "Li–Fraumeni syndrome" (LFS) is the prototype of the familial cancer predisposition syndrome. The genetics of LFS were described over 2 decades ago,[15] and it involves mutations in the "*TP53*" tumor suppressor gene on chromosome 17. Normally, this gene acts to encode a DNA repair protein called p53, which functions as a tumor suppressor. Having this p53 mutation will lead to a higher incidence in family members of developing solid tumors (sarcoma, adrenocorticocarcinoma), cancer in younger people (leukemia, breast cancer), and brain tumors (especially choroid plexus carcinomas). Because cancer is already quite common in the general adult population, criteria to define LFS have been developed, which serve to guide genetic testing strategies and a rational screening program.[16,17]

The retinoblastoma gene Rb-1 was the first tumor suppressor gene identified, and the development of bilateral retinoblastoma in an individual is often associated with a germ line mutation in Rb-1. These patients are also at risk of having a tumor in the pineal region with similar histology (called "trilateral" retinoblastoma)[18,19] and for developing other solid tumors (sarcomas) later in life.

Despite our better understanding of these and other genetic cancer predisposition syndromes, very few children diagnosed with a brain tumor will have a familial cause linked to their cancer. In most patients, taking a detailed family history will guide the need for a genetics referral and possible further testing. Genetic testing should always be arranged in consultation with a Cancer Genetics Program, because the screening implications and the psychological impact of the results can be tremendous for family members.[20]

Neurofibromatosis Type 2. Neurofibromatosis type 2 (NF-2) is due to a mutation in the gene on chromosome 22 that encodes for the protein "Merlin." Patients with NF-2 often will present in the second or third decade of life, typically later than in NF-1 patients.[21] Like NF-1, the diagnosis is usually made clinically based on first-degree relatives and the finding of bilateral acoustic neuromas. Acoustic neuromas are often detected during an evaluation for hearing loss and sometimes can be surgically resected. Patients with NF-2 are at increased risk for developing other rare tumors, such as cardiac sarcomas, and they are at particular risk for developing schwannomas, which can transform into malignant peripheral nerve sheath tumors.[22]

Tuberous Sclerosis. Tuberous sclerosis (TS) is an autosomal-dominant disorder linked to 2 genes, TSC1 (chromosome 9) and TSC2 (chromosome 16). Patients can develop widespread hamartomatous lesions, which lead to multiple organ problems. Cognitive delay and seizures are common, and over 90% of patients are believed to demonstrate some form of CNS involvement. Neuroimaging can reveal "tubers" in the brain; generally these do not require a biopsy or need treatment.[23] Children with TS will be at significant risk for developing a low-grade type of brain tumor called a subependymal giant cell astrocytoma, which seems to respond to therapy with mammalian target of rapamycin inhibition.[24] Having TS also increases the risk for developing other brain tumors, such as malignant gliomas.[23,25]

Von Hippel Lindau. Von Hippel Lindau (VHL) disease is a systemic disorder caused by a mutation in the VHL gene on chromosome 3.[26] Patients develop multiple hamartomatous lesions called hemangioblastomas, which can arise anywhere throughout the CNS. Although these are typically benign lesions with a low-grade histology, they can cause a multitude of problems based on their location. They are extremely difficult to treat surgically because of the high risk of bleeding; radiation is sometimes used to treat severe cases in older children.[26] Children with VHL also have a higher incidence of retinal, pancreatic, adrenal (pheochromocytomas), and renal tumors.[25,27]

Other Syndromes. Gorlin syndrome, also known as basal cell nevus syndrome, results from a known mutation in the "*patched*" gene. Patients with Gorlin syndrome are at high risk of developing a medulloblastoma, and it is this association that has actually led to identifying a potential cell of origin for medulloblastoma.[28] These patients are very sensitive to the effects of radiation; there have been dramatic reports of extensive basal cell tumors developing in the radiation field of patients with undiagnosed Gorlin syndrome.[27,29]

The vast majority of pediatric central nervous system tumors are completely sporadic and have no known cause.

Patients with Turcot syndrome have an increased risk of developing both a brain tumor and colon cancer. These patients are at increased risk for developing malignant gliomas and medulloblastomas.[28,29] This is due to a mutation in 1 of the mismatch repair genes or the APC gene on chromosome 5.

Cowden syndrome, 1 of the "*PTEN* hamartoma syndromes," is an autosomal-dominant disorder with mutations in the *PTEN* encoding region on chromosome 10. These patients can develop numerous hamartomas, including a characteristic CNS tumor called a hamartomatous cerebellar gangliocytoma.[25,30]

There are many other rare genetic syndromes that have been associated with a higher incidence of CNS tumors. Physicians caring for these patients should be aware of this increased risk and be vigilant for any signs or symptoms that might suggest the presence of a CNS tumor.

General Concepts

Clinical Presentation of Children with Brain Tumors

As rare as pediatric brain tumors are, it is a diagnosis feared by both parents and general practitioners alike. Pediatricians are well aware that some parents worry

about a brain tumor when their child presents with common problems, such as headaches or seizures.[31] The confirmation of suspected brain tumors relies on neuroimaging. The decision of whether to obtain an MRI or CT scan with an acute presentation in the emergency room is usually straightforward. By contrast, primary care practitioners may be following the earlier, more subtle signs in their office and face a more challenging decision about when neuroimaging is justified.

Several different types and grades of pediatric brain tumors are described. It should be recognized that whatever the final diagnosis, the symptoms of initial presentation will generally relate to the tumor location and the rate of growth. With so many critical structures confined within the cranial vault, even the most "benign" type of CNS tumor can sometimes be responsible for life-threatening symptoms. Tumors in the frontal lobe may lead to personality changes, seizures, or headaches. A tumor located in the temporal lobe can cause seizures or speech alterations. Tumors of the suprasellar region will present with endocrinopathies or visual changes. Those in the thalamus likely will result in motor and sensory deficits. Tectal plate tumors (top of the brainstem) and pineal region tumors may lead to obstructive hydrocephalus, as will tumors invading the third or fourth ventricles. Cerebellar lesions often will cause nystagmus, ataxia, and vomiting because of hydrocephalus, whereas lesions of the brainstem can disrupt individual cranial nerves or basic life-supporting functions. Spinal tumors can cause weakness and sensory disturbances and affect bowel/bladder function.[32,33]

The presenting symptoms of CNS tumors can generally be categorized into 2 groups.

Obstruction/Raised ICP. Children with brain tumors will often present with an acute or chronic history of raised intracranial pressure (ICP). Infratentorial tumors are more common in children than supratentorial tumors[3,34] and the anatomy in this area is susceptible to blockage in the flow of the cerebrospinal fluid (CSF). An elevated ICP may be building up for days to months, depending on the growth rate of the tumor and its location. The classic presentation includes daily headaches that worsen with Valsalva pressure or lying flat. Vomiting is more common during the night or early morning; any report of morning vomiting should be a trigger for immediate investigation. Hydrocephalus can also cause papilloedema, optic disk pallor, and vision loss; some children present with significant visual impairment. "Sunsetting eyes" or sixth nerve palsies can be "false-localizing" signs; rather than indicate a specific cranial nerve problem, they can be a sign of raised ICP. In the more extreme presentation, a rapidly rising ICP can lead to a decreased level of consciousness and "Cushing's triad" of raised blood pressure, bradycardia, and altered pattern of respiration.

Despite the "classic" signs and symptoms, clinical recognition of rising ICP can be challenging. Infants can have less dramatic symptoms because of the accommodation of their skull bones, before closure of the fontanels and suture lines. Therefore, closely following the head circumference and fontanel size may be more useful than looking for the classic signs of raised ICP. In older children, a pattern of headaches and vomiting may be diagnosed initially as a migraine variant, especially when there is a strong positive family history of headaches. One must appreciate that migraines are exceedingly more common than brain tumors, but close follow-up and measuring the response to therapy should help in deciding which patients to investigate further.[35-37]

Patients with acute hydrocephalus will often require urgent treatment before receiving tumor-directed therapy. For the most acute cases, Cushing's triad represents a medical emergency that requires resuscitation and lowering of the ICP with dexamethasone, mannitol, or hyperventilation. Neurosurgical CSF diversion techniques (third ventriculostomy, ventriculoperitoneal shunt, or extraventricular drain) are often needed to stabilize the patient and allow for further diagnostic investigations. Patients with hydrocephalus who are medically stable may be symptomatically managed on steroids (usually dexamethasone) until more definitive treatment can begin.

Compression or Infiltration of Specific Parts of the CNS.

Headaches. Headaches frequently are of great concern to parents and pediatricians alike. Statistically, only a minute fraction of children who experience headaches will have a brain tumor.[36] Most headaches related to a brain tumor will be accompanied by some sign or symptom of obstructive hydrocephalus, as described in the previous section. Some slow growing tumors will cause head pain by direct compression of the surrounding tissues (skull, meninges).[37] However, many tumors in the brain will present without head-

aches, because much of the brain parenchyma does not have pain receptors.

Vomiting. Most children who vomit because of a brain tumor will have some degree of obstructive hydrocephalus, as described above. In other cases, isolated vomiting can be a presenting sign when a brain tumor presses on 1 of the "vomiting centers" of the brain. A slow-growing tumor near the "area postrema" in the floor of the fourth ventricle can create a prolonged history of vomiting,[38] which may be misdiagnosed as "cyclic vomiting" or a migraine variant.

Neuropathies. Isolated neuropathies can be an ominous sign on presentation; initially, these may be subtle and not noticed by the physician or parents. Children have a remarkable ability to compensate for neurological deficits, and they may not know to draw attention to a particular symptom. A "head tilt" can be a way to correct double vision from a cranial nerve palsy and many children with diplopia will be able to watch television or read without any complaints. Subtle signs, such as an "uneven smile" or ptosis, may happen so gradually that they are hard to notice by people who see them every day. Other diagnoses, such as torticollis, Bell's palsy, postviral cerebellitis, strabismus, and many others, can be at the forefront of the differential that is developing in the clinician's mind.[36]

Occasionally, children will present with a classic syndrome that should raise suspicion of a tumor involving a specific location.[37] The "diencephalic syndrome" is 1 example used to describe the presentation of emaciation, euphoria, and emesis. Children will have a thin, wasted appearance with normal linear growth, a ravenous appetite, and often seem overexuberant on examination. This syndrome can represent the presence of a tumor in the diencephalon, placing the child at high risk of hypothalamic disturbance.[39,40] Parinaud's syndrome (also known as dorsal midbrain syndrome) can be found in patients with tumors in the pineal region or upper brainstem.[41] These patients have supranuclear upgaze palsy, and pupils that are reactive to accommodation but not direct light. When they attempt to look up quickly, they demonstrate convergence-retraction nystagmus, with the globes pulling inward.

Before the initiation of tumor-directed therapy, patients with compressive symptoms may benefit from a short course of steroids (usually dexamethasone). Steroids often will alleviate symptoms within several hours and stabilize the patient until the initiation of the definitive therapy. For symptoms that are severe or life-threatening, early neurosurgical intervention must be prioritized.

Seizures. Despite the assumption of many worried parents, a very small proportion of new onset childhood seizures is related to a brain tumor.[33,42] However, low-grade tumors located in the cerebral cortex can cause seizures with very few other presenting symptoms. The tumor creates a seizure focus and may initiate partial or generalized seizures because of direct tumor compression or invasion. The seizures can be difficult to control, and multiple anticonvulsants may be required. Ultimately, if the area of seizure focus can be identified, surgical resection may provide a curative solution. Electroencephalography can assist in the surgical planning by mapping the area of focality, and intraoperative electrocorticography can help guide the surgeons in determining when a sufficient resection has occurred.[43]

Endocrinopathies. Tumors involving or compressing the hypothalamic–pituitary axis can lead to endocrinopathies, which may serve as the only presenting symptom of a childhood brain tumor. New onset diabetes insipidus should lead to neuroimaging and a full evaluation, but this disorder can be subtle in its early presentation. Fluctuations in serum sodium levels with diabetes insipidus can lead to excessive thirst, extreme water intake, and seizures. Correction should be gradual and cautiously monitored. Patients with compression or invasion of their pituitary stalk from a tumor can have adrenal insufficiency and may require stress dose steroids at diagnosis or presurgery.

Precocious or delayed puberty and disturbances in growth can be other ways in which brain tumors present, even though the differential diagnosis for these findings is extensive.

Spinal Cord. Although generally less common than intracranial tumors, isolated spinal cord tumors can present with back pain, scoliosis, neuropathic pain, areas of numbness, or limb weakness. Bowel or bladder signs usually represent a late and very concerning finding.[37] Acute spinal cord compression warrants an immediate neurosurgical consultation, and steroids should be started while further treatment planning occurs. In situations where surgical resection or debulking cannot be performed, emergency radiation therapy or chemotherapy may be used in an attempt to save spinal cord function.[44]

Diagnosis

Centralized Care. When a brain tumor is suspected, the acuity of the presentation dictates whether a child can be referred to an outpatient neurosurgery clinic or urgently transported for emergency care. In the more acute setting, stabilizing a patient locally is critical but every effort should be made to transport a new patient to a regional center that specializes in pediatric brain tumors. If transport is not possible, most large medical centers are able to provide recommendations for the best initial direction of care based on the patient's history, examination, and neuroimaging studies.

Imaging. Children experiencing a slow progression of their symptoms may wait appropriately for the scheduling of an elective outpatient MRI; however, patients presenting with acute symptoms will typically undergo a noncontrast head CT as their first imaging technique. One exception might be for infants with an open fontanel, where an ultrasound may be a safer and more useful initial test for investigating a rapid increase in head circumference. Generally, the role of CT for imaging a suspected brain tumor should be reserved for potentially unstable patients, given the degree of radiation exposure. Once a lesion is suspected by clinical examination or initial imaging, the definitive imaging test is a high-quality MRI with and without contrast. Neuroradiologists use a wide variety of imaging techniques, but the following image types describe some of the neuro-oncology basics:

T1 image: used to define anatomy, will reveal area with concentrated blood products, fat in the brain, and visualize cystic areas of fluid

T1 + contrast: areas that are "contrast-enhancing" represent breakdown in the blood–brain barrier, often due to swelling and distorted tumor vasculature, or necrotic areas within a tumor

T2: "bright" or hyperintense areas represent an increased amount of fluid (water signal), with the ventricles and eye globes appearing bright

FLAIR (fluid attenuated inversion recovery): 1 imaging type that is used to show areas of swelling or edema surrounding tumor tissue

Diffusion-weighted imaging, fast steady-state acquisition imaging, spectroscopy, and many other MRI tools are used at the discretion of the neuroradiologist to help further investigate some tumor types.[45,46]

The role of functional neuroimaging is evolving in the diagnosis of pediatric brain tumors. Positron imaging tomography scanning is now widely used in studying extracranial solid tumors and is able to provide additional useful information about some CNS tumors. New imaging technologies and contrast molecules are being investigated that may facilitate the differentiation of high-grade from low-grade tumors. This would help to determine the appropriate timing of surgery and even help guide the extent of initial surgical resection required.[47,48]

Histology. One of the first questions that many parents have is whether their child's tumor is "benign" or "malignant"; these words have tremendous implications to the layperson and are often interpreted to mean the difference between "life or death." However, the distinction between "benign" and "malignant" is complicated when dealing with most pediatric brain tumors. Location is often an important factor in determining the prognosis; a "benign" tumor in an unresectable location could signify as poor a prognosis as a "malignant" tumor in a surgically accessible region of the brain. The age of the child often dictates the amount and type of treatment that can be used, which therefore also significantly affects prognosis. Although the "grading" of a pediatric brain tumor refers to its microscopic appearance, it does not always reflect prognosis. Tumors are graded 1 through 4, with 1 being the lowest grade and 4 the highest; grade 1 and 2 usually are called "low grade," whereas grades 3 and 4 are considered "high grade."

The accuracy of classification and grading pediatric brain tumors does depend on the expertise and experience of the neuropathologist. A main reference source for subtypes and nomenclature is provided by the World Health Organization (WHO), in the publication "Tumors of the Central Nervous System." The latest version, issued in 2007 (4th edition), describes hundreds of different tumors. The clinical team relies on the neuropathologist to use the appropriate diagnostic tools to determine the final pathologic diagnosis. Depending on the tumor type and complexity of the case, identification after surgery may take several days or even weeks.

The primary tool for the pathologist remains the microscopic examination of the histologic specimen focusing on cell size, spacing, shape, nuclear division, and other factors. Immunohistochemistry is an evolving field that uses special stains to distinguish tumor subtypes. The field of tumor genetics is rapidly growing and sophisticated tools are being used to detect genetic mutations that act as a "molecular signature" to identify tumors. As the diagnosis of rare pediatric brain tumors is challenging, difficult cases often are

sent for second opinions from other experienced pathologists.

Treatment

Multidisciplinary Team Approach. The treatment and care of children with brain tumors are increasingly complex and require an array of disciplines and resources from within the health care system. Consequently, many small pediatric oncology centers attempt to centralize their resources when treating brain tumors.

For any pediatric solid tumor, the principles of treatment rely on a combination of surgery, radiation, and medical therapy. The primary treating physician team will usually include a neuro-oncologist, neurosurgeon, and radiation oncologist. Pediatric neuro-oncology is a growing subspecialty and refers to the physician who guides and coordinates medical treatment (ie, chemotherapy) and the follow-up care. At most centers this will be either a pediatric-trained hematologist/oncologist or a pediatric neurologist. The pediatric neurosurgeon who has a special interest and experience in tumor surgery is critical to any program. A radiation oncologist with pediatric expertise also is crucial during the consultation and care of most children with brain tumors.

Beyond this primary team of clinicians, it is necessary to have expertise available from other pediatric specialists and general pediatricians. The availability of consultants is very important in cancer care, because the impact of the tumor and/or treatment can involve almost every organ system in the body. The diagnostic medical team also plays a vital role in the quality of any neuro-oncology program. Specially trained pediatric neuroradiologists and neuropathologists are needed to provide the most accurate diagnosis possible, which is critical in choosing proper treatment. Pediatric ophthalmologists are critical in evaluating optic pathway tumors and conducting surveillance for tumor growth or recurrence.

Comprehensive pediatric neuro-oncology programs also need to have a specialized multidisciplinary team for the successful management of children with brain tumors. The tremendous impact of this diagnosis on a family demands that psychologists or a counseling team be involved from the time of diagnosis. A neuropsychologist and school liaison professionals can measure cognitive status accurately and address school reintegration issues. Physical, occupational, and speech-language therapists play a vital role in the rehabilitation of children after surgery and treatment. Social workers assist with the tremendous burden of cancer treatments on the family, financially and otherwise. Throughout their treatment, children and families benefit from having nursing staff with pediatric neuro-oncology expertise, both on the hospital wards and in the clinic setting. For symptom management and end-of-life care issues, an experienced hospital- or hospice-based palliative care team is an invaluable asset.

Surgery. Children with brain tumors should be assessed by surgeons who have specific expertise in pediatric neurosurgery. The level of surgical expertise has been shown to have a positive impact on outcomes,[49] and because surgery is needed to treat most pediatric brain tumors, it is a central component of any brain tumor program. Patients with acute deterioration on presentation often will need urgent intervention to deal with compression or hydrocephalus. Sometimes a biopsy will be most appropriate, with the surgeon obtaining just enough tissue to determine a diagnosis or guide therapy. Some tumors will need to be "debulked," where the goal is to remove as much of the tumor as possible to provide a diagnosis and relieve symptoms, while avoiding more aggressive approaches. Finally, for some tumor subtypes, the patient's survival truly depends on achieving a "gross total resection," where the surgeon balances the potential morbidity against a life-saving aggressive resection.

Advances in surgical skill sets and technology are continuously improving the rate of successful complete resection while decreasing surgical morbidity. Endoscopic surgery has allowed for minimally invasive approaches for tumor biopsy, or the relief of hydrocephalus by an "endoscopic third ventriculostomy." This technique involves creating a hole in the third ventricle to divert CSF flow around an obstruction. An endoscopic third ventriculostomy can spare children from potentially requiring a ventriculoperitoneal shunt and therefore decrease rates of shunt complications and the potential for extracranial spread of tumor cells. Increasingly sophisticated neuromonitoring during brain and spine surgical procedures has allowed surgeons to recognize exactly how close they are to critical nerve structures during the resection. Intraoperative MRI suites are becoming available, allowing surgeons to take a "live-time" image of the surgical resection cavity and continue to remove residual tumor that is identified. These and many other

techniques have allowed for great advances in the surgical aspects of neuro-oncology.[50]

Radiation. Radiation therapy refers to the delivery of high-energy beams to areas of suspected or known tumor. Most commonly, centers use photon energy (X-rays) delivered to a focal area (ie, the tumor bed) or to the entire craniospinal axis (whole brain and spinal cord). Radiation is given in daily fractions in an outpatient setting, usually for a total course lasting 6 or 7 weeks. This schedule allows a patient to tolerate large doses without suffering significant damage to the surrounding normal tissues, thus maximizing the chance of killing tumor cells. A different technology known as "proton" radiation is being offered in a growing number of centers in the USA.[51] Although the total dose delivered to the tumor remains the same with protons, there is an ability to provide a more focused beam with sharper margins, and to determine the endpoint at which the maximal radiation will be delivered. In some cases, this can be advantageous for treating young children to reduce long-term side effects.[52,53]

Whatever source of radioactive energy is used, technology is continually improving our ability to spare normal tissue by delivering radiation to the tumor in a more precise fashion. Concurrently, many pediatric clinical trials are addressing the question of whether reducing the radiation dose will provide a comparable cure rate for a given tumor.[54] Increasing the knowledge of the long-term physical and neurocognitive impact of radiotherapy on young children is critically important in making treatment decisions about the optimal dose of radiation.[55-59]

Chemotherapy. The role for chemotherapy in the treatment of brain tumors was realized more recently than for surgery or radiation. Multiple challenges exist in delivering chemotherapy to the CNS, including overriding the blood–brain barrier that is designed to prevent toxins from infiltrating of the CNS. Systemic toxicity can be significant even when drug delivery into the CNS is minimal. Although delivery of chemotherapy directly into the CSF space can treat disease close to the CSF–brain interface, drug penetration deep into the brain parenchyma remains poor.[60]

Given the rarity with which brain tumors are seen in children and adolescents, efforts should focus on enrolling patients into clinical trials whenever possible. Because even large referral centers may treat a small number of each specific tumor types per year, cooperation among centers is crucial to understanding the efficacy and impact of treatments. The largest network in North America is the National Cancer Institute funded "Children's Oncology Group," which includes over 200 centers worldwide. The Children's Oncology Group is responsible for the design and operation of some of the largest clinical trials in children. Other groups operate in fewer centers and are designed to provide access to more experimental therapies; examples include the Pediatric Brain Tumor Consortium and the Pediatric Oncology Experimental Therapeutics Investigators Consortium. Information about pediatric clinical trials for brain tumors can be found at the US National Institutes of Health web site, http://www.clinicaltrials.gov.

Chemotherapy for childhood brain tumors can be used in different situations. First, lower doses of chemotherapy are used over extended periods in an attempt to slow or halt the growth of low-grade tumors. Because the duration of treatment could potentially be years, this therapy must be well tolerated and designed to minimize long-term toxicity. One example of this is the weekly use of intravenous vincristine and carboplatinum in the management of unresectable low-grade gliomas.[61] Second, higher doses of chemotherapy are used as adjuvant (after) or neoadjuvant (before) treatment to enhance treatment with surgery and/or radiation. The classic example is in medulloblastoma, where patients will have a better chance of survival if they receive chemotherapy after their surgery and radiation.[62] Third, high doses of multiagent chemotherapy are being used to treat infants and young children to prevent or delay the need for radiation therapy. Over the past 2 decades this treatment approach has been used with some success, and many protocols will use autologous stem cell rescue to help children recover from the bone marrow toxicity of their chemotherapy. It must be recognized that these treatments are acutely more toxic and survival rates may be lower than using standard radiation techniques, but for the youngest patients this has to be balanced against the devastating long-term effect of radiation.[63] A fourth way of using chemotherapy is in its role as a radiation "sensitizer"; patients will receive daily or weekly chemotherapy during radiation therapy to increase its effectiveness in some tumors.

Having used traditional cytotoxic chemotherapy for decades, the field of neuro-oncology is now looking toward the use of more targeted therapies and biological agents. Many newer drugs have been designed to

target known pathways in tumor cell signaling, rather than relying on nonspecific toxicity to the cell. Inhibition of tyrosine kinases, histone deacetylases, the sonic hedgehog pathway, and mammalian target of rapamycin represent just a few examples being explored in clinical trials. There may be a role for tumor "maturation" agents, with oral drugs, such as retinoic acid, being used in current trials. Other approaches, such as the "antiangiogenic" vascular endothelial growth factor antibody bevacizumab, have shown promise in adult studies and therefore are being investigated in pediatric patients. Phase I and II clinical trials aim to learn more about the safety and efficacy of novel agents, many of which will have been used in adult trials and other solid tumors first. Clinical trials are also underway to investigate viral and gene therapy in the treatment of brain tumors, infecting tumor cells directly or stimulating the body's own immune system as a way of targeting tumor cells.[64-66]

Types of Pediatric Brain Tumor Gliomas

The word "glioma" can refer to any tumor originating from glial tissue, whether benign or malignant (Fig 1). Glial tissue is found throughout the CNS. It acts as a scaffolding network and connective tissue array that plays different roles in different parts of the brain. Thus, glial origin tumors can be found in every different part of the brain and spinal cord; some form of glioma is almost always on the differential diagnosis when looking at a new CNS lesion on an MRI. The primary glioma subtypes are defined by the 3 most common types of glial tissue:

- Astrocytes—cells found throughout the CNS that play many supportive and regulatory functions
- Ependymal cells—cells that line the ventricles
- Oligodendrocytes—myelin-forming cells found at the gray--white junction (which will not be discussed separately in this article).

Astrocytomas

Low-Grade Astrocytomas

"Low-grade astrocytomas" (LGA) include the WHO grade I and II astrocytomas and are the most common type of brain tumor found in childhood. Because glial tissue is found everywhere in the CNS, these tumors can occur in any area of the brain or spine, but in children LGAs most often occur in the posterior fossa.[67] By histology, the most common subtype is called "juvenile pilocytic astrocytoma" (JPA), which is classified as WHO grade I. JPAs account for approximately 20% of brain tumors in children.[3] WHO grade II tumors are referred to as "fibrillary astrocytomas" and are considerably less common than JPA.

- Glial origin tumors
  - Astrocytoma & other gliomas
    - Low grade
    - High grade
  - Ependymoma
- Embryonal tumors
  - Medulloblastoma
  - CNS Primitive neuro-ectodermal tumor
  - Atypical Teratoid Rhabdoid Tumor
- Choroid Plexus Tumors
  - Papilloma
  - Carcinoma
- Germ Cell Tumors
  - Germinoma
  - Non-germinomatous germ cell tumor
- Craniopharyngiomas

FIG 1. Main categories of childhood CNS tumors.

Background and Presentation. Like most childhood brain tumors, astrocytomas will often present in the infratentorial region; therefore, the typical clinical presentation is that of ataxia, vomiting, or headache because of raised ICP (Fig 2). However, it should be noted that by implication low-grade tumors grow very slowly and therefore many children will present with months or even years of symptoms. With subtle, slowly worsening symptoms, it can be difficult for the clinician to recognize these signs as being suggestive of or compatible with a brain tumor.

FIG 2. Juvenile pilocytic astrocytoma of the posterior fossa. Note the large cystic and smaller components (MRI sagittal image, T1 + contrast).

Another common area of presentation in childhood is in the optic pathway, where these tumors clinically can present with proptosis or with gradual visual deterioration. As mentioned in the previous section, children with NF-1 are particularly susceptible to developing optic pathway gliomas and should have regular ophthalmology follow-up.

On MRI imaging, JPAs usually appear as well-circumscribed and strongly enhancing lesions that are bright on T2 imaging. Cystic areas are commonly seen. Very little surrounding edema is seen on FLAIR imaging. Occasionally low-grade tumors in the posterior fossa can result in actual thinning of the occipital skull bone as they slowly grow over long periods.

Treatment

Surgery. LGA generally occur in 1 location and do not tend to spread throughout the CSF. JPAs typically are well-circumscribed, and if they are in a surgically accessible location, then excision can be curative. By contrast, optic pathway gliomas make up a significant portion of LGAs in children. These are generally not surgically resectable without compromising the child's vision, and even a biopsy in this area can be risky. Thus, some optic pathway gliomas are diagnosed based on a characteristic MRI appearance, rather than subjecting the patient to a surgical procedure.

Radiation. For most children with LGA, every attempt should be made to delay radiation as long as possible. Although most of these tumors will respond to radiation therapy, the significant long-term side effects make radiation hard to justify as an initial therapy in a patient population with excellent long-term survival. In older patients, radiation is generally tolerated better and can be quite effective in treating a growing unresectable lesion.

Chemotherapy. Because surgical resection is the goal of treating LGA, chemotherapy is not always necessary. However, with the desire to avoid radiation therapy, several clinical trials have been able to demonstrate a role for chemotherapy in stabilizing or shrinking LGA.[61,68] Today, most children with progressive, unresectable LGA are given chemotherapy for at least 1 year, recognizing that re-treatment is often needed later in life.[69]

Prognosis and Follow-Up. The general prognosis for pediatric LGAs is very good, and overall survival at 5 years is greater than 90%.[67] Complete surgical resection usually is curative, but even after a gross total resection, children generally should be followed on a routine basis and have a repeat MRI scan every few months for a few years after surgery. The intervals between MRI scans will increase if no recurrence is seen, and eventually children will require follow-up appointments every 1 to 2 years. Children with residual disease benefit from closer follow-up, including MRI scans and ophthalmologic assessments to look for change in the tumor size, enhancement, ventricle size, and visual fields. This information will assist in the decision of when to start (or restart) treatment.

Because LGA tend to recur locally, routine surveillance imaging is focused on the primary site of disease. For patients with tumors of the optic pathway, visual screening is a key component of follow-up and often can be more useful than MRI imaging in determining significant changes.

High-Grade Astrocytomas

Background and Presentation.

Case 1: Diffuse Pontine Glioma. A 4-year-old girl presents with an acute 2- to 3-day history of ataxia. Her parents report that she is "walking like she is drunk." Of note, she is drooling, her speech is a little slurred, and she is having difficulty swallowing. On physical examination, she has bilateral sixth cranial nerve palsies, facial asymmetry, and significant gait ataxia.

FIG 3. High-grade astrocytoma, posterior fossa. A heterogeneous or "ring-enhancing" appearance is a common finding (MRI axial image, T1 + contrast).

"High-grade gliomas" primarily include the WHO grade III or IV high-grade astrocytomas (HGA) (Fig 3). These make up most primary brain tumors in adults, but account for only 10% to 20% of pediatric tumors.[3] Like LGAs, these can occur in any location within the brain or spine. By nature, these are more infiltrative, more aggressive in the speed at which they grow, and more likely to recur after treatment. By histology, WHO grade III astrocytomas are called "anaplastic astrocytomas," and WHO grade IV is designated as "glioblastoma multiforme."

Although "high grade" is a histologic description, it implies faster tumor growth. Children with HGA usually will have a shorter duration of symptoms before presentation when compared to those with an LGA. The presenting clinical features will depend on the location of the tumor and usually involves direct invasion or compression of the brain resulting in neurologic deficits. Thus, seizures, cranial neuropathies, and hemiparesis are common findings at the patient's presentation.

HGA will typically have a heterogenous appearance on MRI with absent enhancement or areas of ring enhancement, and significant edema on FLAIR imaging. Lesions typically have poorly defined margins and can demonstrate "mass effect" by compressing or displacing the surrounding structures.

HGAs tend to occur in 1 primary location and do not typically spread throughout the CNS. However, they occasionally present with a diffuse pattern of spread throughout different parts of the brain parenchyma, a radiologic pattern referred to as "gliomatosis cerebri." In this case a biopsy most often will reveal histology consistent with glioblastoma multiforme, which will not be amenable to surgical resection because of its diffuse pattern.

When arising in the pons of the brainstem, a unique entity called "diffuse intrinsic pontine glioma" (DIPG) will generally behave in a high-grade fashion. DIPGs make up almost 10% of all pediatric brain tumors. They cause significant neurologic deterioration, typically with a brief history of progressive cranial nerve deficits. The diagnosis of a DIPG most often is based on neuroimaging alone. The risk of surgical biopsy of a tumor in this location is not insignificant and usually can be avoided if the MRI features are compatible with the diagnosis. The classic findings of these tumors on MRI are nonenhancing and hypointense on T1-weighted imaging, and hyperintense on T2-weighted imaging.[45]

Treatment

Surgery. Surgery has a role in the treatment of most HGA.[70] However, the higher the grade, the more locally infiltrative the tumor, thus making complete surgical resection of most HGA practically impossible without resecting a significant amount of surrounding normal brain tissue. Radical surgical resection has been shown to improve outcomes[71] but often a biopsy or debulking surgery is all that can be achieved. The thalamus and the pons are 2 such locations where extensive surgery is generally not feasible. For diffuse pontine gliomas, there is no curative role for surgery and the vast majority of cases will not need to be biopsied to establish the diagnosis. However, some oncology centers are starting to biopsy diffuse pontine glioma tumors to understand their biological characteristics better, with the hope of being able to identify therapeutic targets.[72,73]

Radiation. As most HGA will respond to radiation, this therapy is a critical component for prolonging survival in most patients.[74,75] High-dose focal radiation after maximal surgery is the best known strategy for treating high-grade gliomas. Craniospinal radiation

typically is unnecessary as these tumors do not tend to spread via the CSF.

Chemotherapy. Historically, chemotherapy has not played a major role in the treatment of HGA.[76] Although not yet part of "standard" treatment in children, there have been studies with chemotherapy agents that have shown some promise.[66,77,78] One of the current chemotherapeutic drugs of interest in adults is temozolomide, an alkylating agent with relatively good CNS penetration.[79,80] In 2005, a large adult series was published that demonstrated an increased duration of survival in patients who received radiation plus temozolomide vs radiation alone.[81] Subsequent analyses revealed that the methylation status of the promoter of a DNA repair gene differentiated those patients who would have a better response to temozolomide.[82] When methylated, the DNA repair gene promoter is "turned off," which downregulates the transcription of a protein called methylguanine methyltransferase. As an example of epigenetic modification, being "methylated" seems to make the tumor cell less resistant to treatment with drugs like temozolomide. These same promising clinical data for adults have not yet been reproduced in pediatrics.[75]

Prognosis and Follow-Up. High-grade gliomas generally have a very poor prognosis; despite aggressive treatment with surgery and radiation, fewer than one-half of patients are alive 2 years following diagnosis and long-term survival rates are very low.[83] Patients with anaplastic astrocytoma do tend to survive longer than patients with glioblastoma multiforme tumors. Long-term survivors of a true DIPG tumor are almost unheard of. After their initial therapy, children should be carefully monitored with follow-up MRI scans, and when their disease recurs, they may be offered participation in phase I or II clinical trials and have palliative care services available.

Ependymoma

Background and Presentation

Ependymomas account for approximately 6% of all childhood CNS tumors[3] (Fig 4). These tumors typically arise from the ependymal lining of the ventricles, and most commonly the fourth ventricle in children.

Microscopically, the "classic" ependymoma pattern is classified as WHO grade II, whereas an anaplastic variety exists as WHO grade III. There also is a unique form of spinal ependymoma called myxopapillary ependymoma, which is classified as WHO grade I.[84]

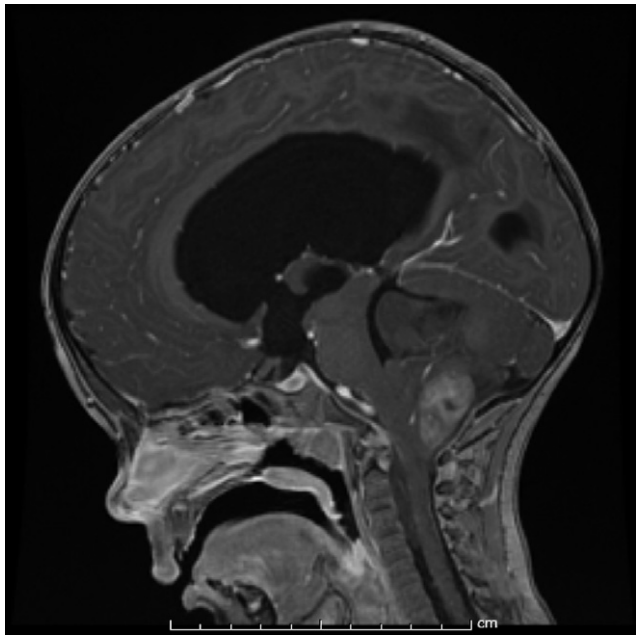

FIG 4. Ependymoma arising from the fourth ventricle, causing severe obstructive hydrocephalus (MRI sagittal image, T1 + contrast).

On MRI imaging, an ependymoma appears as an enhancing lesion that often extends through various foramina. Obstructive hydrocephalus is a common presentation because of the typical location of the tumors in the fourth ventricle, with cranial neuropathies and cerebellar signs often found as well.

Ependymomas typically present as unifocal disease, but in up to 10% of cases,[85] they can spread throughout the brain or spine, and very rarely outside of the CNS. Diagnostic workup should include a baseline spine MRI and CSF sampling.[86]

Treatment

Surgery. The benefit of complete surgical resection has been demonstrated for pediatric ependymomas, and therefore, gross total resection by an experienced neurosurgeon should be the first line of therapy whenever possible. The extent of resection is believed to be very important for survival, and re-resection is justified when the postoperative imaging suggests residual disease.[87-89]

Radiation. Postsurgical radiation therapy to the resection cavity improves survival for children with ependymomas, even after complete resection.[90] High

doses of radiation are given locally, unless there is evidence of distant metastases (ie, disease on spine MRI or tumor cells identified in the CSF). The 1 exception is for a complete resection of the tumor in the supratentorial region, with studies revealing a classic histologic pattern. For these patients, some studies have limited follow-up to close observation only, without up-front radiation.[89,91]

Chemotherapy. An ependymoma is not a very "chemoresponsive" tumor.[88] Because the prognosis of these children is so dependent on the ability to achieve a total resection, chemotherapy has been used in an attempt to shrink residual tumor and allow surgeons to achieve total resection in a "second-look" surgery. This has been done with some success in the past,[92] and current clinical trials are investigating the role for postradiation chemotherapy in preventing recurrence.

Prognosis and Follow-Up. Children with ependymomas having undergone gross total resection followed by focal radiation have a good prognosis, with an approximately 80% 5-year survival. If gross total resection is not achieved, their 5-year survival dramatically worsens with most studies reporting a drop to 20% to 30%. Thus, the accessibility of the tumor to resection (and the availability of experienced surgeons) determines the chance of survival. Patients with ependymomas require follow-up for many years, because late recurrences can occur. If the tumor regrows in an accessible location, there is often a role for surgical re-resection, which often can provide months or years of extended survival.[93]

Embryonal Tumors

Background and Presentation

Case 2: Posterior Fossa Mass. *A 6-year-old boy presents with a 3- to 4-week history of intermittent headaches and vomiting. He has had no diarrhea, fever, or rash. He describes diplopia and his parents report that he now is walking unsteadily. His physical examination is notable for gait ataxia, dysmetria, and diminished rapid alternating movements. The remainder of his physical examination is unremarkable*.

Embryonal tumors (sometimes referred to as neuronal tumors) represent the largest group of malignant tumors in childhood and can occur anywhere throughout the brain and spinal cord (Fig 5). They often are referred to in a broad category as "primitive neuroectodermal tumors" (PNET), which is a distinct term

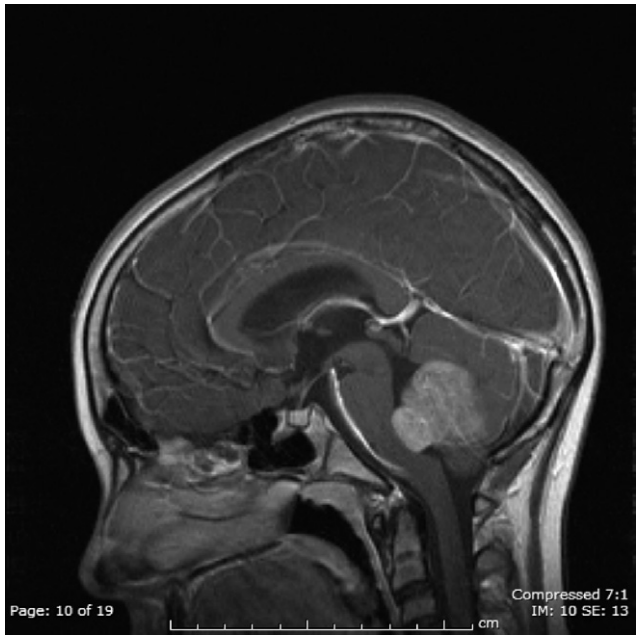

FIG 5. Medulloblastoma, arising from the cerebellum and growing into the fourth ventricle (MRI sagittal image, T1 + contrast).

from the "peripheral neuroectodermal tumor" label given to certain extracranial sarcomas (ie, Ewing's family of tumors). Embryonal tumors generally are classified by their location: in the posterior fossa they are called medulloblastoma; in the pineal region they are called pineoblastomas; and in other locations they fall under the category of "central nervous system PNET." There is also a relatively new entity called the "atypical teratoid rhabdoid tumor" of the CNS, which carries a distinctive genetic mutation on chromosome 22.[94] These can develop anywhere throughout the CNS, generally occur in young children, and carry a worse prognosis than all other embryonal tumors.[95]

Medulloblastoma is the most common type of embryonal tumor found in childhood. It is further classified by its microscopic appearance into various subtypes: classic, nodular/desmoplastic, or large cell/anaplastic.[84] These subtypes are related to prognosis and therefore have traditionally been used to guide treatment. More recent studies have shown that there are different molecular subtypes and genetic patterns that are able to predict better outcomes, and these will likely be incorporated into the next generation of clinical trials.[96-99]

The current treatment for embryonal tumors is based on accepted criteria for risk stratification: "standard

risk" patients are designated by having a medulloblastoma with classic histology, a successful gross total resection (allowing up to 1.5 cm^2 of residual disease on MRI), and no metastatic disease on spine MRI or CSF sampling.[100] All other patients are considered high risk. The age of the patient also plays a major role, because craniospinal radiation can be so detrimental to very young children. Tumor location is critical in deciding the intensity of treatment, because only the cerebellar location (ie, medulloblastoma) has been studied sufficiently to justify a decrease in therapy intensity. Pineal region PNET tumors have been shown to have a worse prognosis than those in other areas.[101,102]

A significant proportion of embryonal tumors already will have metastatic disease at presentation.[103,104] All patients require an MRI of their spine, and lumbar puncture for CSF sampling (usually 2 weeks after surgery). Although metastatic disease outside of the brain and spine is very rare, it can occur.[105] Any signs or symptoms of extracranial metastasis should lead to prompt baseline investigation, and many clinicians will include a bone marrow aspirate as part of their staging workup.

Treatment

Surgery. Surgery plays a vital role in the treatment of all embryonal tumors. Gross total resection should be the goal, yet because these tumors generally respond to chemotherapy and radiation, surgery may be slightly less aggressive to preserve neurologic function.

Radiation. Radiation therapy has been used for decades as a key component of therapy for embryonal tumors.[106] The frequency of metastatic spread throughout the CNS suggests that the entire craniospinal axis needs to be treated to maximize cure and prevent distant recurrence. For medulloblastoma, specifically, large clinical trials have stratified patients to determine whether the total radiation dose can be safely reduced.[54,62] Using adjuvant chemotherapy, this seems to be possible while achieving similar survival rates.

Chemotherapy. The embryonal tumors respond to chemotherapy to varying degrees and the use of postradiation chemotherapy have been demonstrated clearly to improve survival.[54,62] Traditional cytotoxic chemotherapy, such as vincristine, etoposide, alkylators, and platinum agents, are used in most protocols for newly diagnosed patients. Determining organ function is important before therapy, with particular attention to baseline hearing and kidney assessments because of chemotherapy toxicity. Intensified postsurgical chemotherapy has been studied for younger patients to avoid or delay the need for radiation.[107-109] Although survival rates are probably not quite as good without radiation, this strategy aims to provide an acceptable cure rate for patients while limiting the devastating neurocognitive consequences of radiation.[55,104]

Prognosis and Follow-Up. The embryonal tumors in childhood are treatable, and moreover, they are often curable. For example, standard risk medulloblastoma treated with radiation and chemotherapy after gross total resection has a 5-year survival of over 80%.[103,104]

Outside of the posterior fossa, pineoblastomas and CNS PNETs usually carry a worse prognosis than medulloblastoma. Currently these are treated with more intensive protocols with less emphasis on reducing radiation and chemotherapy doses. Further studies are needed to understand better these tumors as they appear to have distinct molecular and genetic features from medulloblastomas.[110] Atypical teratoid rhabdoid tumor has demonstrated an even worse prognosis on standard therapy, although recent studies have been using an intensive sarcoma-based treatment approach with some improvement in survival rates.[111]

Surveillance imaging has been shown to improve survival for patients with medulloblastoma.[112] Patients should be followed with regular interval MRI scans, including the brain and spine, as any of the embryonal tumors can recur outside of the initial tumor bed.

Choroid Plexus Tumors

Background/Presentation

Tumors of the choroid plexus (CPT) represent a rare group of tumors that generally present in young children less than 2 years of age (Fig 6). They account for fewer than 2% of all pediatric CNS tumors.[3] Normal choroid plexus tissue plays a role in the production and reabsorption of CSF, and it is primarily located in the lateral and fourth ventricles. Choroid plexus tumors are divided into "choroid plexus papilloma" (WHO grade I) and "choroid plexus carcinoma" (CPC, WHO grade III). This distinction is extremely important because the prognosis and treatment implications are very different. An intermediate grade of CPT also exists, called "atypical choroid plexus papillomas," and this is considered WHO grade II. Atyp-

FIG 6. Choroid plexus carcinoma arising from the lateral ventricle, causing midline shift (MRI axial image, T1 + contrast).

ical choroid plexus papillomas tend to occur in children even younger than the grade I papillomas[113] and have a slightly more aggressive course.

The presenting signs of a CPT in children can include a bulging fontanel with accelerated head circumference growth, irritability, seizures, vomiting, and lethargy. Metastatic disease is not uncommon at presentation, especially with CPC. Because of the nonfused skull sutures and open fontanels in infants, these tumors can grow to be exceptionally large at presentation.

There is an association with CPC tumors and the Li–Fraumeni familial cancer predisposition syndrome.[114] Although this is a rare occurrence, every newly diagnosed patient with a CPC should have a detailed family history taken, and referral for cancer genetics screening should be strongly considered.

The low incidence of childhood choroid plexus tumors creates a challenge in determining the optimal treatment protocols. International clinical trials are being carried out to gather sufficient patient data to assess and improve the treatment outcomes.

Treatment

Surgery. Surgery plays an important role in the treatment of choroid plexus tumors. For the lower grade choroid plexus papillomas, surgical resection or debulking may be the only treatment required. In the treatment of the more aggressive choroid plexus carcinomas, gross total resection with adjuvant chemotherapy or radiation will offer the best opportunity for cure.

Radiation. Postsurgical radiation therapy improves survival for children with CPC.[115] The challenge of deciding to deliver radiation therapy to a population with a median age around 2 years of age is daunting because of the long-term side effects. CPC tumors have a tendency to metastasize, which means that the radiation oncologist needs to consider craniospinal radiation in the treatment planning. Although this treatment may offer a better chance for cure, it is also associated with the most severe side effects.

Chemotherapy. The treatment of choroid plexus papillomas is primarily surgical and does not usually involve adjuvant chemotherapy. This is in contrast to choroid plexus carcinomas, which are more aggressive, yet sensitive to chemotherapy. Postsurgical chemotherapy for CPC does improve survival rates[116] and intensive chemotherapy is often used with the aim of delaying or avoiding radiation. Although several studies have demonstrated a benefit from combining the 2 modalities, the chemotherapy-only approach is appealing for a tumor with such a young age at presentation.[117]

Prognosis and Follow-Up. The rarity of choroid plexus tumors makes it difficult to establish exact rates of recurrence and cure. However, follow-up recommendations for CPC survivors are similar to those for other pediatric brain tumors, with routine MRI scanning at 3- or 4-month intervals in the first year. The prognosis for choroid plexus papilloma tumors is excellent after surgery, but there have been rare reported cases of malignant transformation,[118] so these patients also require routine MRI surveillance. Neuropsychologic assessments are critical to follow the neurocognitive development in this young group of vulnerable patients. Those that have received intensive chemotherapy require specific follow-up according to the medications used in their protocol.

Germ Cell Tumors

Background/Presentation

Case 3: Germ Cell Tumor. *An 11-year-old boy presents with new onset diabetes insipidus. His mother reports that he has been bumping into objects in the last few months.*

Primary CNS germ cell tumors (GCT) usually present in children between 6 and 14 years old (Fig 7). For

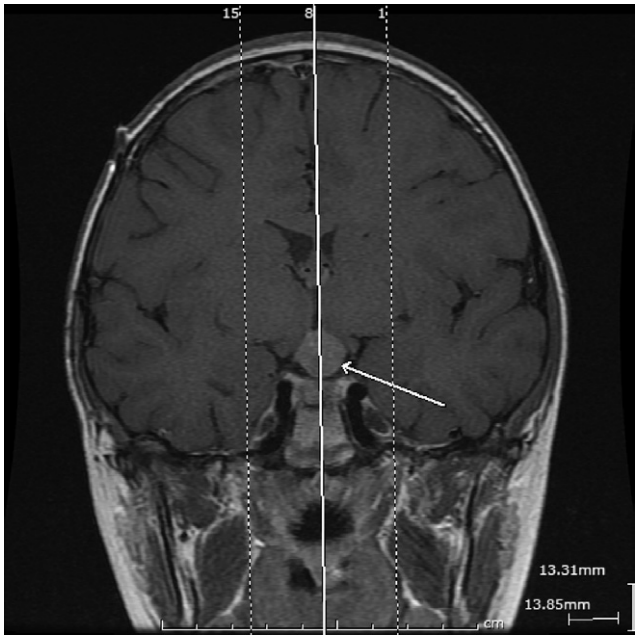

FIG 7. Germinoma (arrow indicates tumor) with a presentation in the midline suprasellar region. Note the pituitary stalk thickening (MRI coronal image, T1 + contrast).

reasons not well understood, they have a geographic and racial predisposition, with a higher incidence in parts of Asia (especially Japan). These tumors are thought to derive from cells that have migrated from the primary gonadal ridge during embryogenesis and subsequently undergo malignant transformation. It should be emphasized that this discussion does not include metastatic tumors from a gonadal germ cell tumor, but rather true primary CNS tumors. They are classified by 2 subtypes: germinomas and nongerminomatous germ cell tumors. Pure germinomas are more common, comprising two-thirds of all GCT. The "nongerminomatous germ cell tumors" consist of a more heterogeneous group, which can be further subclassified as embryonal yolk sac tumors, choriocarcinomas, endodermal sinus tumors, and malignant teratomas.[119]

Germ cell tumors grow in the midline of the brain, and the vast majority will present in either the suprasellar region or the pineal region. The growth rate can vary, but often symptoms will precede the diagnosis by several months. Midline lesions can present with visual disturbances, hydrocephalus, endocrinopathies, personality and sleep pattern alterations, dramatic weight changes, school performance decline, headaches, or seizures. On clinical examination, patients with pineal lesions may exhibit Parinaud's syndrome.

Germ cell tumors are unique in that they can potentially be diagnosed by a laboratory test. In the diagnostic evaluation of a midline CNS lesion, samples of serum and/or CSF can be analyzed for tumor markers (primarily alpha-fetoprotein and beta-human chorionic gonadotropin). These proteins are normally not present in normal children, with the exception of infants or pregnant adolescents. Tumor markers are distinctly elevated for most nongerminomatous GCTs, but will be normal or very low in pure germinomas.

On MRI germ cell tumors have a heterogeneous appearance. Most are T2 bright and contrast-enhancing with distinct margins, and cystic components are not unusual.[120]

Germ cell tumors can spread locally or via the CSF. Spine metastases at diagnosis are not uncommon and a spine MRI with a lumbar puncture for CSF analysis should be part of the diagnostic workup. This evaluation may also include imaging of the chest, abdomen, and pelvis if symptoms of extracranial disease are suspected.

Treatment

Surgery. With the ability to use laboratory tests in the diagnostic workup, this is 1 of the few CNS tumors that will not always require surgery. GCT will often warrant a diagnostic biopsy, but generally there is less emphasis on achieving a gross total resection. Urgent surgical intervention may be required for patients presenting with obstructive hydrocephalus, with the goal of debulking and performing a CSF bypass procedure.

Radiation. Germ cell tumors are very sensitive to radiation, which has been a critical treatment modality for many years. When the diagnosis can be made based on positive tumor markers, radiation may even be curative in some patients. However, the goal for treating children is generally to reduce or eliminate their radiation exposure, and chemotherapeutic regimens are usually used as part of the treatment protocol.[119]

Chemotherapy. Chemotherapy is very successful in treating most germ cell tumors.[121] Protocols primarily include a platinum-based regimen along with drugs, such as cyclophosphamide and etoposide. Recent clinical trials have explored the role for preradiation chemotherapy, allowing for response-based radiation dosing (for germinomas). Achieving an appropriate

balance between radiation and chemotherapy side effects is challenging but a key aspect in the treatment for GCT.[122]

Prognosis and Follow-Up. As would be expected with a tumor that responds well to chemotherapy and radiation, cure rates are quite good for germ cell tumors. Germinomas have the best outcome, with long-term survival rates greater than 90%. Despite more intensive treatment being used, the prognosis for nongerminomatous germ cell tumors is not as good, showing a 60% to 70% overall survival.[119,123] The posttreatment follow-up plan for patients with GCT is similar to that of other CNS tumors in children. In patients with detectable tumor markers at diagnosis, routine serum and/or CSF samples will be useful in the early detection of recurrent disease. Regular interval MRI scans of the brain and spine should be done every 3 or 4 months at first and then occur with decreasing frequency in the progression-free years after treatment.

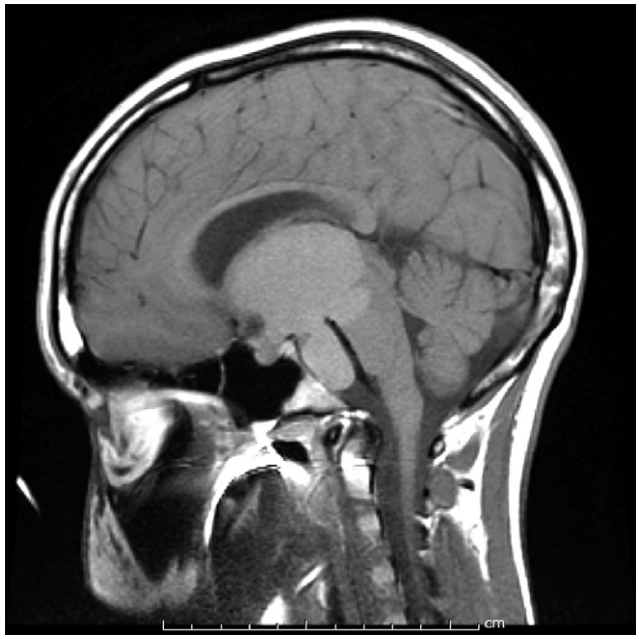

FIG 8. Craniopharyngioma. Note the distortion artifact coming from the face, most commonly due to dental appliances (MRI sagittal image, T1 + contrast).

Craniopharyngioma

Background/Presentation

Case 4: Supratentorial Mass. *A 16-year-old boy presents with a 2-month history of progressive headaches followed by a several day history of intermittent vomiting. He was seen and treated in a local emergency room for dehydration and sinusitis. However, now he is experiencing intractable vomiting and his headaches have increased in severity. His physical examination shows loss of visual fields.*

Despite its classification as a WHO grade I tumor, craniopharyngiomas can cause a tremendous amount of morbidity and long-term complications (Fig 8). This is primarily due to their location in the suprasellar region. These tumors will inevitably disrupt the hypothalamic–pituitary axis, which can lead to the full spectrum of endocrinopathies. Patients may present with growth deficiencies, visual changes or loss, adrenal crisis, headaches, or seizures.

On imaging, craniopharyngiomas appear as a multicystic enhancing mass with some solid components. Calcification is frequently found, and CT scanning can often be helpful to distinguish a craniopharyngioma from other tumor types.

Histologically, these are low-grade WHO grade I lesions with a characteristic appearance under the microscope. As craniopharyngiomas cause problems locally in the suprasellar region and do not tend to spread throughout the CNS axis, routine spinal imaging or CSF collection is not essential for staging purposes.

Treatment

Surgery. Craniopharyngioma is primarily viewed as a surgical disease, and all patients should be managed by neurosurgeons who have specific expertise with this tumor. Although complete surgical resection would theoretically be curative, it is rarely accomplished due its proximity and adherence to surrounding vital structures in the brain. These tumors can also be very calcified, revealing rock-like characteristics intraoperatively. Multiple surgical approaches sometimes are needed to provide a durable remission.

Radiation. For an unresectable craniopharyngioma, radiation can play an important role in preventing recurrence. However, because there are many critical structures in the target field, radiation should be delayed or spared in very young children. Modern techniques, such as 3-dimensional (conformal) radiation or proton beams, may help minimize scatter and side effects of the radiation.[124]

Chemotherapy. Chemotherapy plays a minor role in the treatment or stabilization of craniopharyngiomas. As a relatively benign tumor, high-dose chemotherapy has not been shown to be of benefit. Systemic

chemotherapy also has limitations in treating the cystic aspects of craniopharyngiomas. Some studies have suggested a benefit of injecting chemotherapy directly into the cysts.[125] However, this approach to therapy is complicated by the presence of multiloculated cysts and the risk associated with chemotherapeutic agents leaking into the surrounding brain tissue.[126]

Prognosis and Follow-Up. A craniopharyngioma often progresses into a chronic condition with significant morbidity. Even if tumor cysts are surgically drained and cyst walls are removed, regrowth is common and multiple surgeries are often required. The adverse effects of the tumor, surgery, and radiation can have a profound impact on patients, who are often left with hypothalamic dysfunction and panhypopituitarism.[127] Severe problems with sleep, learning, vision, and weight gain are not uncommon and these patients definitely benefit from a multidisciplinary team approach.[128] Patients should receive routine surveillance MRI scans but nonetheless symptoms will often recur rapidly because of cyst reaccumulation.[129]

Late Effects in Pediatric Neuro-Oncology

The late effects of brain tumors in childhood can manifest in a wide array of problems. Neurocognitive decline, memory difficulties, social skill deficits, secondary malignancies, neurologic deficits, seizures, growth deficiencies, and endocrinopathies are just a few of the many aspects requiring long-term care in these patients.

Late Effects—Tumor

A growing brain tumor compressing the surrounding structures inevitably will lead to devastating consequences for children. The duration of time from the development of symptoms to diagnosis impacts the reversibility of the damage incurred. Those tumors that develop in an unresectable location (eg, brain stem, thalamus) can lead to significant motor and neurologic dysfunction despite being slow growing. Hydrocephalus itself can be a risk factor for long-term morbidity, including cognitive impairment and visual loss.[130]

Late Effects—Surgery

The late effects of surgery can be quite significant for children, even in the absence of complications.[131] Because the survival rates for some tumors are dramatically improved by more aggressive surgery (ie, ependymoma), these patients may be at higher risk of neurological consequences because of the procedures.

An entity known as *posterior fossa mutism syndrome* (also known as cerebellar mutism) can occur after surgical resection of a posterior fossa mass. Risk factors are not well understood, but it is estimated that up to 10% to 20% of patients undergoing resection for medulloblastoma will develop this syndrome. Soon after the immediate postoperative period, patients become unable to speak or express themselves and generally have pronounced mood dysregulation and hypotonia. With regards to long-term effects, almost all patients with cerebellar mutism will demonstrate a slow steady recovery, but most will suffer some measurable degree of neurocognitive impairment[132,133] and the emotional dysregulation can be longstanding.

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Late Effects—Radiation Therapy

Therapeutic doses of ionizing radiation are well recognized to cause significant neurocognitive injury to the developing brain.[56,134] As might be expected, the severity of this impact is inversely proportional to age. Full-dose radiation to the brain of a young infant will probably lead to mental retardation and the need for lifelong assisted living. For a young child, there may be a measurable drop in intelligence quotient of approximately 20-30 points, resulting in significant learning difficulties.[135]

Radiation to specific parts of the brain can lead to an increased risk of particular side effects. The blood vessels in the brain are particularly susceptible, which predispose to an increased risk of vascular events. Moya-moya syndrome refers to a particular vasculopa-

thy that can be due to radiation, associated with an increased risk of ischemia and stroke.[12] The hypothalamic pituitary axis is quite sensitive to the impact of radiation, with varying degrees of effect depending on the affected hormone.[136] Although the maximum dose of radiation is generally focused on the tumor or tumor resection cavity, there is a certain amount of "scatter" that can affect surrounding nontargeted organs as well. The most obvious examples are the hair and skin, which are always involved in the radiation field. Although generally a cosmetic issue, partial or complete alopecia is not uncommon during radiation, and this can sometimes be a permanent effect. As the inner ear also is quite sensitive to radiation, treatment of the posterior fossa with radiation can cause secondary hearing loss. Although the eyes generally are spared, scatter doses can cause cataracts to develop later in life. As the thyroid gland is very sensitive to the effects of radiation, patients exposed to craniospinal radiation have a significant increased risk of developing secondary hypothyroidism later in life. Moreover, as craniospinal radiation results in a certain amount of exposure to the chest and abdominal organs, its toxic effects can result in pulmonary fibrosis or cardiotoxicity.[134]

Radiation also leads to an increased risk of secondary malignancies, or "radiation-induced tumors." In the brain these are most commonly meningiomas, which can present anytime during a person's lifetime. Although surgery most often is curative in these cases, anaplastic variants have been reported. Secondary high-grade gliomas arising within the radiation field have also been reported, and these have a dismal prognosis.[5]

Late Effects—Chemotherapy

With the increasing use of chemotherapy in the treatment of brain tumors, physicians need to be aware of the long-term impact. Chemotherapy can lead to secondary malignancies; the most common form is treatment-related leukemia associated using drugs, such as etoposide and cyclophosphamide. Alkylating agents, such as cyclophosphamide, can also have a dose-dependent impact on fertility and result in early menopause. Pretreatment fertility counseling should be offered to all patients as an important component of treatment planning. Platinum-containing drugs are important in the treatment of brain tumors, but come with an increased risk of sensorineural hearing loss and kidney damage. Although peripheral neuropathies usually improve after the discontinuation of drugs, such as vincristine or cisplatinum, the effects can occasionally be permanent. Anthracyclines (such as doxorubicin) are less commonly used in the treatment of brain tumors compared to other pediatric cancers, but exposure to these medications is associated with long-term cardiotoxicity.[137,138]

Less is known in children about the long-term toxicity of newer experimental agents. Many of the new therapeutic approaches use drugs that target the molecular pathway implicated in tumor growth. Others target the ability of a tumor to create its own blood supply, in an "antiangiogenic" approach.[78] Even if a new drug is not "cytotoxic" like classic chemotherapy, it could have the potential for unique and even more potent toxicities to the growing child. Although most of these agents first will have been studied in adults, there is obviously a lack of emphasis placed on growth and development in adult trials. Therefore, it will be increasingly important to track young patients that have been exposed to new agents over the long term, to understand the multifactorial impact that new drugs will have on growth and development.

Follow-up screening of patients who are long-term survivors of brain tumors should occur in conjunction with a multidisciplinary oncology program. Many large pediatric centers operate clinics that provide care to patients until early adulthood, but the issue of patients being "lost to follow-up" is common. Patients and their families should be aware of the treatment they received, including the cumulative doses of chemotherapy and radiation that were given. Providing this information in a format they can share with their general practitioners will help facilitate them in receiving the best care in the future.

Conclusions and Future Perspective on Pediatric Tumors of the CNS

Conventional treatment approaches to pediatric brain tumors have historically been based on the histology of the tumor and the patient's age. However, the advances in recent years among all disciplines have led to knowledge that will impact management. Advances in neuroimaging techniques have improved histologic prediction capability, as well as offering insights into potential markers of response. From the surgical perspective, cooperative group studies have demonstrated that extensive tumor resection is impor-

tant in successful outcomes for several tumor types, and improved operative techniques have enhanced the percentage of patients able to achieve extensive tumor removal. New operative techniques have also allowed for the investigation of new drug delivery technologies. New radiation techniques, such as conformal intensity-modulated radiation and proton beam therapy, have allowed for reduction in both fields and doses, sparing children from some of the untoward long-term effects of radiation. Adjuvant chemotherapy has permitted reduction in the total dose of craniospinal radiotherapy for treating standard-risk medulloblastoma, whereas intensifying chemotherapy regimens has improved survival for children with high-risk disease. The successful use of chemotherapy has also permitted a reduction in the size of radiation fields and dosage amounts for children with germ cell and choroid plexus tumors.

It is the burgeoning information emanating from laboratory research that offers the greatest promise for the advancement and ultimately improved survival in pediatric neuro-oncology. Biological studies have identified molecular factors that correlate with therapeutic outcomes for several tumor types in children, including medulloblastoma, PNET, and high-grade gliomas. There is a greater understanding of age-related differences within tumor types, specifically medulloblastoma and high-grade glioma. In addition, the identification of molecular pathways implicated in tumor growth has provided the biological rationale that has led to specific targeting with investigational agents. Moving forward with these new and exciting discoveries will enhance the stratification in upfront therapeutic approaches, resulting in the next great leap toward improved outcomes.

Another major effort today lies in improving the long-term quality of life, particularly in those children who survive their disease but commonly suffer morbidity from treatment or the tumor itself. With the ability of identifying subgroups of brain tumors with similar favorable characteristics, risk-adapted therapeutic strategies are being investigated to balance overall survival with quality-of-life issues. Detailed assessments and analyses are now emphasized in follow-up, particularly in the neuroendocrinologic and neuropsychological domains; these will guide future refinements in therapeutic approaches. For affected patients, timely institution of hormone replacement or educational interventions may be beneficial in optimizing long-term functional outcome. In addition, current studies examining strategies, such as neural protection and pharmacologic remediation, offer additional hope for improving the quality of life for long-term survivors.

The field of pediatric neuro-oncology requires a multidisciplinary approach, including the experienced pediatric neurosurgeon's hands, the detailed neurologist's assessments, the careful planning of the radiation oncologist, the coordinating treatment efforts of the neuro-oncologist, and ongoing case management and family support by the child's primary care provider. Access to specialists in neuroendocrinology, neuro-ophthalmology, neuropsychology, and school liaison personnel is also of significant importance. It is this collaborative and coordinated care approach that benefits these children, so that despite their brain tumors and various treatments, each may achieve their very best outcome and highest potential.

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