

# Neuroblastoma

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## Abstract

*Neuroblastoma is a malignant tumour of neural crest cells which give rise to the sympathetic nervous system. It is a childhood tumour occurring in infants and young children (5 years and less in 90% of all cases) that accounts for 8 to 10% of pediatric cancers. It may arise at any site in the sympathetic nervous system, most commonly in the abdomen. At diagnosis the tumour may be limited to a single organ, locally or regionally invasive, or widely disseminated. Bone, bone marrow, liver and skin are among the most common metastatic sites. Neuroblastoma is clinically characterized by its variable evolution. Most localized tumours have an excellent prognosis when treated by surgical resection with or without chemotherapy. Infants less than 1 year have a better prognosis than children regardless of tumour stage. Some of these tumours may even show spontaneous regression. In contrast, approximately 60% of children (> 1 year) with neuroblastoma present metastatic disease at diagnosis with poor outcome, despite intensive treatment protocols including megatherapy with hematopoietic stem cell transplantation. Neuroblastoma mass screening in infants under 1 year is not useful since it reduces neither the incidence of metastatic disease nor the mortality of disease. Disease-free survival ranges from 95% for some localized tumours to 30% for metastatic disease in children over 1 year. This clinical diversity correlates with numerous biological and molecular factors (DNA content, amplified expression of MYCN oncogene, expression of TRK neurotrophin receptors, loss of chromosome 1p, excess 17q....). Patients management should follow national or international treatment protocols/recommendations and requires a medical team with expertise in the field of pediatric cancers.*

## Key-words

Pediatric cancer, neural crest cells, ganglioneuroma, ganglioneuroblastoma, chemotherapy

**Disease name and synonyms**

-Neuroblastoma  
-Sympathoblastoma

**Definition**

Neuroblastoma is a malignancy of neural crest cells which usually give rise to the sympathetic nervous system. It affects infants and young children (5 years and less in 90% of all cases). It may arise at any site in the sympathetic nervous system, most commonly in the abdomen.

**Differential diagnosis**

Clinically, dumbbell tumours and opsomyoclonus syndrome may first resemble to primary neurological disease.

Diagnosis of pheochromocytoma can be suspected in presence of adrenal gland tumours associated with arterial hypertension and pulmonary metastasis.

Histologically, especially in the absence of increased urinary catecholamine secretion, other blue round cell tumours must be excluded (rhabdomyosarcoma, PNET/ Ewing's sarcoma, lymphoma, extrarenal nephroblastoma, leukemia). Moreover, neuroblastoma should be differentiated from other neuroblastic tumors which are divided into three classic histopathologic patterns reflecting a spectrum of maturation and cell differentiation: ganglioneuroma is the fully differentiated, benign counterpart of the malignant, undifferentiated neuroblastoma, whereas ganglioneuroblastoma forms the intermediate tumor with immature and mature components.

**Etiology**

Most neuroblastomas are sporadic cancers. Family history is reported in only about 1% of patients. The potential role of environmental exposures remains unknown.

**Clinical description**

At diagnosis, the tumour may be limited to a single organ, locally or regionally invasive, or widely disseminated. Bone, bone marrow, liver,

and skin are among the most common metastatic sites.

Clinical symptoms depend on the location of the primary tumour, the locoregional and metastatic dissemination. Symptoms are frequent but non specific. About 60% of primaries are localized in the abdomen. They may be associated with palpable mass, digestive problems, discomfort and pain. Thoracic neuroblastomas ( $\approx 20\%$ ) are often diagnosed coincidentally by chest X-rays. Respiratory distress, dysphagia and circulatory problems may be observed in upper thoracic tumours. Cervical location ( $\approx 5\%$ ) often shows palpable mass and Horner's syndrome. Pelvic neuroblastoma ( $\approx 5\%$ ) may cause constipation, voiding urine and oedema. In about 10%, the localization of the primary remains unknown. Dumbbell tumours may be responsible for neurological symptoms such as radicular pain, paraplegia, bladder or bowel dysfunction by compressing the spinal cord. In about 2% of patients, opsomyoclonic syndrome (myoclonic jerks, random eye movement and/or cerebellar ataxia) may occur.

Clinical symptoms in metastatic disease also vary widely. In infants, metastatic involvement of the liver (Pepper syndrome) may result in prolonged jaundice, circulatory and respiratory problems. In this age group, subcutaneous metastases (bluish nodules) may be the presenting sign. Older children show a different pattern of metastatic spread. Diffuse bone pain, proptosis and periorbital ecchymoses (Hutchinson syndrome) may be present in case of bone, bone marrow and orbital tumour location. Lymph node metastases are also frequent. Constitutional symptoms include failure to thrive, fever, hypertension, bouts of sweating and pallor.

The major clinical staging systems (International Neuroblastoma Staging System (INSS)) based on the Evans staging system is shown in **Table 1**.

**Table 1: The international neuroblastoma staging system (INSS)**

Stage 1	Localized tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumour microscopically (nodes attached to and removed with the primary tumour may be positive).
Stage 2A	Localized tumour with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumour microscopically.
Stage 2B	Localized tumour with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumour. Enlarged contralateral lymph nodes must be negative microscopically.
Stage 3	Unresectable unilateral tumour infiltrating across the midline (vertebral column) with or without regional lymph node involvement; or localized unilateral tumour with contralateral regional lymph node involvement; or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement.
Stage 4	Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined for stage 4S).
Stage 4S	Localized primary tumour (as defined for stage 1, 2A or 2B), with dissemination limited to skin, liver and/or bone marrow (limited to infants <1 year of age).

**Outcome**

Neuroblastoma is characterized by its variable evolution. Most localized tumours have an excellent prognosis when treated by surgical resection, with or without chemotherapy. Infants less than 1 year have better prognosis than children regardless of tumour stage. Some of these tumours may even show spontaneous regression (localized or stage IVs). In contrast, approximately 60% of children with neuroblastoma present metastatic disease at diagnosis with poor outcome despite intensive treatment protocols. The clinical diversity correlates with numerous biological and molecular factors. Regardless of

patients age and stage of disease, amplified expression of *MYCN* oncogene is the worst paraclinical prognostic factor. Other variables associated with poor survival include elevated serum ferritin, lactate dehydrogenase and neuron-specific enolase, lack of CD44 expression and unfavorable histologic features at diagnosis. Moreover, tumour DNA content, as well as expression of TRK neurotrophin receptors also influences outcome. Taken together, three types of neuroblastoma with distinct clinical features and behaviours were identified by Brodeur *et al.* (1994) on the basis of these genetic characteristics (**Table 2**).

**Table 2: Types of neuroblastoma (Brodeur 1994)**

Feature	Type 1	Type 2	Type 3
<i>MYCN</i>	1 copy	1 copy	amplified
DNA ploidy	hyperdiploid/ near triploid	near diploid/ near tetraploid	near diploid/ near tetraploid
1p LOH	absent	± present	usually present
14q LOH	absent ?	± present	usually present
TRK-A expression	high	variable	low or absent
Age	usually < 1 year	any age	usually 1-5 years
Stage	usually I, II, IVs	usually III, IV	usually III, IV
3-Year survival	95%	20-25%	< 5%

Three risk groups may be identified on the basis of age at diagnosis, tumour stage and the prognostic effect of *MYCN* gene amplification:

Patients of all ages with stage 1, 2, or 4S disease without *MYCN* amplification have an excellent prognosis with a 5-year survival rate of over 95%.

Patients with stage 3, as well as infants with stage 4 neuroblastoma without *MYCN* amplification have a survival rate of approximately 75%.

Children (>1 year) with stage 4 neuroblastoma (regardless of *MYCN* status), *MYCN* amplified

stage 2 and 3 disease as well as infants (<1 year) with metastatic, *MYCN* amplified neuroblastoma have about 30% chance of recovery.

**Diagnostic methods**

Increased urinary catecholamine metabolites and positive meta-iodobenzylguanidine (MIBG) scintigraphy of the primary support the diagnosis of neuroblastoma. CT scan and /or MRI should be carried out to localize the tumour accurately, to provide anatomical information and mass measurements. For the detection of metastases, MIBG scan, bone

scan and/or standard radiography may be indicated. Bone marrow aspiration and trephine biopsies are required from different sites to detect microscopic tumour involvement.

Histological material is required to confirm diagnosis and to study prognostic factors in order to define treatment strategy.

**Mass screening:** identification of neuroblastoma in the preclinical stages by detection of urinary catecholamines reduces neither the incidence of metastatic disease, nor the mortality of disease and therefore seems useless.

### Epidemiology

Neuroblastoma is the most common extra-cranial solid tumour in childhood. Its annual incidence is approximately 9 per million children with approximately 150 new cases diagnosed yearly in France and 650 new cases in the United States.

### Treatment

Different treatments are required at different stages of disease. Moreover, age at diagnosis, as well as prognostic factors influence treatment strategies. Patients should be treated following national or international treatment protocols or recommendations.

Briefly, localized tumours are treated by primary surgery if possible (stage 1 and 2). In case of unfavourable prognostic factors, adjuvant chemotherapy may be indicated. Pre-operative chemotherapy is recommended in inoperable stage 3 neuroblastoma. Megatherapy followed by autologous stem cell transplantation is indicated for children with *MYCN* amplified tumours. Local radiotherapy may be indicated in aggressive tumours with or without total resection of the primary.

Metastatic neuroblastoma (stage 4) requires neoadjuvant chemotherapy followed by surgery of the primary if possible. Megatherapy followed by autologous stem cell transplantation is indicated for patients with good responsiveness. Following megatherapy, retinoic acid as treatment for minimal residual disease was shown to increase survival. Treatment strategies in infants (less than 1 year) are similar to those in children, but whether megatherapy is indicated in infants remains matter of debate.

The treatment of the particular stage 4S disease may be extremely variable. About 50%

are clinically "silent" tumours which may benefit from a "wait and see" strategy. They may regress spontaneously without any treatment, but half of them may need treatment because of tumour progression. In case of rapid evolution, chemotherapy, and/or radiotherapy are indicated. Surgery of the primary should be discussed after tumour response.

In case of opso-myoclonus syndrome, treatment may also include corticosteroids, Immunoglobulines or ACTH.

### Unresolved questions

Future challenges are the application of either optimised treatment strategies or novel therapies to patients who cannot be cured with the most intensive current approaches. On the other hand, therapy reduction and even the need of surgery should be evaluated within international protocols for patients who have an excellent survival rate with current treatments.

Advances in understanding the biology and genetics of neuroblastoma will be the key in the individual management of disease as well as in development of new drugs.

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