Neuroblastoma — Symptoms, Classification, and Survival Rate

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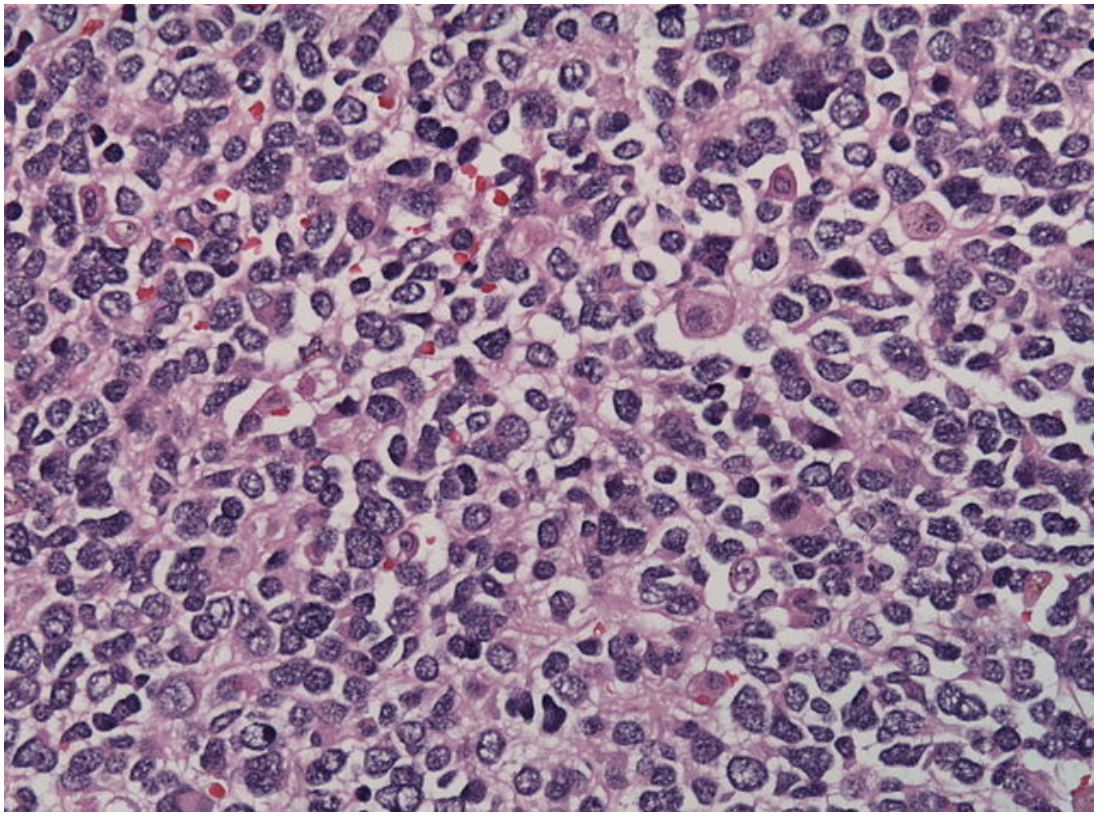
Neuroblastoma is a peripheral tumor of the sympathetic nervous system. After brain tumors, it is the second most common malignant solid tumor in children. Since neuroblastoma can manifest with various symptoms, like ecchymosis of the eyelid or paraplegia, it is crucial to keep it in mind as a differential diagnosis and to be aware of clinical diagnostics and the basic treatment options.



Definition

Neuroblastoma is an embryonal tumor of the post-ganglionic sympathetic nervous system. It mostly occurs during infancy and originates from the stem cells of the sympathetic nervous system (neuroblasts).

Approximately half of all neuroblastomas will have metastasized at the time of diagnosis, yet the prognosis is promising, and spontaneous remission is common.

Epidemiology

Neuroblastoma as an extracranial malignant solid tumor

Neuroblastoma is one of the **most common extracranial malignant solid tumors** during infancy and accounts for 10% of childhood cancers. There are about 700 new cases of neuroblastoma each year in the United States, with 90% of patients falling ill before school age. The prevalence is 1 in 7000 children and is second to that of brain tumors.

Neuroblastoma is more common among white children. The disease has a slight male preponderance with a male: female ratio of 1.2:1. The average age of onset is **2 years**, but older children may also develop neuroblastoma. Particularly, in infants, **spontaneous remissions** can occur even with metastatic cancer.

Etiology

Causes of neuroblastoma

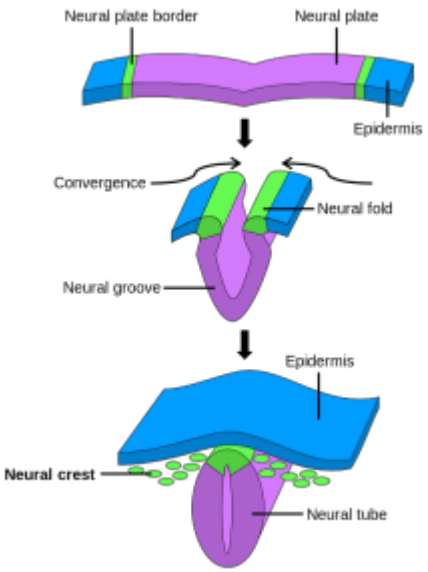


Image: Neural crest formation during neurulation.
By: NikNaks. License: CC BY-SA 3.0

The tumor is thought to be genetic and inherited in an autosomal dominant fashion, with germinal mutation being the main pathologic lesion.

The tumor is believed to arise based on Knudson's two-hit hypothesis theory where 2 hits in DNA are involved in the causation of the disease.

The distribution of the tumor involves the pattern taken by the migration of neural crest cells because neuroblastoma originates from the cells of the **neural crest**, which later develop into the sympathetic ganglia and adrenal medulla. The neuroblasts remain in an immature state instead of differentiating, and they mutate into malignant cells. It is assumed that the amplification of the cellular oncogene **N-myc** contributes to the progression of neuroblastoma.

This amplification, which is observed in 20% of tumors, is the consequence of a **1p-**

deletion—a loss of the p-arm of the first chromosome. Spontaneous tumor regression does not occur when an *MYCN* (N-myc) amplification is present. Hence, *MYCN* amplification has a profound impact on treatment decisions.

About **50%** of neuroblastomas develop in the **adrenal medulla**. Other locations are the cervical, thoracic, and abdominal areas along the sympathetic trunk, with the abdominal cavity being involved in about 70% of the cases.

Note: Neuroblastomas can appear as an **hourglass tumor** with intraspinal and extradural parts.
Metastases primarily appear in the bone marrow, bones, and locoregional lymph nodes. If metastases appear in the liver, the condition is referred to as the **Pepper syndrome**. In rare cases, an intracranial metastasis is found.

Clinical Presentation and Symptoms

Site-related symptoms of neuroblastoma

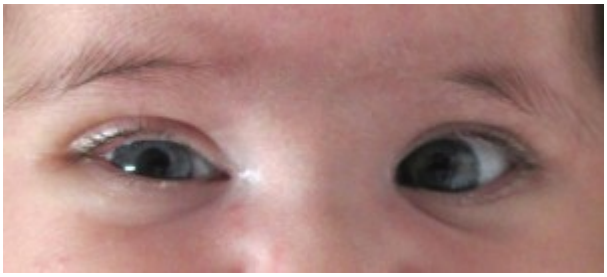


Image: Horner syndrome. By: Davplast. License: CC BY-SA 4.0

Typical symptoms can be observed depending on the localization.

Neuroblastoma in the cervical region can provoke Horner's **syndrome**, which involves miosis, ptosis hemifacial anhidrosis, and enophthalmos. This arises from the compression and involvement of the sympathetic chain.

Cervical or thoracic localization leads to cough and dyspnea.

An hourglass tumor typically presents with **paraplegia** and nerve lesions since the tumor infiltrates through the neuroforamina into the intraspinal space.

A protruding abdomen is frequently associated with an abdominal localization. In this presentation, hypertension may arise from renal artery compression and not hormone secretion.

General symptoms of neuroblastoma

General symptoms like fever, pain, loss of appetite, fatigue, bone pain, fractures, and deformities are signs of metastases.

Due to the **production of hormones** by the tumor, symptoms that indicate sympathetic overactivation, such as arterial hypertension or diarrhea, can occur. This diarrhea is resistant to therapy and is the result of higher secretion of vasoactive intestinal peptide (VIP); although this rarely occurs, it is characteristic of neuroblastoma.

Neuroblastoma as opsoclonus-myoclonus-ataxia (Kinsbourne syndrome)

In rare cases (approx. 2%), the neuroblastoma is associated with the paraneoplastic syndrome of cerebellar ataxia, myoclonus of the trunk and extremities, and spontaneous nystagmus (opsomyoclonus). For this reason, it is also referred to as **dancing feet and dancing eye syndrome**. Occasionally, for unknown reasons, this opsoclonus-myoclonus-ataxia syndrome leaves permanent neurological and cognitive deficits associated with psychomotor retardation even if the neuroblastoma is successfully cured.

Diagnostics

Sonography and radiology

If neuroblastoma is strongly suspected, sonographic and radiological imaging of the tumor can help to rule out an hourglass tumor because of the imminent development of paraplegia.

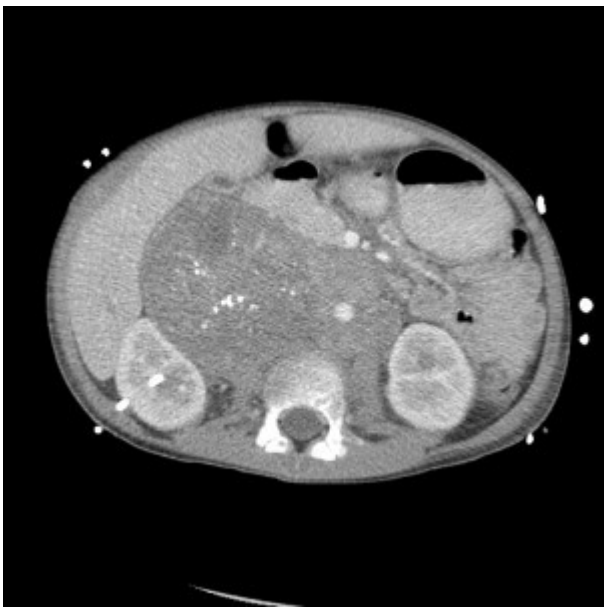


Image: Neuroblastoma, CT of the abdomen. By: RadsWiki.
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Scintigraphy

Neuroblastoma can be identified using **iodine-131-meta-iodobenzylguanidine (MIBG)**, which is an analog of noradrenaline because the adrenergic tissue absorbs this substance. Scintigraphy is also a convenient method for assessing the progression of the disease because a reduction in size can be well observed.

Urine can be used to detect higher excretion, while serum is convenient for the detection of a higher concentration of **vanillylmandelic acid and homovanillic acid**. These are metabolites of the increased metabolism of catecholamines and represent evidence for neuroblastoma since neuroblastoma produces catecholamines (as do the chromaffin cells of the adrenal medulla).

Nephroblastomas and lymphomas are possible differential diagnoses; however, these tumors do not cause an increased level of catecholamine degradation products. Often, nonspecific tumor-associated parameters (such as lactate dehydrogenase, ferritin, and the neuron-specific enolase) are also elevated.

Note: Vanillylmandelic acid and homovanillic acid also qualify as markers for the progression of the disease as their production decreases with atrophy of the tumor. Importantly, an infiltration of the bone marrow must always be ruled out by confirming the amplification of the N-myc oncogene using tumor material and **bone marrow punctures** at 4 puncture sites since this would require a different treatment approach.

Classification

Histological classification of neuroblastoma according to Hughes

The histological classification of neuroblastoma is made in 3 degrees of malignancy **according to Hughes;** 50% of all cases are grade 3 neuroblastoma. If the neuroblastoma differentiates by forming numerous mature ganglionic cells, it is called a **benign ganglioneuroblastoma**.

Grade of Malignancy	Result
Grade 1	Mix consisting of undifferentiated cells and mature ganglionic cells
Grade 2	Immature cells and few mature ganglionic cells
Grade 3	Undifferentiated small blue cells, sometimes rosette formation

Histological characteristics of neuroblastoma

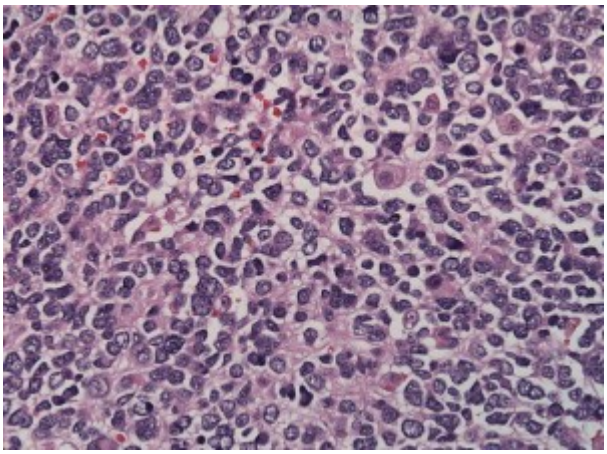

Image: Histopathology specimen of neuroblastoma.
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Macroscopically, a dark, sanguineous cross-section with calcifications can be seen. The most common degree of malignancy, the undifferentiated neuroblastoma, does not show any forms of differentiation such as neuropil or ganglionic cells. Occasionally, neuroblasts are arranged in rosette patterns with a neuropil center, known as **Homer-Wright rosettes**.
In contrast, diffuse ganglioneuroblastoma consists of a mixture of neuroblasts, Schwann

cells, and ganglion cells. Nodular ganglioneuroblastoma shows a nodose structure consisting of neuroblastic foci and tumor parts made of ganglioneurons.

International Neuroblastoma Staging System (INSS)

The classification of neuroblastoma into 5 clinical stages, according to the **International Neuroblastoma Staging System (INSS),** is important. **More than 60%** of children are diagnosed at **stage IV**.

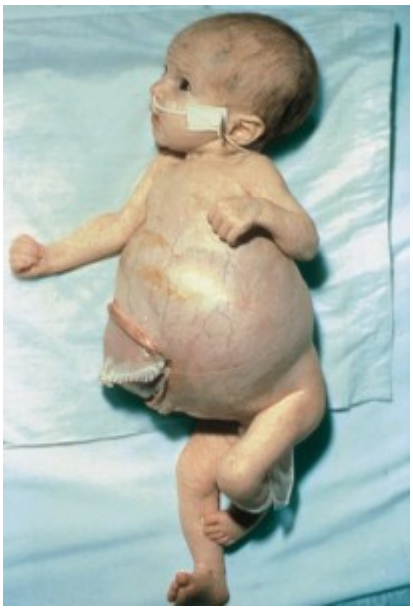

Image: Stage IV-S neuroblastoma with a bulging abdomen and collateral circulation

Stage I: Tumor is confined to the organ of origin.

Stage II: The neuroblastoma is localized, but infiltrates the surroundings, yet without infiltrating across the midline.

Stage III: Tumor infiltrates across the midline.

Stage IV: Hematogenic metastases to other organs are present.

Stage IV-S: The neuroblastoma is detected during early infancy and metastases can be found in the liver, skin, and bone marrow. There are no metastases in the skeleton (better prognosis than stage IV).

Treatment

Types of treatment for neuroblastomas

The treatment for neuroblastoma depends on the age of onset and the stage at diagnosis. In cases of local foci without *MYCN* amplification, **spontaneous regression** of the tumor is not uncommon so that treatment can be temporizing at first. In stages I and II, **surgery** would be the first step. Surgery is also performed in stage III with **combined chemotherapy** and possibly **radiation**. In stage IV, additional **131J-MIBG therapy** and an autologous bone marrow transplant become necessary.

For maintenance treatment, retinoids and arsenic trioxide are administered. Retinols

trigger decreased proliferation and *MYCN* expression. Additionally, topoisomerase-I inhibitors such as topotecan are being used more frequently.

Prognosis of neuroblastoma

Note: The average rate of spontaneous healing in stage IV-S is 80%.
The prognosis in stages I and II is promising, with a **cure rate above 90%**. In stage III and IV-S, the 5-year survival rate is approx. 60–70%. For stage IV, the prognosis is notably poor.

Negative prognostic factors include high lactate dehydrogenase, age > 1 year, poor resectability of the tumor, and amplification of N-myc.

Follow-up diagnostics and aftercare of neuroblastoma

Follow-up diagnostics include radiological procedures to track a reduction in size and to determine if the patient responds to the treatment. Moreover, the tumor markers homovanillic acid and vanillylmandelic acid can be used to assess the progress of therapy. In aftercare, tumor markers and radiological tests are used not only to rule out a relapse but also to determine the occurrence of any delayed side effects of chemotherapy such as cardiotoxic effects and audiologic damage.

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Notes