Neuroblastoma

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Abstract

Neuroblastoma is the most common extra cranial solid tumour in childhood. It is a fascinating and enigmatic tumour showing behaviour ranging from biological resistance to multimodal cancer therapies to complete spontaneous regression. The majority of children presenting with neuroblastoma have 'high risk disease' with distant metastases at primary diagnosis associated with considerable (more than50%) mortality. New targeted therapies are crucial to improve survival. These are being pursued through advances in the basic sciences alongside energetic translational clinical research efforts.

Keywords childhood cancer; clinical trials; neuroblastoma; surgery

Epidemiology, genetic predisposition and risk factors

Neuroblastoma is the most frequently diagnosed neoplasm during infancy and accounts for more than 7% of malignancies in patients younger than 15 years and around 15% of all paediatric oncology deaths. The incidence of neuroblastoma in predominantly Caucasian populations is 9–12 per million children. The median age at diagnosis is 17 months, as would be expected of a disease of developing tissues. This malignant tumour consists of undifferentiated and/or differentiating cells originating from neural crest-derived sympathoadrenal precursors. A family history of neuroblastoma has been reported in 1–2% of patients and when present this follows an autosomal dominant pattern of inheritance. Supporting Knudson's two-mutation hypothesis, the median age at diagnosis for familial neuroblastoma cases is 9 months compared to 18 months in sporadic cases. Germline mutations of anaplastic lymphoma kinase (ALK) are responsible for the majority of inherited cases. Less commonly the genetic defect is in the PHOX2B gene, leading to association with Hirschsprung's disease and congenital central hypoventilation syndrome. Cases have been reported in children with neurofibromatosis type 1 (NF1). At present, the genetic predisposition to neuroblastoma appears to be heterogeneous and hence tumourigenesis is postulated to need multiple genetic alterations.

The clinical problem

Neuroblastoma is extraordinary for its broad spectrum of clinical behaviour. The tumour is often described as enigmatic and unpredictable because it is associated with contrasting patterns of clinical behaviour ranging from life-threatening progression, maturation to ganglioneuroblastoma or ganglioneuroma, and even spontaneous regression. Maturation toward, or initiation as 'benign ganglioneuroma' may be unpredictable and also linked with compromise of critical vital structures. Although outcome for certain subsets of patients has improved over the past few two decades, children with 'high-risk' neuroblastoma continue to have poor (less than40%) long-term survival.

Clinical features

The clinical features of neuroblastoma are highly variable and ultimately depend on the site of the primary lesion, the extent of metastatic disease and the presence of associated paraneoplastic syndromes. Neuroblastoma may occur as an incidental finding or be discovered with elevated urinary catecholamine metabolites during screening apparently healthy infants or children. Non-specific symptoms such as pain and malaise may accompany early stage disease. Thoracic tumours may present as an '*incidentaloma*' on chest radiography, associated with Horner's syndrome (ptosis, miosis, and anhidrosis) or with symptoms related to cord compression with intraspinal extension. Abdominal neuroblastoma often features with swelling and/or symptoms due to organ compression such as constipation or urinary retention. In contrast, children with extensive metastatic disease tend to be quite unwell. Characteristic periorbital ecchymosis ('racoon eyes') and proptosis are observed in children with metastatic neuroblastoma to the orbital regions. A minority of cases may present with profuse watery diarrhoea secondary to vasoactive intestinal peptide secreting tumours ('VIPomas'), flushing and excessive sweating in catecholamine-secreting tumours or with immune-mediated nystagmus/" dancing eyes " with the cerebellar "opsoclonus-myoclonus" syndrome.

Neuroblastoma can arise anywhere within the sympathetic nervous system although the majority of lesions occur in the medulla of the adrenal gland. Tumours often infiltrate local structures and surround nerves or vital vessels such as the coeliac artery axis. Tumours typically metastasize to regional lymph nodes and bone marrow. Neuroblastoma metastasizing to the liver in young infants (less than18 months) with stage 4S tumours are a unique fascinating group in whom transient and complete regression may occur with no active intervention.

Diagnostic markers

Urine collection for elevated catecholamine metabolites including dopamine (DA), vanillylmandelic acid (VMA) and homovanillic acid (HVA) is valuable in diagnostic work-up. The VMA/HVA ratio and DA/VMA ratio have also been shown to provide additional information. Although not specific markers for neuroblastoma – high levels at diagnosis of serum markers ferritin (more than142 ng/ml), neuron specific enolase (NSE, more than100 ng/ml), and lactate dehydrogenase (LDH, more than1500 IU/l) have been shown to be predictive of poorer outcome.

Imaging

Ultrasound is the most useful imaging study initially although contrast-enhanced CT scan will demonstrate the extent of

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primary disease and help identify metastases. CT ± 3D reconstructions to display vascular anatomy is also crucial in the pre-surgical assessment of tumour resectability. MRI is very helpful in assessing tumours with spinal involvement.

In patients with neuroblastoma, MIBG scintigraphy is a sensitive and specific tool to demonstrate bone, bone marrow and soft tissue metastases. Meta-iodobenzylguanidine (MIBG) structurally resembles norepinephrine and enters the neuroendocrine cell by an active re-uptake mechanism with storage in the neurosecretory granules thus resulting in its specific concentration compared to non-neuroendocrine cells. As 10% of neuroblastoma tumours do not show MIBG uptake, ^{99m}Technetium methylene diphosphonate (MDP) bone scintigraphy is used in conjunction with ^{131}I or ^{123}I MIBG to accurately stage disease.

^{18}F-fluorodeoxyglucose (^{18}FDG) is avidly taken up by rapidly proliferating tumour cells. Positron emission tomography scanning (PET) using ^{18}FDG is useful for monitoring tumours which fail, either at diagnosis or following treatment, to concentrate MIBG.

Tissue diagnosis

Adequate tumour tissue sampling at diagnosis is required for accurate risk stratification and treatment assignment. Open surgical biopsy has been traditionally deployed in many centres worldwide but minimally invasive image-guided biopsy is also highly efficient at tumour diagnosis and has decreased complication rates. Multiple bone marrow biopsies and aspirates are also taken at diagnosis to stage metastases.

Pathology and genetic features

The new International Neuroblastoma Pathology Classification (INPC) system is based on age at diagnosis, mitosis-karyorrhexis index (MKI), neuroblastic differentiation and stromal content. INPC has a proven role in predicting outcome. MYC oncoproteins are transcription factors which may cause deregulated tumour growth on overexpression. In neuroblastoma – MYCN amplification (more than10 copies per cell) is strongly associated with rapid disease progression and poor outcome in patients at all ages, infants included, and at all tumour stages. However almost 80% of neuroblastomas harbour non-amplified MYCN. Several other somatically acquired chromosomal aberrations associated with DNA copy number alterations (CNAs), together with tumour cell DNA content, have been shown to predict neuroblastoma outcome(s). Aggressive tumour behaviour with poorer outcomes are associated with deletions at the chromosomal region 1p36.3 or 11q23, and with unbalanced gain of the long arm of chromosome 17. Tumour cell DNA content in neuroblastoma fall into two main categories, near-diploidy or hyperdiploidy (more often triploidy). In patients younger than 18 months with metastatic disease near diploid DNA content is a predictor of poor outcome. The Biology Committee of the International Neuroblastoma Risk Group (INRG) has issued recommendations that for accurate and reproducible risk class stratification, neuroblastoma tumours should at least be assessed for MYCN, tumour cell DNA content and 11q23, whilst the implications of several other genetic aberrations deserves further prospective study.

Staging

The currently accepted International Neuroblastoma Risk Group Staging System (INRGSS) was developed to provide consensus guidelines in the pretreatment risk stratification and to facilitate comparison of 'risk-based' clinical trials across the world. INRGSS uses age, stage, histology and molecular pathology to risk-stratify patients and plan treatment. The risk categories in INRGSS are defined according to event-free survival (EFS). To improve the outcome and safety of surgical treatment, the European International Society of Pediatric Oncology Neuroblastoma Group activated the LNESG1 study on localized neuroblastoma aimed at identifying Surgical Risk Factors (SRFs) or Image-Defined Risk Factors (IDRFs) based on radiology characteristics of the tumour. IDRFs have been reported to predict the outcome of surgery including risk(s) of postoperative morbidity and residual disease, but have not been shown to predict overall patient survival (OS).

Role of screening

In view of the significantly better outcome(s) for younger children and those with localized disease screening studies were conducted many years ago in Japan, Europe and North America using urinary HVA and VMA analysis. Reports from these key studies showed that the detection rate(s) of neuroblastoma in a screened infant population increased roughly two-fold compared to that seen in unscreened cohorts. The vast majority of neuroblastoma tumours detected by screening had however favourable clinical and biological features. Therefore screening was found not to reduce either the prevalence of advanced disease over 1 year of age or overall disease mortality. Population screening for neuroblastoma has been abandoned.

Spontaneous regression and stage 4S disease

A small number of neuroblastoma tumours (~10%) may undergo spontaneous regression without active treatment. Tumours may also differentiate to a benign phenotype notably ganglioneuroma. The incidence of spontaneous regression in neuroblastoma is between 10 and 100 times greater than that for any other human cancer. The underlying biology responsible for spontaneous regression of tumours is not yet fully understood. Outcomes are generally associated with a clinically well defined recognizable syndrome in infants called stage MS or 4S disease (S for 'special') herein defining patients often with a small primary tumour in the abdomen or thoracic cavity coexistent with widespread metastasis to the liver or bone marrow and skin (or both) but not in the cortical bone and/or skin.

Management

The various modalities deployed in the treatment of neuroblastoma include surgery, chemotherapy, radiotherapy, differentiation therapy, immunotherapy and in selected cases 'careful observation only'. Patients are stratified into INRG groups – 'very low', 'low', 'intermediate' or 'high-risk' categories. For tumours deemed to have favourable biology a clear trend has emerged to reduce the intensity of therapeutics. In contrast, the approach to tumours with adverse prognosis has shifted over the past two decades toward intensifying therapy.