

Medulloblastoma, Primitive Neuroectodermal Tumor (PNET), Ependymoma and Glioma in Children

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Medulloblastomas, primitive neuroectodermal tumors and ependymomas constitute a significant number of central nervous system tumors in children. Medulloblastomas and PNETs are more likely to have been metastasized at the time of diagnosis, compared to ependymomas. The clinical presentation of medulloblastomas and ependymomas is usually due to increased intracranial pressure, while PNETs usually present with head and neck masses. Surgical resection of the tumors is the mainstay of treatment which should be followed by radiotherapy in most cases. Chemotherapy in medulloblastoma and PNET has a proven effect on survival, but its role in ependymomas is still unknown.



Overview

Brain tumors are a group of abnormal cells that are found in the brain. They can be classified as:

1. Benign or malignant tumors
2. Primary brain tumors or metastatic brain tumors. Among children, primary brain tumors make up more than half of the malignant tumors in the brain

As per the WHO classification, brain tumors are classified based on their cells of origin into subtypes such as:

1. Tumors arising from glial cells which are known as gliomas that may include both low grade and high-grade astrocytomas
2. Tumors arising from meningeal cells (meningiomas)

Epidemiology of Pediatric Medulloblastomas, PNETs and Ependymomas

The most common malignant brain tumor in children is medulloblastoma. The tumor occurs before the age of 10 years. Medulloblastomas are responsible for up to 20% of central nervous system tumors in pediatrics. 250 new cases of medulloblastomas are diagnosed per year in the United States.

The patient's presenting age; postoperative residual disease after tumor resection and the [metastasis](#) stage at the time of diagnosis are predictive of mortality in patients with medulloblastomas. Patients older than 3 years of age who do not have any **subarachnoid or hematogenous spread** of their tumor at the time of diagnosis have a 5-year survival of more than 80%.

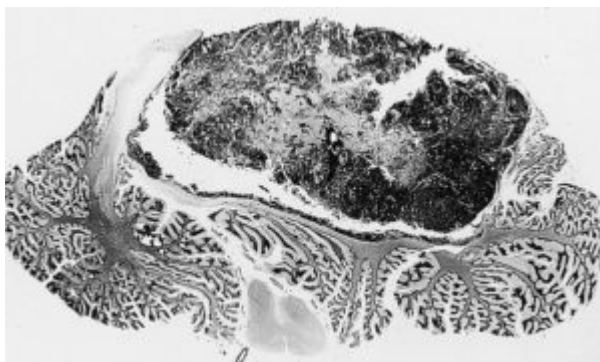


Image: "Medulloblastomas are densely cellular and usually rather discrete." by The Armed Forces Institute of Pathology (AFIP) - PEIR Digital Library (Pathology image database). Image# 405852.
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On the other hand, the 5-year survival of patients with microscopic metastatic disease (M1), nodular seeding of the cerebellum or other central nervous system structures (M2), nodular seeding of the spinal subarachnoid space (M3) or hematogenous spread of the tumor (M4), ranges between 30 and 60%.

Infants who have medulloblastomas have a very low 5-year survival rate regardless of their metastatic stage. Most patients with medulloblastomas are **diagnosed between 3 and 5 years** of age and there is a **slight predominance in boys**.

The exact incidence of **PNETs** is unknown, but some hypothesize that the condition might have an incidence of **around 2.9 per million**. Patients with PNETs are usually older compared to those presenting with medulloblastomas. PNETs are **more common in the white population**, compared to Asian or African-American populations.

Ependymomas are considered as the third most common form of central nervous system tumors in children. **140 new cases** of pediatric ependymomas are reported per year. The survival rate after resection of the tumor is again dependent on the patient's age. Infants have the worst prognosis with a 5-year survival rate of 25%. Children aged 1 to 4 years have a 46% survival rate, whereas those older than 5 years have a 70% survival rate. The peak incidence is reported in children aged between 5 and 6 years.

Pathophysiology of Pediatric Medulloblastomas, PNETs and Ependymomas

Medulloblastomas might arise from the **cerebellar vermis**. The most likely origin of malignant cells in medulloblastomas is the **external granular cerebellar layer**. Some studies suggest that malignant cells in medulloblastomas arise from more than one cell of origin.

The molecular alterations in medulloblastomas have an impact on the tumor's progression and metastatic potential. Tumors that express the **neurotrophin (NT3)** and **Trk C receptor** are known to undergo **apoptosis** more often to have a favorable prognosis. Tumors that express the oncogenes ERBB2 and MYCC are more likely to spread and are associated with poor prognosis.

Because medulloblastoma usually arise in the posterior fossa, which has limited space, **cerebrospinal fluid passage obstruction** is common. Patients might develop **hydrocephalus** consequently.

The most commonly identified cytogenetic abnormalities in PNETs include **reciprocal translocations between chromosomes 11 and 22**. PNETs are usually aggressive tumors with a worse clinical outcome, and more potential for metastasis compared to other central nervous system tumors. PNETs can arise from the central nervous system, peripheral nervous system, or from the autonomic nervous system. Neuroblastomas are PNETs arising from the autonomic nervous system.

Ependymomas arise from the **radial glia cells** which can proliferate. These tumors arise from the floor, roof or lateral recesses of the fourth ventricle. The tumors can also arise from the ependymal lining of the lateral ventricles or the spinal canal.

Low-grade ependymomas are characterized by having a low mitotic index and being well differentiated. **High-grade ependymomas** usually have a higher mitotic index, a necrotic center and endothelial proliferation. High-grade ependymomas are more likely to spread, compared to low-grade tumors.

CNS tumors



- Second most common pediatric malignancy.
- 20% of all cases of childhood cancer.
- Younger patients are more likely to have embryonal tumors (**medulloblastomas**).
- Sporadic, without risk factor or cause.
- The genetic syndrome may predispose.

Clinical Presentation of Pediatric Medulloblastomas, PNETs and Ependymomas

Patients with medulloblastomas are usually **young children** who complain of **headaches**, nausea, blurring of vision, loss of balance, behavior changes, seizures, drowsiness, coma, **vomiting**, and fatigue. The duration of the symptoms is usually more than 3 months. Headaches are usually more severe in the morning.

These symptoms are attributed to **increased intracranial pressure**. Severe increases in the intracranial pressure can cause **Cushing triad**, i.e. **hypertension**, a slow heart rate, and hypoventilation.

Because the most common site of the tumor is within the cerebellum, patients can develop **ataxia**. **Brainstem tumors** can cause diplopia, facial weakness, hearing problems, or a stiff neck due to cranial nerve involvement. Back pain, leg weakness, and respiratory problems can also be attributed to metastatic disease, which is common with medulloblastomas.



Image: "Papilledema is a swollen optic disc caused by increased intracranial pressure." by Jonathan Trobe, M.D. - University of Michigan Kellogg Eye Center - The Eyes Have It. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

Central nervous system PNETs usually present with signs and symptoms of **neurological deficits**. Peripheral PNETs present with pain, swelling and masses that are localized to the site of the tumor. The most common site of peripheral PNETs is the head and neck; therefore, head and neck masses are commonly seen in patients with peripheral PNETs. Bony metastasis is very common with peripheral PNETs.

The semiology of ependymomas is very like medulloblastomas as they arise from increased intracranial pressure. Vomiting, headaches and fatigue are common findings. Ependymomas are more likely to be associated with **seizures**, compared to medulloblastomas. A fundoscopic examination might reveal **papilledema**, a sign of increased intracranial pressure.



- Presenting symptoms depend on the **location** of the tumor in the brain
- Symptoms of increased intracranial pressure (ICP)
 - Morning headache
 - Emesis
 - Lethargy

Diagnostic Workup for Pediatric Medulloblastomas, PNETs and Ependymomas

Historical findings – initial signs of elevated ICP



- Poor school performance
- Fatigue
- Behavioral change
- Weight gain/loss
- Increased clumsiness
- Walking difficulty
- Focal seizures with prolonged postictal paralysis

Brain computed tomography scans have excellent sensitivity for the detection of medulloblastomas and other brain tumors. **Brain magnetic resonance imaging** is superior to computed tomography in the differentiation between the different types of posterior fossa tumors, i.e. medulloblastomas, ependymomas or [astrocytomas](#).

Patients who complain of back pain should get a **bone scan** to exclude bony metastasis. The spinal metastatic disease can be reliably excluded by magnetic resonance imaging. Microscopic metastatic disease is common with medulloblastomas and a **lumbar puncture** with the **cerebrospinal fluid cytologic examination** is indicated. Histologic examination reveals an undifferentiated tumor of the cerebellum of embryonal neuroepithelial origin.

PNETs can also be diagnosed based on magnetic resonance imaging of the involved sites and histologic examination of the suspected lesions. Patients with peripheral PNETs should undergo a **chest computed tomography scan**, a **bone scan**, and perhaps a **positron emission tomography study** to exclude metastatic disease, which is very common.

Computed tomography scanning of the head is also indicated in the diagnostic workup of ependymomas. Almost all patients with ependymomas have [hydrocephalus](#) on computed tomography scan. Magnetic resonance imaging is also indicated.

Tumors appear hypointense and homogenous on T1-weighted images and hyperintense on T2-weighted images. Patients who are confirmed to not have hydrocephaly should undergo a **lumbar puncture** to obtain cerebrospinal fluid for **cytologic examination**. In contrast to medulloblastomas, ependymomas are more likely to be well-differentiated. Cysts, calcification, and hemorrhage can also be seen on histologic examination of an ependymoma.

Treatment of Pediatric Medulloblastomas, PNETs and Ependymomas

After **total or near-total resection** of the primary medulloblastoma, **adjunctive radiotherapy** and **chemotherapy** are indicated in most cases. Radiotherapy should be administered to the whole central nervous system while focusing on the primary site of the tumor and the locations of the metastatic lesions.

Chemotherapy for patients with non-metastatic medulloblastoma includes **limustine**, **vincristine**, and **cisplatin**. Patients with metastatic medulloblastoma should undergo

surgery, followed by radiotherapy and finally chemotherapy.

The chemotherapeutic combination of **cisplatin, carboplatin, cyclophosphamide**, and **vincristine** is recommended. **The gentle suction of the tumor** is usually possible due to its fragility.

Postoperative magnetic resonance imaging is indicated to estimate residual disease, which is predictive of survival. A **ventriculoperitoneal shunt** or a **third ventriculostomy** are indicated to relieve hydrocephalus.

Complete resection of peripheral PNETs is more complicated as vital organs might be involved. Adjunctive chemotherapy and radiotherapy are needed in the treatment of PNETs. Radiotherapy in peripheral PNET puts the patient at an increased risk of developing a **sarcoma**.

The mainstay treatment for ependymoma is **surgical resection** of the tumor. Once the tumor is resected, radiotherapy is usually indicated in the postoperative period. In contrast to medulloblastoma, the benefit of chemotherapy in ependymoma is unknown. If chemotherapy is going to be used, single-agent chemotherapy with cisplatin or carboplatin is recommended.

Complications related to radiation therapy



- Growth failure
- Endocrinological abnormalities
- Secondary brain tumors
- Vasculopathy
- Long-term cognitive deficits

→ Avoid excessive irradiation to the head (head CT)

References

[Pediatric Ependymoma](#) via medscape.com

[Pediatric Medulloblastoma](#) via medscape.com

[Primitive Neuroectodermal Tumors](#) via medscape.com

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