# CHAPTER 105
# NEUROBLASTOMAS

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## Introduction

Neuroblastomas, along with most other paediatric solid tumours, should no longer be considered a single disease. Within the histological appearance of small round blue cells with rosette formation and background neuropil are an infinite number of behaviour patterns, each reflecting the genomic characteristics of the tumour cells. Thus, in some patients with neuroblastomas, the tumour spontaneously disappears or matures into a benign ganglioneuroma. In other patients with histologically identical neuroblastomas, the tumour rapidly disseminates and is resistant to even the most aggressive treatment. Refinements in nosology will ultimately recognise that these are different diseases that share morphological characteristics and a common cell of origin.

As morphological characteristics alone are insufficient to allow a prediction of behaviour, the concept of "risk stratification"—a process that encompasses assessment of the innate aggression of the tumour—has become important. Prediction of behaviour is an inexact science, but it is becoming more precise as genomic markers of aggression are identified. Thus, loss of part of chromosome 1p, amplification of N-Myc oncogene, and abnormalities of chromosomes 6p22, 2p, 11q, and 17q deletions in the malignant cell are all thought to code for aggressive behaviour.[1] Not only do tumour genomics affect behaviour, but certain features of the host, most notably age, are also critical in determining outcome.

## Demographics

Neuroblastoma is, fortunately, infrequent in Africa.[2] Whether this reflects a low prevalence or a low rate of diagnosis is uncertain. It may be that neuroblastoma is another noncommunicable disease that is in some way influenced by industrialisation and the environmental insults associated with the process.[3]

In Europe and North America, neuroblastomas are the most common solid tumours of childhood; in Africa, however, the incidence of neuroblastomas lags far behind that of lymphomas, retinoblastomas, Wilms' tumours, and sarcomas.[4] The tumour may be recognised antenatally, but the median age at diagnosis is 2 years.

## Pathophysiology

### Sites of Origin

Neuroblastomas arise from neural crest cells. These are the cells that populate the adrenal medulla, the sympathetic ganglia, and the olfactory apparatus. They demonstrate a wide range of neuronal differentiation, but their distribution defines the sites at which primary neuroblastomas may occur. The most common site is the adrenal gland. Tumours arising from the sympathetic ganglia may occur in the abdomen, commonly around the origin of the celiac axis, or in the pelvis around the organ of Zukerkandl. In the chest, they present as posterior mediastinal tumours. Occasional tumours arise in the neck from the cervical sympathetics. Tumours arising from olfactory elements are termed esthesio-neuroblastomas.

### Paraneoplastic Effects

Neuroblastomas may secrete catecholamines or their precursors. Thus, hypertension and diarrhoea are common. Opsomyoclonus occurs in 2–3% of affected children.[5]

### Maturation

Neuroblastomas are unique in their potential to "mature" towards benign ganglioneuromas. It is also likely that a histological picture indistinguishable from neuroblastoma forms part of the normal maturation of the adrenal medulla, as "neuroblastoma-in-situ" has been found in autopsies in premature babies dying of unrelated causes.[6] Maturation is more likely to be seen in neonates and infants with stage 4S disease.

### Histology

Neuroblastomas clearly demonstrate the limitations of the light microscope as a means of predicting cellular behaviour. Nonetheless, histological findings of ganglioneuroma presage a benign clinical course. Shimada defined histological features that predict poor behaviour, which have been incorporated into risk stratification protocols.[7] Frequently, in the absence of immunohistochemical stains, the pathologist can offer little beyond "small round blue cell tumour", and the clinical features must be considered when making a diagnosis.

## Staging

The concept of staging as a predictor of outcome is being replaced by the concept of risk stratification, which incorporates cytogenetic markers and histological appearance as well as patient characteristics. Such studies allow the risk of treatment-related morbidity to be matched to the risk of progressive disease, and to avoid aggressive treatment in children who have biologically favourable tumours.[8] "Surgical risk factors", which predict the ease of resectability, are defined by preoperative imaging,[9] and should carefully be reviewed before any surgery is attempted.

Staging, however, is still important to allow comparisons between studies and experiences, as well as contributing to risk stratification.

The current international neuroblastoma staging system (INSS) is shown in Table 105.1.

*Table 105.1: International neuroblastoma staging system.*

| Stage | Description |
|---|---|
| **Stage 1** | Localised tumour with complete gross resection; ipsilateral nonadherent lymph nodes negative |
| **Stage 2A** | Incomplete gross resection; nodes negative |
| **Stage 2B** | Either stage 1 or stage 2A with ipsilateral nodes positive |
| **Stage 3** | Tumour crossing midline or unilateral tumour with contralateral nodes positive |
| **Stage 4** | Metastatic disease |
| **Stage 4S** | Patient younger than 18 months of age with specific disease pattern |

This system depends upon the surgeon understanding that the "lymphatic" midline lies along the aorta and that nodes between the aorta and the cava are ipsilateral to right-sided tumours and contralateral to left-sided tumours.[10]

The system also draws attention to stage 4S, which describes children younger than 18 months of age with a primary adrenal tumour that would otherwise be stage 1, but with metastases limited to the liver, skin ("blue berry" nodules) (Figure 105.1), and bone marrow. Less than 10% of the marrow cells should be blast cells. Such patients do much better than expected. In these patients, the liver may be massive and interfere with the mechanics of breathing. Under such circumstances, chemotherapy may be indicated, or, rarely, surgery may be needed to temporarily house the liver in a silo.[11]

## Clinical Presentation

Presentation depends upon the site of the primary tumour as well as the stage of disease. Many children will have obvious metastatic disease when they are first seen. In addition to liver secondaries, neuroblastomas have a propensity to metastasize to the orbits, causing exophthalmos and "raccoon eyes" (Figure 105.2); to the skull and long bones, causing painful swellings and increasing the risk of pathological fractures; and into the epidural space through intervertebral foramina, leading eventually to paraplegia. The bone marrow is very frequently invaded. Additionally, some patients present with paraneoplastic syndromes such as hypertension and opsomyoclonus.

Cervical neuroblastoma may present as Horner's syndrome.

Abdominal neuroblastoma has a characteristic nodularity, akin to palpating a bag of potatoes, which may help the clinician differentiate it from a nephroblastoma. Neuroblastoma also is frequently a central abdominal tumour (Figure 105.3).

The challenge is the patient who presents with an abdominal or posterior mediastinal mass with no other clues to its origin. In such a child, urgent investigation is required.

Presenting complaints may include any from Table 105.2; a nonspecific range of symptoms makes diagnosis difficult.

## Investigations

In many instances, little more is needed than a needle biopsy of the primary or metastatic site. Few African centres currently have facilities for cytogenetic studies, or for metiodobenzylgaunidine (MIBG) radioisotope imaging, magnetic resonance imaging (MRI; Figure 105.4), or axial tomography. Plain abdominal x-rays often show a mass with speckled calcification displacing bowel. Intravenous pyelography may show displacement of the kidney and help to differentiate neuroblastoma from an upper pole nephroblastoma, although clinical features are also important.[12] In cases of difficulty, urine can be assessed for catecholamines or their precursors. Ultrasound may help in the localisation of the tumour as well as in the assessment of retroperitoneal lymph nodes and liver.

In patients who present with spinal compression, it is useful to have some idea of the extent of disease within the spinal canal so that a surgical approach can be planned if possible. This may involve myelography if no other imaging is available (Figure 105.5).

Skeletal x-rays will reveal bony cortical metastases, and a bone marrow biopsy will define marrow involvement. A chest x-ray with a lateral view is important in the assessment of thoracic lesions (Figure 105.6).

## Surgical Management

The mainstay of treatment for neuroblastoma is chemotherapy. In most patients presenting in Africa, neuroblastoma is manifestly a systemic disease that requires a systemic treatment; at best, surgery can provide local control. Surgery has, however, an important role in palliation and, infrequently, in cure.

The surgeon may be called upon to obtain biopsy material to establish the diagnosis of neuroblastoma, although this can usually be

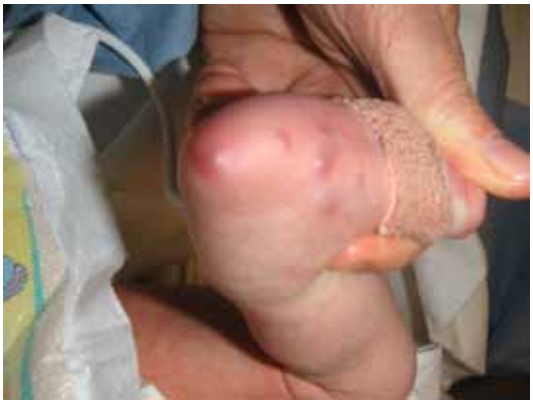

*Figure 105.1: "Blue berry" nodules.*

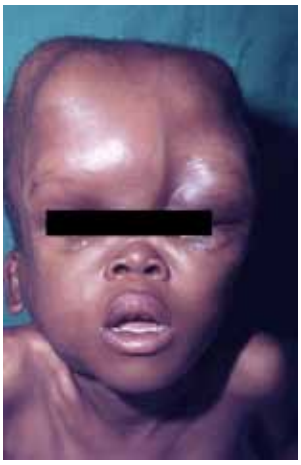

*Figure 105.2: Example of raccoon eyes.*

*Figure 105.3: Abdominal mass.*

*Table 105.2: Presenting complaints with neuroblastoma.*

| | |
|---|---|
| • Mass | • Myoclonus/opsoclonus |
| • Limp/ bone pain/refusing to walk | • Neurological |
| • Generally unwell | • Constipation |
| • Decreased appetite | • Diarrhoea |
| • Vomiting | • Skin lesions |
| • Hypertension | • Proptosis |
| • Anaemia | • Antenatally diagnosed mass |
| • Fever | • Incidental (e.g., single incidence of urinary tract infection) |
| • Abdominal pain | • Horner's syndrome |
| • FTT/ weight loss | • Urinary retention |

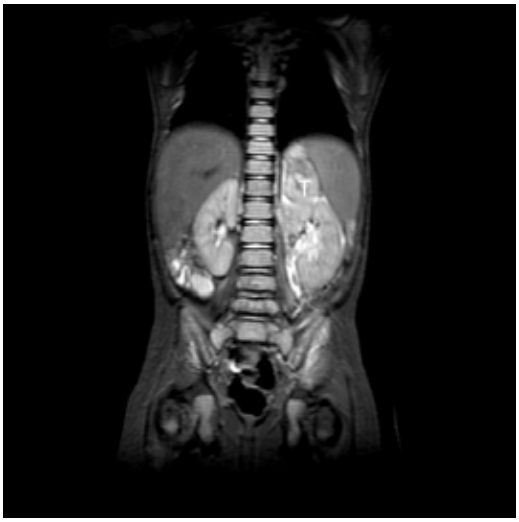

*Figure 105.4: MRI showing left adrenal neuroblastoma marked "T".*

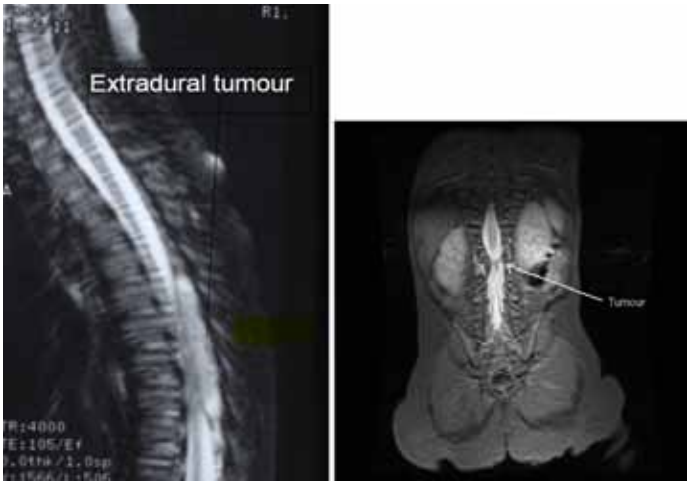


*Figure 105.5: Imaging showing spinal extension.*

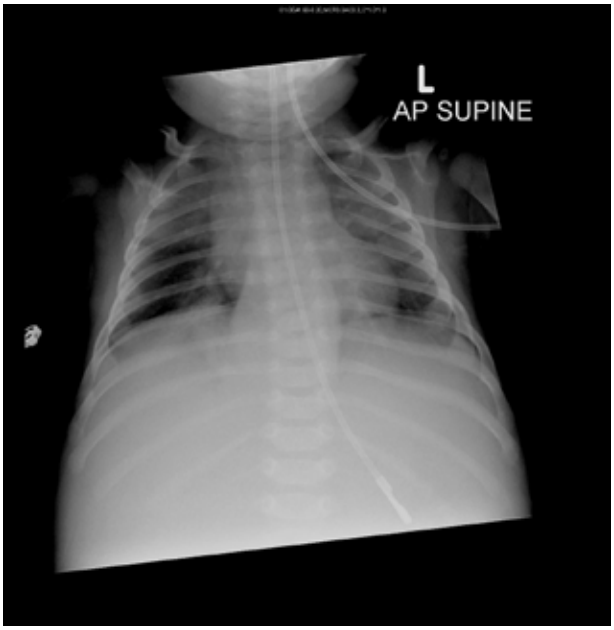


*Figure 105.6: Chest radiograph showing posterior mediastinal mass.*

achieved by bone marrow aspiration or other noninvasive means. In Europe and North America, biopsy is used for assessment of MYCN gene status. In Africa, however, it is usually impossible to assess risk in greater detail than considerations of stage of disease and histological appearance. In the absence of immunohistochemistry, it is important to correlate the pathologist's finding of a small round blue cell tumour with the clinical pattern of disease in order to reach a diagnosis.

Surgery may also be required to decompress the spinal canal in children who present with a short history of cord compression. Paraplegia of more than a few days duration is unlikely to be reversible.

Pathological fractures of long bones may require internal fixation to improve quality of life and to facilitate nursing care. Single-dose radiotherapy, as little as 5 Gy, resolves the pain of bony metastases.

Uncommonly, there is a need to resect localised primary tumours in patients who have responded well to either chemotherapy or *per primam* (with little scarring). As neuroblastomas tend to surround the major abdominal vessels, especially the coeliac trunk and the superior mesenteric artery, such resections can be mammoth undertakings,[13] and careful review of imaging studies should precede any such operations. Even in the most experienced hands, aortic and other major vessel injuries occur.[13] Intractable diarrhoea following retroperitoneal nerve injury occurs postoperatively in 30% of resections.[14] In infants younger than 18 months of age, surgical resection is more frequently possible.

Resection of the primary tumour in children with metastatic disease that has responded to chemotherapy remains controversial and is not thought to improve survival.[15]

## Outcomes

In the authors' experience, without the resources for bone marrow transplantation and high-risk chemotherapy, metastatic neuroblastoma is a lethal disease, with the exception of babies with stage 4S disease. Even in centres with the proper resources, the outlook is dismal.[16] The role of the surgeon is palliative.

In patients with localised disease (stages 1 and 2), surgery may be curative, but sadly, such patients are few. It is believed that such tumours have favourable biological characteristics, and this limits their growth potential and confers a favourable prognosis. Patients with stage 3 intraabdominal disease may be made surgically curable by preoperative chemotherapy when this is available.

## Key Summary Points

1. Neuroblastoma is rare in Africa.
2. Neuroblastoma is of neural crest origin and usually secretes catacholamines.
3. Neuroblastoma may mature into benign ganglioneuroma.
4. The clinical presentation is nonspecific as well as site and stage dependent.
5. In the absence of sophisticated imaging, plain radiographs may reveal a soft tissue mass with or without calcification.
6. Molecular biology and cytogenetics are key to the diagnosis; however, if these are not available, histopathology may be the only diagnostic tool.
7. Surgery for neuroblastoma in Africa is mainly palliative.
8. Neuroblastoma in Africa, with the continent's limited resources, is a lethal disease.

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