Introduction

Background

First used by Bailey and Cushing in 1925[1], the term medulloblastoma described a series of tumors found in the cerebella of children. Originally classified as a glioma, medulloblastoma is referred to now as a primitive neuroectodermal tumor (PNET). This tumor accounts for approximately 7-8% of all intracranial tumors and 30% of pediatric brain tumors.

Pathophysiology

In the brain, medulloblastoma most often arises in the posterior fossa as shown in the image below. The tumor has the propensity of spreading throughout the CNS. Systemic metastases of this tumor, especially to bone, also have been recognized.

CT scan demonstrates a hyperdense lesion within the posterior fossa of an 8-year-old boy who presented with nausea and vomiting.

Frequency

United States

Incidence of medulloblastoma is 1.5-2 cases per 100,000 population, with 350 new cases in the United States each year. Although the majority occur as sporadic cases, hereditary conditions have been associated with medulloblastoma, including (1) Gorlin syndrome (nevoid basal cell carcinoma syndrome), (2) blue rubber-bleb nevus syndrome, (3) Turcot syndrome (e.g., glioma polyposis syndrome), and (4) Rubinstein-Taybi syndrome.
International

Incidence of medulloblastoma worldwide seems to approximate that in the United States.

Mortality/Morbidity

- Hydrocephalus: The most common complication is hydrocephalus due to compression of the normal cerebrospinal fluid (CSF) pathways. Although this is a common complication, only 10-50% of patients with preoperative hydrocephalus will need a long-term ventricular shunt. Some children can be treated with an endoscopic third ventriculostomy.

- Cerebellar dysfunction: Tumor infiltration of the cerebellum usually is in the midline, leading to difficulties with ambulation and truncal ataxia. This is more common than signs attributable to the cerebellar hemisphere (eg, extremity dysmetria).

- Leptomeningeal dissemination: One of the most feared complications of medulloblastoma is dissemination within the CSF. Medical and, less commonly, surgical therapy must be directed at controlling dissemination to cranial nerves and spinal cord and related structures. This dissemination of disease portends to a high-risk stratification.

Race

No specific predilection for a particular racial or ethnic group has been noted.

Sex

Medulloblastoma is more common in males than females (1.5:1). Males also tend to have a poorer prognosis.

Age

Although predominantly a pediatric tumor, medulloblastoma can affect patients of any age from neonates to the elderly. Three quarters of all cases occur in children, with a median age of 9 years.

Clinical

History

- Hydrocephalus
  - Patients with medulloblastoma most commonly have symptoms related to increased intracranial pressure (as a consequence of hydrocephalus). Symptoms usually precede presentation by no more than 2 months.
  - Presenting symptoms are related to the age of the patient.
    - The younger, nonverbal patient presents with behavioral change.
    - Symptoms in younger children include listlessness, irritability, vomiting, and decreased social interactions.
    - Older children and adults complain of headache, especially upon awakening in the morning.
  - Vomiting without nausea is more common in the morning, since being recumbent (eg, sleeping) increases intracranial pressure.
  - Often, symptoms of headache and vomiting prompt an extensive and lengthy workup of the gastrointestinal tract prior to consideration of the CNS.
  - Patients may develop double vision as the sixth cranial nerve becomes stretched from the hydrocephalus. Visual disturbances more commonly are a result of papilledema.

- Cerebellar symptoms
  - Most commonly found in children, the tumor involves the cerebellar vermis and causes gait ataxia more readily than unilateral symptoms.
  - Adults more commonly harbor the desmoplastic variant of medulloblastoma, which arises in the cerebellar hemisphere. These patients often have symptoms of ipsilateral dysmetria.
  - Head tilt and neck stiffness, caused by meningeal irritation, are complications of tonsillar herniation below the foramen magnum.
  - Alternatively, head tilt can result from trochlear nerve palsy caused by direct tumor compression.

- Leptomeningeal dissemination
  - Presenting symptoms rarely are related to dissemination of tumor in the CSF.
  - Patients can complain of severe weakness from tumor compression of the spinal cord or nerve roots (eg, radiculopathy).

Physical
Physiognomy
- Increasing head circumference often is the only presenting symptom in infants.
- These infants have full anterior fontanelles with widely split cranial sutures.

Funduscopic examination
- Visual difficulty usually is due to papilledema; however, it also may originate from cranial nerve palsy.
- Some studies have found papilledema (the most common physical finding) to be present in as many as 90% of patients.

Extraocular examination
- As a consequence of hydrocephalus, the sixth cranial nerve can be compressed at the petroclival ligament, resulting in diplopia and lateral gaze paresis.
- Fourth cranial nerve palsy can be detected on careful extraocular examination and should be considered in any patient with a head tilt.
- Patients with fourth cranial nerve dysfunction have greatest difficulty when eyes are rotated medially and depressed (e.g., going down stairs). The fourth cranial nerve usually is compressed by direct tumor extension into the cerebral aqueduct.

- Examination of the extraocular muscles may detect nystagmus, which, although nonspecific, can be related to a lesion of the cerebellar vermis.

Cerebellar signs
- Medulloblastoma most commonly is located midline. Therefore, unilateral dysmetria is less common than either truncal ataxia or a wide-based gait. Latter symptoms are easily observable on tandem gait.
- As stated previously, desmoplastic medulloblastoma is more common in adults and usually arises in the cerebellar hemisphere.
- Signs of ipsilateral cerebellar dysfunction in the arm or the leg are more common in this subtype.

- Torticollis: Head tilt can be a manifestation of either foramen magnum involvement or fourth cranial nerve palsy.

Causes
Debate exists over the cellular origin of medulloblastoma.

- One hypothesis is that the tumor is derived from cells of the external granular layer of the cerebellum.
  - Medulloblastoma cells are cytologically similar to cells of the external granular layer.
  - This is an area of germ cell origin that persists for the first year of life before involuting.

- Another proposed source of medulloblastoma is the posterior medullary velum, from which undifferentiated cells migrate to the external granular layer. These cells persist only for a short time after birth.

Differential Diagnoses
- Brainstem Gliomas
- Cavernous Sinus Syndromes
- Cerebellar Hemorrhage
- Cerebral Aneurysms
- Craniopharyngioma
- Ependymoma
- Glioblastoma Multiforme

Other Problems to Be Considered
- Cerebellar astrocytoma
- Choroid plexus papilloma
- Brainstem syndromes

Workup

Laboratory Studies
No specific biochemical test exists for the presence of medulloblastoma, although several molecular studies have revealed that...
histologically identical medulloblastomas are composed of distinct subgroups with different prognosis. The expression of ErbB2 has been shown to be a negative predictor of outcome. Conversely, expression of TrkC or neurotophin-3 receptor is associated with a favorable outcome. However, these markers are not standard testing at this time.

**Imaging Studies**

- **Computed tomographic scan**
  - Because most patients present with headache, a noncontrast head CT scan usually is performed because of its easy availability. These tumors typically are located midline in the cerebellum and extend into and fill the fourth ventricle.
  - Prior to administration of intravenous (IV) contrast, the tumor is hyperdense to the brain as a result of its high cellularity as shown below. Preoperatively, high density on CT scan can help distinguish medulloblastoma from the hypodense appearance of a cerebellar astrocytoma. Medulloblastoma shows marked contrast enhancement. Surrounding hypodensity is indicative of vasogenic edema. Owing to compression of the fourth ventricle and outflow of CSF, marked hydrocephalus is the rule.

- **Magnetic resonance imaging**
  - MRI with the administration of gadolinium DTPA is the diagnostic test of choice for medulloblastoma. Unlike CT scan, MRI can obtain multiplanar views without significant bony artifact in the posterior fossa.
  - Nevertheless, with any increased intracranial pressure, MRI of children must be considered carefully. Younger children usually require sedation for this study. Without careful monitoring, cerebral carbon dioxide levels may increase, further aggravating intracranial hypertension.
  - Tumor appears hypointense on pre-gadolinium T1-weighted images, usually seen expanding the fourth ventricle from its origin in the cerebellar vermis as depicted in the following images. Brain stem is compressed and shifted ventrally.

CT scan demonstrates a hyperdense lesion within the posterior fossa of an 8-year-old boy who presented with nausea and vomiting.

- Ependymoma is another hyperdense tumor that affects the posterior fossa of children. Unlike medulloblastoma, however, it often contains calcifications that can be recognized easily on CT scan. Choroid plexus papilloma usually arises in the trigone of the lateral ventricle in children; however, in adults it is most common in the fourth ventricle. Similar to ependymoma, choroid plexus papilloma commonly contains calcifications.
T1-weighted sagittal MRI of an 8-year-old boy who presented with nausea and vomiting reveals an enhancing tumor within the fourth ventricle. The child underwent a suboccipital craniotomy and resection of his medulloblastoma.
T1-weighted sagittal MRI of 4-year-old boy who presented with gait ataxia and precocious puberty. MRI shows a heterogenous enhancing tumor located within the fourth ventricle with marked hydrocephalus.
T1-weighted axial MRI shows heterogeneous enhancement of the medulloblastoma in a 4-year-old boy who presented with gait ataxia and precocious puberty.

Coronal MRI confirms the presence of the tumor within the fourth ventricle of a 4-year-old boy who presented with gait ataxia and precocious puberty.

- Upon administration of gadolinium in children, homogeneous enhancement commonly occurs, whereas in adults, a more heterogeneous pattern usually is seen. Proton density and T2-weighted imaging displays a hyperintense mass with a surrounding area of edema.
- If the tumor extends upward into the cerebral aqueduct and third ventricle, marked hydrocephalus with transependymal reabsorption of CSF may occur. Extension also can be inferior into the cervical canal.
- Occasional areas of hemorrhage or cyst can be distinguished. Because calcifications are very rare, any area of signal loss must be considered a vascular flow void.
- MRI can help differentiate medulloblastoma from ependymoma: the latter extends further into the lateral recess of the fourth ventricle or even further into the cerebellopontine angle.
- MRI also can help distinguish between medulloblastoma and exophytic brainstem glioma (the latter having a broader attachment to the floor of the fourth ventricle).
- Adults, more frequently than children, can have the desmoplastic variant of medulloblastoma. This form of the tumor is situated laterally in the hemisphere with indistinct borders and small cystic or necrotic areas.
- Besides identifying the primary lesion, MRI is beneficial in detecting metastatic lesions. To rule out drop metastases, MRI of the spine is obligatory when medulloblastoma is either considered or diagnosed.
- Imaging of the spine is best performed prior to surgery in order to avoid postoperative artifacts, which may be interpreted as tumor metastasis. Metastases can occur in the basal cisterns. Both recurrent lesions and metastases show sparse enhancement.

- **Myelography**
  - In the past, myelography was the standard diagnostic test for medulloblastoma metastases to the spine.
  - Today, when MRI is contraindicated, myelography is utilized, accompanied by CT scan.
Skeletal imaging
- Metastasis to the bone must be considered in any child with medulloblastoma and bone pain.
- A skeletal survey helps elucidate lytic or sclerotic lesions.

Other Tests
- Cerebrospinal fluid
  - Cytology of CSF is important for the staging of medulloblastoma; however, no standardized method has been agreed upon for how and when to obtain CSF.
  - Lumbar puncture is the most common method for obtaining CSF; however, this can precipitate cerebellar tonsillar herniation (coning) in a patient with increased intracranial pressure.
  - Although safer, lumbar puncture performed shortly after surgery can have misleading results; the fluid may contain clinically insignificant cells that have been disturbed during surgery. This may be performed 2 weeks following surgery.
  - If a ventricular drain is placed, it can be used to obtain CSF for cytologic testing; however, ventricular samples of CSF will contain malignant cells less commonly than a sample obtained from the thecal sac.
  - Some authors suggest obtaining CSF at the time of surgery from the cisterna magna for cytologic analysis.

Tumor genetics
- To date, use of cytogenetic studies has been controversial.
- Some original reports found a correlation between aneuploid DNA content and a better prognosis. Interestingly, DNA content of most medulloblastoma cells is diploid, signifying a poorer outcome. More recent studies, however, have failed to reproduce this relationship between ploidy and outcome.
- The most common genetic abnormality found in medulloblastoma, 17qi, is an isochromosome on the long arm of chromosome 17. Found in one third to two thirds of medulloblastomas, it is common in other tumors, including leukemias.
- Accompanying the isochromosome 17qi is the loss of genetic material from the short arm of chromosome 17, where the tumor-suppressor gene p53 is located.
- Studies have shown that loss or damage to the p53 site is rare in medulloblastoma. Theories now implicate another focus on the short arm of chromosome 17, which is either a tumor-suppressor gene in itself or a modulator for the function of p53.

Procedures
- Lumbar puncture: To obtain CSF, a lumbar puncture may be necessary. Consider this very carefully since obstructive hydrocephalus, common in medulloblastoma, is an absolute contraindication.
- Ventriculostomy: If the patient is symptomatic from obstructive hydrocephalus, placement of an external ventricular drain may be a lifesaving procedure. Some centers also advocate an endoscopic third ventriculostomy to bypass the obstruction. This may also obviate the need for a shunt in the future following surgical removal of the tumor.

Histologic Findings
- Upon gross examination, medulloblastoma appears as a pinkish-gray mass usually arising from the cerebellar vermis in children. Cysts, areas of necrosis, or calcification are rare.
- On microscopic examination, cells are small and poorly differentiated, with scant cytoplasm and little stroma (see the image below). A high mitotic index is common. Classic Homer-Wright rosettes can be seen in one fifth of cases. Elongated cells surrounding eosinophilic circular zones devoid of lamina and blood vessels form these pseudorosettes. Differentiation can be seen along astrocytic, neuronal, ependymal, or even mesenchymal lines.
High-power magnification hematoxylin and eosin (H&E) section of a typical medulloblastoma

- Rorke classified this tumor with other primitive neuroectodermal tumors, which include pineoblastoma, ependymoblastoma, retinoblastoma, central neuroblastoma, and peripheral neuroblastoma. This classification system is not accepted universally.

- Desmoplastic medulloblastoma is a variant more often seen in adults and more common in the cerebellar hemisphere. In addition to containing all microscopic characteristics of childhood medulloblastoma, the desmoplastic type contains a dense reticulin network; cells are arranged in a biphasic pattern with areas of high and low cellularity. Cells in this variant may assemble along reticulin fibers.

- Histologic subtypes
  - Three other histologic subtypes exist: Medullomyoblastoma, melanotic medulloblastoma, and large cell medulloblastoma.
    - Medullomyoblastoma: Striated and smooth muscle cells are the hallmark of medullomyoblastoma. The tumor can contain cells that show elements of neuronal and glial differentiation. If the presumptive medullomyoblastoma contains elements of ectodermal, mesodermal, and endodermal differentiation, the tumor must be considered a teratoma.
    - Melanotic medulloblastoma: Small, undifferentiated cells containing melanin are characteristic of the very rare melanotic medulloblastoma.
    - Large-cell medulloblastoma: This subtype has large vesicular nuclei with prominent nucleoli. Cells of the large-cell medulloblastoma are remarkable in their immunoreactivity for synaptophysin. This particular tumor is associated with a poorer clinical outcome.
  - Although large-cell medulloblastoma is associated with a more aggressive course, medullomyoblastoma has a clinical course similar to that of ordinary medulloblastoma. However, the desmoplastic variant has a more favorable outcome.

- Aside from these findings, associating histologic findings with outcome has been very difficult. As in other tumors, vascularity and endothelial hyperplasia do not seem to influence recurrence rates. In some studies, however, the presence of necrosis (or a high mitotic index) has been associated with a shorter relapse-free interval.

**Treatment**

**Medical Care**
For the patient with few neurological signs and little hydrocephalus, the entire presurgical workup can be facilitated on an outpatient basis. Admit patients with significant neurological symptoms (especially those with either change in mental status or imaging evidence of considerable hydrocephalus such as transepidermal edema) to the hospital in a monitored setting.

- The cranium initially can accommodate a small increase of CSF volume with little change in intracranial pressure. However, since the skull is a rigid container with a finite volume, further increases in ventricular size lead to dramatic increases of intracranial pressure. Decreased mental status is an indication that the ventricular volume is approaching that threshold; enlargement of ventricles beyond the threshold is accompanied by potentially disastrous consequences.
- Frequent neurologic assessment by the nursing staff is extremely important. Any further decline in mental status is indication for administration of mannitol and emergent neurosurgical consultation for placement of an external ventricular drain.

**Staging**

- Postoperatively, medical care revolves around staging, chemotherapy, and irradiation. Within 48 hours of surgery, a follow-up gadolinium-enhanced MRI is necessary to assess residual tumor size prior to the onset of enhancing reactive gliosis, which may be interpreted as tumor.
- Staging is dependent upon extent of resection, radiographic evidence of tumor spread, and CSF cytology. Recently, a move away from the Chang TNM staging system to a simplified high-risk/low-risk categorization has occurred. Those patients who undergo gross total resection, with no radiographic evidence of spread and no malignant cells on CSF cytology, are considered in a low-risk category; however, presence of any of the 3 would place the patient into the high-risk group.

**Irradiation**

- Radiation therapy for medulloblastoma is aimed at destroying cells along the entire neuraxis. Local recurrence has been associated with a lower radiation dose at the primary site. Patients receiving less than 5000 centigray (cGy) have over twice the local recurrence rate as those receiving at least this dose.
- In addition, clinical trials have documented that radiation therapy to only the cranium results in metastasis to the spine (even in the absence of positive cytology or radiographic evidence of spread). Most standard therapy for low-stage disease includes 36 cGy to both the brain and spinal cord with a boost of 18-20 cGy to the primary tumor site. Some institutions use different regimens including higher doses in several fractions. Others recommend proton beam therapy.
- Unfortunately, radiation can have a destructive influence on the developing nervous system. Complications of radiotherapy can include lowered intelligence quotient (IQ) score, small stature, endocrine dysfunction, behavioral abnormalities, and secondary neoplasms (experienced by those fortunate to have prolonged survival).
- White matter necrosis, which can enlarge and produce significant mass effect, is another feared long-term complication of radiation. Reduction in IQ and neurobehavioral function is related directly to the age at which radiation is administered. Radiotherapy, however, remains the most effective adjunct for medulloblastoma and is used in children despite its consequences.

**Chemotherapy**

- Chemotherapy has evolved from use for advanced recurrent disease to use as a common tool in the modern armamentarium against medulloblastoma. However, despite the common use of chemotherapy today, exact benefits remain unclear.
- To reduce radiation dose or postpone irradiation until it can be better tolerated, chemotherapy utilization is focusing on young children. Among the several regimens now being used, one of the most aggressive is the "8 drugs in 1 day" protocol, which employs vincristine, carmustine, procarbazine, hydroxyurea, cisplatin, cytarabine, prednisone, and cyclophosphamide.
- Children's Cancer Group recently reported better results with a vincristine, lomustine, and prednisone (VCP) protocol. The study reported a 63% 5-year progression-free survival rate for VCP as opposed to 45% in the same group for the "8 in 1 day" regimen.
- Pediatric Oncology Group showed similar survival results in the same age group when chemotherapy was followed by radiation. That study protocol utilized vincristine, cyclophosphamide, etoposide, and cisplatin. Thus far, the greatest benefit from the addition of chemotherapy has been seen in those patients with more advanced disease.
- New studies are looking at sensitizing the tumor to irradiation with the concomitant use of chemotherapy. Also, the use of presurgical chemotherapy to treat patients in extremis prior to surgery has been reported.
- Like radiation, chemotherapy involves toxic effects. Adverse effects include renal toxicity, ototoxicity, hepatotoxicity, pulmonary fibrosis, and gastrointestinal disturbances. Most of these effects are transient and reverse with the withdrawal of the drug. However, when methotrexate is used in combination with irradiation, irreversible necrotizing leukoencephalopathy can occur.
Surgical Care

Aside from histologic confirmation, the fundamental goal of surgery is removal of as much tumor as possible. Patients in whom gross total resection is possible are found to have longer recurrence-free intervals than patients who have residual tumor at the end of surgery.

Surgery also has the added benefit of restoring the natural CSF pathways in the brain. A majority of patients will have resolution of their hydrocephalus after surgery.

- At the time of surgery, the extent of subarachnoid spread of the tumor can be assessed. When involved with tumor, the surrounding subarachnoid space is opaque, with a granular appearance often referred to as "sugar coating." This condition is associated with early subarachnoid seeding along the entire neuraxis and early recurrence.
- In one third of cases, the tumor adheres to the floor of the fourth ventricle, precluding gross total resection.
- The purpose of postoperative MRI within 48 hours after surgery is 2-fold. Aside from staging, the MRI delineates any residual tumor; if the surgeon believes the residual tumor is removable, re-exploration of the patient during the same hospitalization for additional tumor removal is a reasonable possibility. The patient spends the first postoperative night in ICU.
- If the surgery entails significant manipulation or invasion of the brain stem, the patient should remain intubated for the first postoperative night and be extubated carefully once lower cranial nerve function has been assessed. However, if the surgeon believes that involvement of the floor of the fourth ventricle was minimal, the patient may be extubated in the operating room.
- If the patient has not had an external ventricular drain placed preoperatively, one usually is placed at the time of surgery.
- Postoperative drainage is maintained for 3 days, after which the drain is clamped and connected to pressure monitoring. If the patient tolerates 24 hours of having the drain clamped, the ventriculostomy is removed.
- Decrease in mental status is an indication for opening the ventriculostomy and continuing drainage. Continued drainage will allow blood and postoperative cellular debris to clear; clamping can be reattempted after an additional 5 days.
- If repeated drainage fails to relieve symptoms, a ventriculoperitoneal shunt must be placed for long-term control of hydrocephalus; however, this is necessary in only approximately 15% of patients. The alternative to shunting is a third ventriculostomy. This can reestablish CSF flow without the potential for peritoneal seeding of tumor.

Consultations

- Oncologist
- Neurosurgeon
- Radiation oncologist

Diet

No special diet is beneficial.

Activity

No activity restrictions are necessary.

Medication

Medulloblastoma is treated primarily with surgical excision followed by radiation therapy and chemotherapy. Few drugs are of benefit in this disease. Exceptions are glucocorticoids, which can aid in decreasing vasogenic edema. Mannitol is useful in the acute setting when the physician is faced with a herniating patient. Chemotherapy is used as adjuvant therapy in some patients. Administration of toxic compounds that affect multiple organ systems is in the realm of the experienced oncologist.

Glucocorticoids

Reduction of vasogenic edema is the role of glucocorticoids in malignant brain tumors. They can be very effective in medulloblastoma and can even alleviate hydrocephalus by reopening CSF pathways in the posterior fossa. Although any of several glucocorticoids can be used, dexamethasone is used most often. Equivalent doses of various glucocorticoids are 0.75 mg for dexamethasone, 4 mg for methylprednisolone and triamcinolone, 5 mg for prednisolone and prednisone, 20 mg for hydrocortisone, and 25 mg for cortisone.

Dexamethasone (Decadron, Dexasone)

Most commonly used drug to treat vasogenic edema secondary to medulloblastoma. Promotes reduction of edema after craniotomy.
Dosing

Adult
Initial: 10 mg IV q6h

Pediatric
Administer as in adults

Interactions
Barbiturates, ephedrine, phenytoin, and rifampin decrease effects; decreases effect of salicylates and vaccines used for immunization

Contraindications
Documented hypersensitivity; active bacterial or fungal infection

Precautions

Pregnancy
C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions
Increases risk of multiple complications, including severe infections; monitor for signs of adrenal insufficiency when tapering drug—abrupt discontinuation may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections are possible complications

Methylprednisolone (Solu-Medrol, Depo-Medrol)
Decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing increased capillary permeability.

Dosing

Adult
2-60 mg/d PO in 1-4 divided doses followed by gradual reduction to lowest level that maintains clinical response

Pediatric
0.5-1.7 mg/kg/d or 5-25 mg/m²/d PO/IV/IM divided q6-12h

Interactions
May increase digitalis (ie, digoxin) toxicity secondary to hypokalemia; estrogens may increase levels; phenobarbital, phenytoin, and rifampin may decrease levels of methylprednisolone (adjust dose); diuretics may cause hypokalemia—monitor patient

Contraindications
Documented hypersensitivity; viral, fungal, or tubercular skin infections

Precautions

Pregnancy
C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions
Hyperglycemia, edema, osteonecrosis, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, growth suppression, myopathy, and infections are possible complications

Prednisolone (AK-Pred, Delta-Cortef, Articulose-50, Econopred)
Decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reducing capillary permeability.

Dosing

Adult
5-60 mg/d PO/IV/IM
**Prednisone (Sterapred)**

May decrease inflammation by reversing increased capillary permeability and suppressing polymorphonuclear cell activity.

**Dosing**

**Adult**

5-60 mg/d PO qd or divided bid/qid; taper over 2 wk as symptoms resolve

**Pediatric**

4-5 mg/m$^2$/d PO; alternatively, 0.05-2 mg/kg PO divided bid/qid; taper over 2 wk as symptoms resolve

**Interactions**

Estrogens may decrease clearance; may increase digitalis (ie, digoxin) toxicity secondary to hypokalemia; phenobarbital, phenytoin, and rifampin may increase metabolism (consider increasing maintenance dose); diuretics increase risk of hypokalemia—monitor patients

**Contraindications**

Documented hypersensitivity; viral infection; peptic ulcer disease; hepatic dysfunction; connective tissue infections; fungal or tubercular skin infections

**Precautions**

Abrupt discontinuation may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections may occur

**Hydrocortisone (Solu-Cortef, Westcort)**

Decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing increased capillary permeability.

**Dosing**

**Adult**

100 mg IV bolus, followed by continuous infusion of 100 mg q8h for 24-48 h; once patient's condition is stable, initiate PO hydrocortisone (50 mg q8h for another 48 h; may taper dose to 30-50 mg/d in divided doses)

**Pediatric**

1-5 mg/kg/d or 75-300 mg/m$^2$/d PO divided q12-24h
Interactions
Estrogens may decrease clearance; may increase digitalis (ie, digoxin) toxicity secondary to hypokalemia

Contraindications
Documented hypersensitivity; viral, fungal, or tubercular skin infections

Precautions

Pregnancy
C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions
Caution in hyperthyroidism, osteoporosis, peptic ulcer, cirrhosis, nonspecific ulcerative colitis, diabetes, or myasthenia gravis

Cortisone (Cortone acetate)
Decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing increased capillary permeability.

Dosing

Adult
25-300 mg/d PO/IM divided q12-24h

Pediatric
0.5-0.75 mg/kg/d PO/IM or 20-25 mg/m²/d divided q8h
Alternative IM administration: 0.25-0.35 mg/kg/d qd or 12.5 mg/m²/d

Interactions
Estrogen may increase levels; may increase digitalis (ie, digoxin) toxicity secondary to hypokalemia

Contraindications
Documented hypersensitivity; viral, fungal, or tubercular skin lesions

Precautions

Pregnancy
D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions
Caution in patients with hyperthyroidism, cirrhosis, nonspecific ulcerative colitis, osteoporosis, peptic ulcer, diabetes, or myasthenia gravis

Diuretics
These agents are used in the acute setting to prevent further increases of intracranial pressure.

Mannitol (Osmitrol)
May reduce subarachnoid space pressure by creating osmotic gradient between CSF in arachnoid space and plasma. Not for long-term use.

Dosing

Adult
1.5-2 g/kg IV as 20% solution (7.5-10 mL/kg) or as 15% solution (10-13 mL/kg) over period as short as 30 min

Pediatric
Initial: 0.5-1 g/kg IV
Maintenance: 0.25–0.5 g/kg IV q4-6h

Interactions
Contraindications

Documented hypersensitivity; anuria; severe pulmonary congestion; progressive renal damage; severe dehydration; active intracranial bleeding; progressive heart failure

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Carefully evaluate cardiovascular status before rapid administration since sudden increase in extracellular fluid may lead to fulminating CHF

Follow-up

Further Inpatient Care

- Admit patients in whom further surgical intervention is being contemplated.
- Chemotherapy usually is administered on an inpatient basis.

Further Outpatient Care

- Imaging is the primary mode of monitoring residual disease, efficacy of continuing medical treatment, and recurrence or metastasis. Because medulloblastoma is aggressive, frequent monitoring is essential. MRI should be repeated every 3 months the first year; every 4 months the second year; every 6 months the following 3 years; and yearly thereafter.
- Radiation therapy is an outpatient procedure.
- Any signs of change in mental status are indications for outpatient visits, as they may herald hydrocephalus and possible recurrence.
- Lower cranial nerve or cerebellar signs also may signal recurrence.
- Taper steroids and monitor adverse effects.

Inpatient & Outpatient Medications

- Taper steroid use. However, chemotherapy and radiation therapy may exacerbate edema and necessitate low-dose corticosteroids for a short period of time.
- Antiepileptic medication usually is not necessary when the tumor is located in the posterior fossa.
- Spread of disease to the supratentorial compartment may cause seizures and indicate antiseizure medication.

Transfer

Transfer may be necessary for treatment at a center familiar with pediatric neurosurgery, pediatric oncology, or pediatric radiotherapy.

Deterrence/Prevention

No known precautions currently exist to prevent the disease or its recurrence.

Complications

- Hydrocephalus (the most common complication of medulloblastoma) can cause secondary visual problems. Cerebellar dysfunction (the second most common complication of the disease) may lead to problems with coordination and gait. Cranial nerve palsy from brainstem involvement can lead to difficulties with vision, speech, and swallowing. With subarachnoid spread to the spinal cord, the unfortunate complications are radiculopathy and weakness.
- Complications accompany the treatment of medulloblastoma. Fortunately, most of these complications are transient. The most common complication after surgery is a temporary worsening of ataxia accompanied by nystagmus. One of the most commonly cited complications is cerebellar mutism. The anatomic site of origin is thought to be the deep cerebellar nuclei. The constellation of symptoms includes apathy, minimal-to-absent speech, emotional lability, and refusal to initiate movement.
Hemiparesis can accompany mutism. Lower cranial nerves are intact, but the syndrome is accompanied by a swallowing apraxia. It becomes apparent several hours after surgery and persists for several weeks, usually resolving completely. Other complications include a temporary Parinaud syndrome and pneumocephalus. A common complication of any surgery in the posterior fossa is aseptic meningitis. This can be alleviated with a short course of corticosteroids.

- Complications of radiation therapy have been discussed previously and include lowered IQ, small stature, endocrine dysfunction, behavioral abnormalities, secondary neoplasms, and radiation necrosis of the white matter.
- Chemotherapy also has numerous adverse effects on multiple organ systems including renal toxicity, ototoxicity, hepatotoxicity, pulmonary fibrosis, and gastrointestinal disturbance. Methotrexate, when used in combination with irradiation, can cause permanent necrotizing leukoencephalopathy.

**Prognosis**

- Medulloblastoma is a very aggressive tumor. Even after a good response to surgery and radiation, recurrence is common; most recurrences occur within 2 years after treatment.
  - The most common location of recurrence is at the primary tumor site in the posterior fossa.
  - With the use of adjuvant chemotherapy, incidence of recurrence in the spinal canal and the supratentorial region seems to decrease.
- Systemic metastases, in the absence of a CSF shunting system, are also a recognized problem in 10-20% of patients. Bone is the most common site of systemic metastasis; regional lymph node sites follow.
- The Collin law was first hypothesized for Wilms tumor and has been expanded since to cover many pediatric tumors thought to be congenital in origin.
  - The Collin law states that, if a tumor has not recurred in a period of time equal to age of patient plus 9 months, that patient can be considered to be cured.
  - The Collin law generally holds for medulloblastoma; however, several late recurrences (longer than 10 years after diagnosis) have been reported. The 5-year progression-free survival rate in that group is 70-80% for patients at low risk and 60-70% for patients at high risk.
- Greater age at diagnosis has been associated with a better prognosis, most likely because adults more often harbor the less aggressive desmoplastic variant of medulloblastoma.
- Why females have a longer recurrence-free interval is not understood.

**Patient Education**

Teach patients and families about early signs of hydrocephalus, especially if the patient has a ventricular shunt in place.

**Miscellaneous**

**Medicolegal Pitfalls**

- Failure to diagnose
  - Children presenting with refractory vomiting should undergo imaging studies of the brain.
  - Perform neuroimaging studies promptly if findings of an exhaustive gastrointestinal evaluation for vomiting are normal.
Media file 1: CT scan demonstrates a hyperdense lesion within the posterior fossa of an 8-year-old boy who presented with nausea and vomiting.

Media file 2: T1-weighted sagittal MRI of an 8-year-old boy who presented with nausea and vomiting reveals an enhancing tumor within the fourth ventricle. The child underwent a suboccipital craniotomy and resection.
of his medulloblastoma.

Media file 3: T1-weighted sagittal MRI of 4-year-old boy who presented with gait ataxia and precocious puberty. MRI shows a heterogenous enhancing tumor located within the fourth ventricle with marked hydrocephalus.
Media file 4: T1-weighted axial MRI shows heterogeneous enhancement of the medulloblastoma in a 4-year-old boy who presented with gait ataxia and precocious puberty.

Media file 5: Coronal MRI confirms the presence of the tumor within the fourth ventricle of a 4-year-old boy who presented with gait ataxia and precocious puberty.
References


Keywords

medulloblastoma, tumor, primitive neuroectodermal tumor, PNET, Gorlin syndrome, nevoid basal cell carcinoma syndrome, blue rubber-bleb nevus syndrome, Turcot syndrome, glioma polyposis syndrome, Rubinstein-Taybi syndrome

Contributor Information and Disclosures

Author

**George I Jallo, MD,** Associate Professor of Neurosurgery, Pediatrics and Oncology, Director, Clinical Pediatric Neurosurgery, Department of Neurosurgery, Johns Hopkins University School of Medicine

George I Jallo, MD is a member of the following medical societies: American Association of Neurological Surgeons, American Medical Association, and American Society of Pediatric Neurosurgeons

Disclosure: Codman (Johnson & Johnson) Grant/research funds Consulting; Medtronic Grant/research funds Consulting

Coauthor(s)

**Alvin Marcovici, MD,** Consulting Staff, Southcoast Neurosurgery

Alvin Marcovici, MD is a member of the following medical societies: American Association of Neurological Surgeons, Congress of Neurological Surgeons, and Phi Beta Kappa

Disclosure: Nothing to disclose.

Medical Editor

**Raj D Sheth, MD,** Professor, Mayo College of Medicine; Chief, Division of Pediatric Neurology, Nemours Children's Clinic

Raj D Sheth, MD is a member of the following medical societies: American Academy of Neurology, American Academy of Pediatrics, American Epilepsy Society, American Neurological Association, and Child Neurology Society

Disclosure: Nothing to disclose.