Brain tumors are the most common solid tumor malignancies in childhood, and among them, medulloblastoma occurs most frequently. Medulloblastoma is a high-grade malignancy that requires extensive treatment. Bailey and Cushing first described the term medulloblastoma in 1925. Although once classified as gliomas, medulloblastomas were identified as a distinct series of tumors found in the cerebellum of children. Throughout the 1920s, Cushing tested surgical techniques to improve the overall survival and surgical morbidities in children with medulloblastoma. Surgery was the only treatment for these tumors until the 1950s, when craniospinal irradiation became a widely accepted adjuvant treatment. Chemotherapy was accepted as another standard treatment modality in the 1990s. Over the years, advanced research has led to improved diagnostic, surgical, and radiation technologies, as well as effective adjuvant chemotherapy regimens. These advances have led to dramatically improved patient outcomes.

Because the patient’s initial presenting symptoms may be vague, clinicians must consider medulloblastoma in the differential diagnosis when evaluating a child with persistent symptoms such as nausea, vomiting, headaches, or other neurologic complaints.

**ABSTRACT**

Brain tumors are the most common solid tumor malignancies in childhood, and among them, medulloblastoma occurs most frequently. Medulloblastoma is a high-grade malignancy that requires extensive treatment. Bailey and Cushing first described the term medulloblastoma in 1925. Although once classified as gliomas, medulloblastomas were identified as a distinct series of tumors found in the cerebellum of children. Throughout the 1920s, Cushing tested surgical techniques to improve the overall survival and surgical morbidities in children with medulloblastoma. Surgery was the only treatment for these tumors until the 1950s, when craniospinal irradiation became a widely accepted adjuvant treatment. Chemotherapy was accepted as another standard treatment modality in the 1990s. Over the years, advanced research has led to improved diagnostic, surgical, and radiation technologies, as well as effective adjuvant chemotherapy regimens. These advances have led to dramatically improved patient outcomes.

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**EPIDEMIOLOGY**

Medulloblastoma accounts for 30% of pediatric brain tumors and 7% to 8% of all brain tumors. Between 1.5 and 2 cases of medulloblastoma per 100,000 people are diagnosed each year, with about 350 new cases in the United States annually. Most cases occur in the first 9 years of life, with a peak incidence between ages 5 and 7 years. Boys are affected between 1.5 and 2 times more often than girls. Although medulloblastoma is mainly a pediatric disease, it can occur in adults.

**PATHOPHYSIOLOGY**

The World Health Organization (WHO) defines medulloblastoma as “a malignant, invasive embryonal tumour of the cerebellum with preferential manifestation in children, predominantly neuronal differentiation and an inherent tendency to metastasize via cerebrospinal (CSF) pathways.” Medulloblastoma is classified by WHO as a grade IV tumor. It originates in the cerebellum or posterior fossa (arising from the fourth ventricle or vermis) and can spread throughout the brain and spine via the cerebrospinal fluid. Metastases outside the central nervous system (CNS) are rare but have been reported in the bone marrow, lymph nodes, and viscera.
The cause of medulloblastoma is the subject of much debate. Several clinical trials have tried to identify a viral cause; however, no cause has been widely accepted and researchers have not identified a clear reason for why medulloblastoma develops. Several known genetic syndromes that are rare in the general population are linked to medulloblastoma, including Gorlin syndrome, familial adenomatous polyposis, and Li-Fraumeni syndrome.

**HISTORY AND PHYSICAL**

A full history and physical examination is essential to determining the need for further diagnostic testing. Early diagnosis (before disease spread) can positively affect the child’s outcome. The critical step of early diagnosis begins in pediatric practices, family practices, the ED, and urgent care centers. However, this may be a challenge to clinicians because early symptoms may be nonspecific.

The presenting features of medulloblastoma depend on the tumor location and the child’s age at the time of presentation. Because most of these tumors arise in the region of the fourth ventricle, hydrocephalus often develops and many of the presenting symptoms are secondary to increased intracranial pressure (ICP). Daily morning nausea, vomiting, and/or headaches are pathognomonic of increased ICP and warrant a prompt diagnostic evaluation.

Symptoms of medulloblastoma frequently start out mild and may mimic more benign childhood illnesses. Common presenting complaints include headache, nausea and vomiting, lethargy, and visual changes such as diplopia. Often, parents and pediatricians assume that a child whose symptoms include nausea and/or vomiting is suffering from gastroenteritis. Headaches may initially be presumed to be a migraine, sinus headache, or attributable to a common childhood infectious process. Imbalance, dizziness, or visual changes may be diagnosed as vertigo. An infant with medulloblastoma often presents with irritability, poor feeding, loss of milestones, or failure to thrive. These symptoms can have an insidious onset and may represent a multitude of diseases, leading to a delay in diagnosis.

In patients who are not experiencing hydrocephalus and increased ICP, the presenting symptoms often are related to nerve compression or focal inflammation. Patients may have ataxia, localized motor abnormalities, seizures, and sensory deficits. Presenting symptoms often correlate with the location of the primary tumor and whether the cancer has disseminated. Medulloblastomas may cause truncal and gait ataxia; lateralized cerebellar masses lead to limb incoordination and palsies of the sixth and seventh cranial nerves (on the ipsilateral side of the tumor). Lepptomeningeal dissemination can lead to seizures and cranial nerve palsies, and secondary supratentorial tumor formation will cause motor and sensory deficits. Occasionally, patients with medulloblastoma may present with an acute onset of altered mental status and lethargy due to hemorrhage within the tumor.

Eventually, the presenting symptoms progress in severity and frequency until a diagnosis is made. These tumors tend to be relatively fast-growing, so symptoms usually are present for fewer than 3 months at the time of presentation. The median interval from symptom onset until diagnosis is 65 days. Rarely, patients may experience symptoms for up to 6 months before diagnosis. A 2014 study found that younger age was significantly associated with a longer interval to diagnosis and that the more aggressive subgroups of medulloblastoma had a shorter prediagnostic interval.

A comprehensive history and physical examination, with a focus on the neurologic examination, should be performed on any patient presenting with progressive or persistent constitutional symptoms or new neurologic symptoms. Physical examination findings concerning for medulloblastoma include papilledema, ataxia, dysmetria (often unilateral when the mass is lateralized), upward gaze palsy, cranial nerve palsies (most notably in cranial nerves IV and VI), and nystagmus. In infants, findings also may include increasing head circumference, bulging anterior fontanelle, fixed downward gaze (sun-setting sign), loss of milestones, poor feeding, and lethargy. Patients generally do not have concomitant illnesses at the time of presentation, so the rest of the physical examination should be normal.

**DIAGNOSTIC TESTS**

Further diagnostic testing is warranted if the patient has suspicious findings on the neurologic examination or if the clinician suspects intracranial pathology based on the patient’s presenting history. The first-line diagnostic test for medulloblastoma is brain imaging. Head CT or brain MRI will show a posterior fossa mass and possibly obstructive hydrocephalus. CT is often used as the first-line diagnostic imaging because it is more readily available in the ED and is quicker. Although it is an excellent diagnostic tool for hydrocephalus, noncontrast CT scans often miss medulloblastomas. If the clinician suspects medul-
medulloblastoma, a contrast CT can be obtained, or preferably an MRI. MRI with and without gadolinium is the best form of diagnostic imaging because it shows the relationship between the tumor and the surrounding brain structures (Figure 1). It also provides a more accurate demonstration of tumor dissemination, if present.6 On diffusion-weighted MRI, medulloblastoma often exhibits restricted diffusion, which is a useful tool to help determine the likelihood of the diagnosis.10 Figure 2 shows medulloblastoma and concomitant hydrocephalus.

An MRI of the whole spinal axis and a lumbar puncture routinely are indicated to evaluate for metastatic disease. MRI of the spine can evaluate for leptomeningeal disease as well as secondary spinal tumors. Obtaining a whole-spine MRI is preferred before surgical resection of the tumor. Lumbar puncture, to evaluate for tumor cells in the cerebrospinal fluid (CSF), generally is not done preoperatively due to risk of brain herniation from increased ICP. The lumbar puncture usually is done between 10 and 21 days (typically, 14 days) after surgery in order to avoid false-positive results.6 Both studies require a delay after surgery because postoperative blood can be misinterpreted for abnormal cells in the CSF and leptomeningeal disease on MRI.

Because medulloblastoma very rarely spreads outside of CNS, diagnostic tests such as positron emission tomography (PET), bone scans, chest imaging, and bone marrow aspirates are unnecessary. Likewise, no blood tests exist for screening or staging medulloblastoma.9 However, routine laboratory tests such as complete blood cell count, comprehensive metabolic panel, coagulation studies (prothrombin time, partial thromboplastin time, and international normalized ratio), and blood typing and crossmatching are helpful in assessing the patient’s overall health and are an essential part of the preoperative evaluation.

PATHOLOGY

Medulloblastoma appears histologically as densely packed cells with hyperchromatic nuclei surrounded by scanty cytoplasm. Mitoses are usually numerous and cells are mostly undifferentiated. If present, differentiation into neuronal cells occurs more commonly than differentiation into glial cells.3 The four main histologic types of medulloblastoma recognized by the WHO are classic medulloblastoma, large cell/anaplastic medulloblastoma, desmoplastic/nodular medulloblastoma, and medulloblastoma with extensive nodularity.3 Each vary in histologic appearance and are associated with their own prognosis (Table 1).

MOLECULAR SUBGROUPS

Over the past decade, distinct molecular subgroups have been found for medulloblastoma based on cytogenetic profiles. Each group is named for the cellular pathway activation or genomic alterations it exhibits: wingless (WNT), sonic hedgehog (SHH), Group 3, and Group 4. Each subgroup is associated with distinct survival outcomes: very good for WNT, good (in infants) and intermediate (in others) for SHH, poor for Group 3, and intermediate for
Group 4. Many clinical trials are studying targeted therapies for each molecular subgroup in order to better individualize treatment.

**STAGING**

Current risk stratification tools for medulloblastoma have been in place for decades and generally are based on clinical features such as age at diagnosis, extent of surgical resection, metastatic status, and histologic features (such as anaplastic or large cell). Chang staging, first described in 1969, still is commonly used for risk stratification (Table 2). This stratification tool initially incorporated the size and local invasion of the primary tumor (T staging) and the presence of metastasis at the time of initial diagnosis (M staging) to assign potential outcomes. Patients were assigned as M0, M1, M2, M3 or M4 and T1, T2, T3a, T3b or T4 based on various clinical features. Over the years, M staging has remained a useful prognostic tool, while studies have shown that T staging is less valuable as a prognostic indicator than previously thought.

Several studies have shown that the amount of residual disease after surgery, age of the patient, pathologic variant, and M staging are good predictors of outcome. Using these variables, patients can be risk-stratified, which predict outcomes and helps direct the treatment plan.

- **High-risk** patients have one of the following features: age 3 years or younger, residual tumor greater than or equal to 1.5 cm$^2$ following maximal safe resection, large cell or anaplastic variants, M1 to M4 staging.
- **Average-risk** patients do not have any of the features listed under high risk.

**FIGURE 2.** Noncontrast CT images showing significant dilation in the third and lateral ventricles (A) and transependymal flow of CSF consistent with acute hydrocephalus. (B) A cystic and calcified posterior fossa mass at the dorsum of the fourth ventricle with efacement of the fourth ventricle. (C) Axial MRI with gadolinium of the brain showing the same mass as depicted in the CT images. Due to the better visualization of soft tissue on MRI, the tumor can be better described in relation to the surrounding structures.
TREATMENT

The standard treatment for childhood medulloblastoma consists of surgery, radiation, and chemotherapy. Doses of radiation and the type of chemotherapy protocol may vary depending on the patient's stage or risk categorization as well as institutional preferences. Many patients require short-term therapy with corticosteroids (such as dexamethasone) to reduce the cerebral edema associated with the tumor and surgery. Corticosteroids, along with surgical intervention, reduce the severity of many of the presenting symptoms.

Surgery

The first-line treatment for medulloblastoma is gross total resection (or maximal safe resection) along with treatment of any concurrent hydrocephalus. The goal of maximal safe resection is to remove as much of the tumor as possible while minimizing the risk of postoperative neurologic damage. The location of the tumor in the posterior fossa and its relationship with surrounding structures is critical to how much can be safely resected. Obtain a postoperative brain MRI within 24 to 48 hours after surgery to assess for the extent of surgical resection. Common postoperative complications include lower cranial nerve dysfunction, cerebellar mutism (defined as severely diminished or absent speech output), aseptic meningitis, and dysconjugate gaze secondary to cranial nerve palsy.

External ventricular drains are placed as a temporary measure to treat hydrocephalus, if present at the time of diagnosis. About 20% of patients require long-term treatment of hydrocephalus with the insertion of a ventriculoperitoneal shunt or an endoscopic third ventriculostomy when tumor removal alone does not adequately treat the hydrocephalus.

Radiation

Postoperative craniospinal radiation is the standard of care for children older than age 3 years. The treatment dose is 23.4 Gray (Gy) for average-risk patients and 36 Gy for high-risk patients. The tumor bed receives an additional boost dose to a total of 55.8 Gy due to the high risk of local recurrence.

A newer technique, intensity-modulated radiation therapy better targets the tumor site and minimizes radiation to the surrounding structures.8 Chemotherapy often is given concomitantly with radiation as a radiosensitizer and again after the completion of radiation. The Children’s Oncology Group is assessing data collected from a recent clinical trial in which the total craniospinal radiation dose was reduced by 25% in children ages 3 to 7 years in hopes of reducing long-term radiation-induced neurotoxicity.

In recent years, several centers across the United States have opened proton beam radiation centers. This type of external beam radiotherapy uses protons to irradiate cancers. Proton beam and photon beam (the standard found in most hospital or treatment centers) irradiation are equally effective but protons have been shown to reduce the dose of radiation to normal surrounding tissues, which may reduce the rate of long-term adverse reactions to radiation.

However, proton beam delivery centers are not widespread across the United States, and the cost and logistics of delivery are significant. Intensity-modulated radiation therapy is more widely available, and this technology is continually evolving to further reduce the dose to normal tissues while achieving high tumor coverage.
nor widely accessible to patients. Although studies seem promising, this therapy is not yet considered standard of care for medulloblastoma.

**Chemotherapy** Various chemotherapy regimens are used to treat medulloblastoma. All drugs involved in these regimens must be able to penetrate the blood-brain barrier. Common chemotherapeutic agents include vincristine, cisplatin, cyclophosphamide, lomustine, etoposide, methotrexate, temozolomide, and carboplatin. Common adverse reactions include neurotoxicities such as foot drop, constipation, hearing loss, neuropathy, nausea and vomiting, immune compromise and bone marrow suppression, renal toxicities with electrolyte abnormalities, hepatotoxicity, infertility, and secondary malignancies.

Common chemotherapy regimens for patients with average-risk medulloblastoma include either a combination of cisplatin, lomustine, and vincristine or a combination of cisplatin, cyclophosphamide, and vincristine. A study by Packer and colleagues compared the above two drug regimens and found no significant difference in event-free survival and overall survival. Five-year event-free survival and survival for both types of treatment were reported as 81% ± 2.1% and 86% ± 9%, respectively. Due to the significant ototoxic effects of cisplatin, some centers use an alternate regimen that reduces the overall amount of cisplatin. This protocol administers three different multigent courses at monthly intervals. The three monthly courses are alternating cycles of IV cisplatin and etoposide, IV vincristine and cyclophosphamide, and IV carboplatin and vincristine. Each cycle is given three times for a total of nine cycles. The results of the study using this regimen showed overall event-free survival rates similar to those found in other studies.

Because children under age 3 years often suffer severe long-term cognitive effects from radiation, they are generally spared of this treatment and instead receive more intense chemotherapy. The Head Start I, II, and III protocols have been developed over the last few decades in order to avoid radiation in younger patients. As an alternative, these protocols have used intense systemic chemotherapy followed by a consolidation cycle with myeloablative chemotherapy and autologous stem cell rescue in patients under age 3 years. The 3-year event-free and overall survival rates for all patients treated on the Head Start III protocol were (±SE) 47% ± 6% and 65% ± 6%. These values are similar to those in older patients treated with standard therapy. The science of molecular subgrouping of medulloblastoma has the potential to drive new targeted therapies. Clinical trials are ongoing but there are no standard targeted therapies to date.

**PROGNOSIS**

Overall survival rates for children with medulloblastoma are reported as 50% to 60%. Average-risk survival rates are 70% to 80%; for high-risk patients, survival rates are 30% to 40%. In a French study that focused specifically on M staging prognosis, results showed a 5-year overall survival rate of 47% for patients with stage M1 medulloblastoma (HR 1), 51% for patients with M2 disease (HR 0.9), and 42% for patients with M3 disease (HR 1). Most recurrences occur within 2 years after surgery, so patients require close monitoring after completion of treatment with routine imaging and physical examinations.

**LATE EFFECTS**

Long-term survivors of medulloblastoma require complex medical care by subspecialists in oncology, neurology, endocrinology, psychology, and psychiatry. Most children who survive medulloblastoma have substantial neurologic and cognitive complications. IQ and overall academic achievement are common challenges in survivors. Other late effects include hypothyroidism, short stature, and other endocrinologic deficiencies, in addition to feelings of social isolation and a poor self-rated quality of life.

**CONCLUSION**

Recognizing that the early detection of the most common childhood solid tumor malignancy can greatly affect the outcome, practitioners need to be aware of the common presenting symptoms of medulloblastoma and be able to consider it in their differential diagnosis. As current outcomes yield varying results, new treatment strategies are continually being tested in order to improve overall outcomes and reduce long-term adverse reactions. Referring patients to specialized multidisciplinary treatment centers that conduct clinical trials is imperative to promote continued research and also will provide patients with optimal care.

**REFERENCES**


