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Solid Tumour Section

Review

Nervous system: Peripheral neuroblastic tumours (Neuroblastoma, Ganglio-neuroblastoma, Ganglioneuroma)

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Identity

Alias
Neuroblastoma

Classification

Note
Peripheral neuroblastic tumours; are derived from developing neuronal cells of the sympathetic nervous system and are found mostly (but not exclusively) in infants and young children.
In the text below, we will stick to the well known term "neuroblastoma" instead of using the more precise but less common term "peripheral neuroblastic tumours".

Clinics and pathology

Disease

Localisation: Adrenal medulla (50%) and para- and prae-vertebral sympathetic ganglia and paraganglia: cervical (5%), thoracic (15%), retroperitoneal (25%) and pelvic (5%).
Metastatic disease: In 60% of patients metastatic tumour spread is found at diagnosis. Common sites of metastases are: bone marrow, bones, lymph nodes, liver and skin. A unique pattern of metastatic spread in infants with favourable prognosis is mentioned below (under stage 4s).
Clinical Symptoms: The presenting clinical symptoms depend on the tumour location, the regional and metastatic dissemination. An "abdominal" localisation can be associated with discomfort, pain, digestive problems and/or a palpable mass. Thoracic tumours are either found coincidentally or may cause respiratory distress, dysphagia and circulatory problems. Cervical neuroblastomas may lead to Horner's syndrome. Dumbbell tumours can cause radicular pain, paraplegia and dysfunction of bladder or bowel. In a low percentage of patients the opsomyoclonus syndrome is found. Metastatic disease can cause jaundice, circulatory and respiratory problems, bone pain, proptosis (Hutchinson syndrome) and periorbital ecchymoses. Also fever and hyper-tension may occur.
Stages: The stages according to the International Neuroblastoma Staging System (INSS) are:
- stage 1: localized tumour, complete gross excision (possible microscopic residual disease);
- stage 2A: localized tumour, incomplete gross excision, ipsilateral nonadherent lymph nodes are not involved;
- stage 2B: localized tumour, complete or incomplete gross excision, ipsilateral nonadherent lymph node positive for tumour, contralateral lymph nodes microscopically tumour free;

- stage 3: unresectable unilateral tumour infiltrating across the midline with or without regional lymph node involvement - or: localised 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: localised primary tumour (stages 1 , 2A or 2B) with dissemination limited to skin, liver and/or bone marrow (limited to infants having less than 1 year).

The currently used staging system will be replaced by a new staging system which is based on the extent of disease at diagnosis, prior to any treatment and midline, lymph node status and age are not included anymore.

- Stage L1: Locoregional tumour not involving vital structures as defined by the list of Image Defined Risk Factors (IDRF);
- Stage L2: Locoregional tumour with presence of one or more Image Defined Risk Factors;
- Stage M: Distant metastatic disease (except Stage Ms);
- Stage Ms: Metastatic disease confined to skin and/or liver and/or bone marrow.

This new staging system has the advantage that all patients are staged in a uniform manner. This system is more robust, reproducible and less liable to subjective interpretations than surgeons' findings and assessment of resectability.

Diagnosis: Measurement of urinary catecholamine metabolites and histologic examination of a tumour biopsy are used diagnostically. For tumour staging, meta-iodobenzylguanidine (MIBG) scintigraphy (or a technetium-99 bone scan in case of negative MIBG), computed tomography or nuclear magnetic resonance, and bilateral bone marrow aspirates and trephine biopsies are valuable methods.

Differential diagnosis: Clinically, dumbbell tumours and opsomyoclonus syndrome may resemble primary neurological diseases. Arterial hypertension and pulmonary metastases may lead to the suspicion of a pheochromocytoma.

Histopathologically, undifferentiated neuroblas-toma (especially in the absence of increased urinary catecholamine secretion) may cause diagnostic difficulties: peripheral primitive neuroectodermal tumour (pPNET), Ewing tumour, lymphoma, and rhabdomyosarcoma and extrarenal nephroblastoma have to be excluded.

Embryonic origin

Neural crest cells of the sympathetic lineage (sympathetic neuronal precursor cells).

Etiology

Most of the neuroblastomas occur sporadically. Family histories are reported only rarely. The possible impact of environmental exposure is still unknown, although the role of maternal exposure to e.g. phenyl hydantoin is under discussion. A possibly increased incidence of neuroblastomas occurs in patients with neurofibromatosis type I and Wiedemann-Beckwith syndrome.

Epidemiology

Neuroblastomas are the most frequently diagnosed tumours in infancy and the most common extracranial solid tumours in childhood. These tumours account for 7-10% of all childhood cancers including leukemias. The incidence, which is almost uniform in industrialized countries, is 5-10 per million children per year. The median age at diagnosis is approx. 18 months. 50% of patients are diagnosed by the age of 2 and 90% before 6 years of age.

Pathology

According to the International Neuroblastoma Pathology Classification (INPC - Shimada system), four categories are discriminated patho- histolo-gically according to the degree of cellular differentiation into ganglionic cells, 'organoid' maturation with the development of a Schwann cell stroma, and co-existence of clones of different maturity or of distinct aggressiveness:

- Neuroblastoma (Schwannian stroma-poor);
- Ganglioneuroblastoma intermixed (Schwannian stroma-rich);
- Ganglioneuroma (Schwannian stroma-dominant);
- Ganglioneuroblastoma nodular (composite Schwannian stroma-rich/- dominant and stroma-poor).

Two of these categories are further divided into subgroups according to cellular differentiation signs, i.e. Neuroblastoma into: undifferentiated, poorly differentiated and differentiating; and Ganglioneuroblastoma into maturing and mature.

For prognostic assessment, the age of the patient at diagnosis (below 1.5, between 1.5 and 5 years or over 5 years) has to be included as well as the number of mitotic and karyorrhectic (apoptotic) cells in the category of Neuroblastoma and the nodular part of Ganglioneuroma nodular.

Risk assessment: In European countries (SIOPEN studies), the treatment of neuroblastoma patients depends on the age at diagnosis (below or over 1 year of age), on the extent of the disease (stage) and on a genetic parameter, i.e. the amplification of the MYCN oncogene (see below). In the United States and Australia, DNA Index of the tumour cells and histopathology (INPC) are also included in therapy stratification in some stages or age groups, respectively. In future studies also other genetic features of the tumour will be taken into consideration. Currently, there are worldwide efforts to construct a robust risk stratification system. Prior to any treatment patients will be put into a risk category, according to age (less than or more than 18 months), stage,

pathology, MYCN status, other genetic aberration as 11q loss and ploidy (International Neuroblastoma Risk Grouping, INRG). Thus, a more precise treatment planning will be possible. Furthermore, use of the International Neuroblastoma Risk Groups will allow international comparisons of different risk-based therapeutic approaches in the same patient population and greatly facilitate joint international collaborative studies in neuroblastoma.

Treatment

According to risk group assignment, there are the following treatment modalities: surgery, standard chemotherapy, intensive multiagent chemotherapy, myeloablative chemotherapy, followed by autolo-gous stem cell transplantation, external radiation therapy, 13-cis retinoic acid, anti-GD2 monoclonal antibody adjuvant therapy, MIBG-therapy.

A "wait and see" strategy is performed in a subgroup of patients with stage 4s disease and some types of localized diseases, but only if no MYCN amplification is found in the tumour cells, no neurologic deficit and no life-threatening symptoms are present according to the Philadelphia scoring system.

Neuroblastoma mass screening: The search for neuroblastomas in a "preclinical" stage with the intention to decrease mortality led to the introduction of the neuroblastoma mass screening which was started in Japan and Canada more than 30 years ago and later in European countries. The results obtained by the mass screening have been discussed very controversially because screening between several weeks up to 6 months of age led to a substantial over-diagnosis of neuroblastomas which almost exclusively showed favourable genetic markers but did not decrease aggressive stage 4 tumours and overall mortality. This indicates that a substantial proportion of genetically and biologically favourable tumours especially in the first half year of life do not become clinically manifest but regress spontaneously. A Consensus conference recommended the discontinuation of the screening

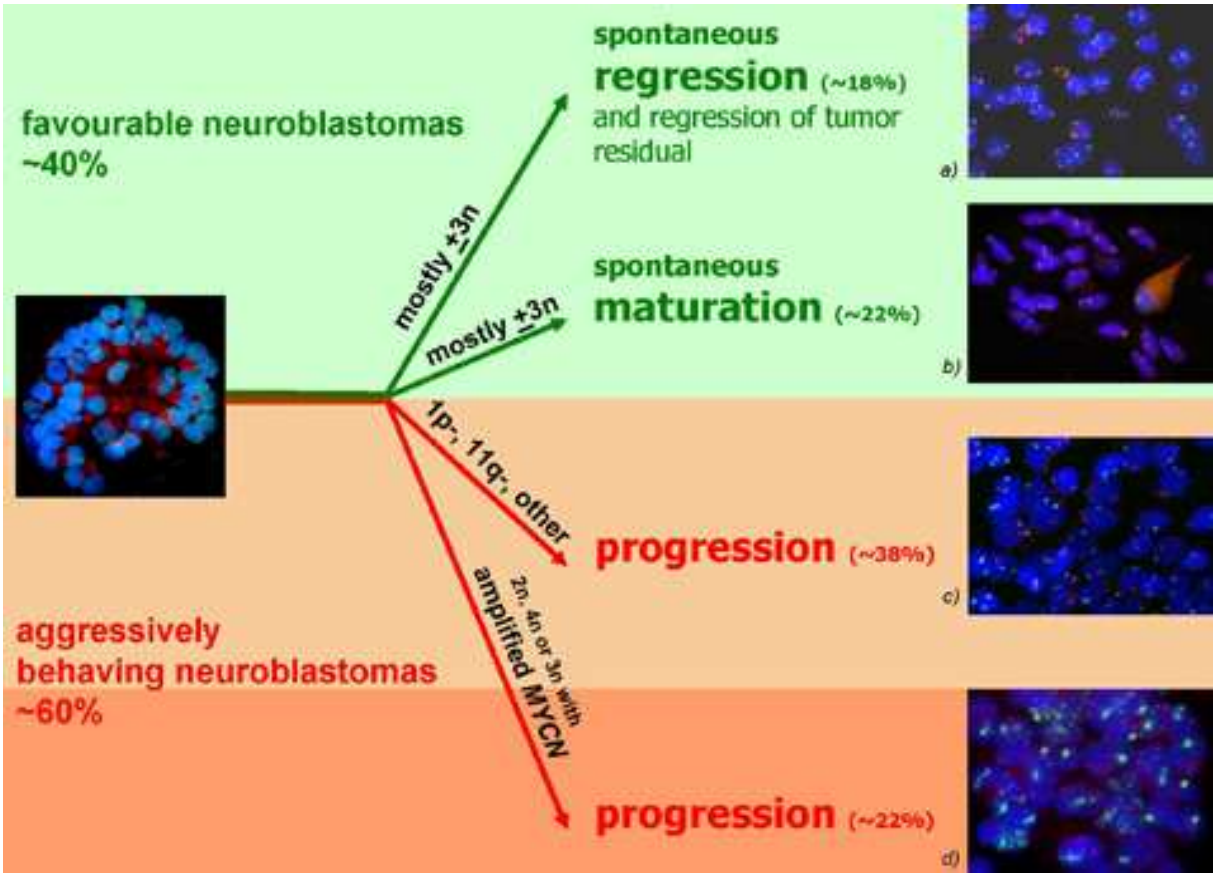

Figure 1 Biologic pathways and genetic features in neuroblastic tumors.

Neuroblastoma tumors can be subdivided into two biological/clinical groups: ³benignly² behaving neuroblastomas are indicated by a green background, aggressive neuroblastomas are marked by a dark red or red background.

The 'beningly' behaving neuroblastomas virtually always show a near-triploid, near-pentaploid or near-hexaploid DNA Index, without any structural aberrations: in a) nuclei with a typical I-FISH picture with 3 spots each for D1Z2 at 1p36 and D1Z1 for the paracentromeric region of chromosome 1 shown. Spontaneously maturing tumours show two types of cells, but only a small fraction of the cells are tumour cells. In b) one aneuploid ganglionic (tumor) cell with reddish cytoplasm is shown beside a majority of cells showing 2 signals with all used FISH probes representing non neoplastic Schwann cells.Neuroblastomas with aggressive clinical behavior can further be subdivided in those without MYCN amplification but with segmental aberrations like del1p, del11q, add17q (shown in c): tumor cells with only 1 sub-telomeric I-FISH signal in red and 2 paracentromeric I-FISH spots in green) and those with MYCN amplification (an example is given in d): tumour cells displaying both types of amplification, dmin and hsr in green, while the reference probe is given in red).

under 7 months of age. This led to the worldwide termination of mass screening programs, although screening at a later time point, such as 9 to 12 months of age, as was carried out in e.g. Japan and Austria, were able to detect genetically unfavourable neuroblastomas or genetically hetero-geneous tumours.

Evolution

Special features: Besides the fact that neuroblastomas can be very rapidly growing and aggressively behaving tumours, there are some peculiarities which are unique for these tumours. Spontaneous regression (without cytotoxic treatment) of even 'metastasised' disease (stage 4s disease) is observed in the first year of life. These tumour cells are characterised by a distinct genotype (see below). After the first year of life, spontaneous maturation of neuroblastomas into ganglioneuroblastomas and ganglioneuromas can be observed. These neuroblastic/ganglionic cells share genetic characteristics with spontaneously regressing neuroblastomas. Moreover, such tumour cells are capable of recruiting non-neoplastic Schwann cells from the tumour adjacent tissue. The tumour cell - Schwann cell interactions are supposed to be crucial for neuroblastoma maturation.

Prognosis

The outcome of patients with neuroblastoma depends largely on the age of the patient at diagnosis, the tumour spread and the tumour biology/genetics. Stage 1 and 2 patients usually have a very good prognosis with surgery alone. However, genetic features like MYCN amplification or other aberrations can change the prognosis drastically. While surgery alone is more the exception than the rule in Stage 3 this strategy can be chosen under certain circumstances depending on clinical and genetic parameters. Recently, different articles argue that any genetic aberration found by pan- or multigenomic techniques like cCGH, aCGH or MLPA change the tentatively benign course of the disease into an aggressive one (see Fig. 1). In stage 4 patients genetic markers do not yet play a decisive role. However, even in this disease group certain patients (e.g. under 18 months) may benefit from a biology/genetic based risk assessment.

Genetics

Note

Neuroblastomas have distinct genomic DNA profiles that predict the clinical phenotype. The whole group of neuroblastic tumours can be subdivided into two main groups according to the tumour cell ploidy:

The near-triploid (-penta, hexaploid) (occurring in approximately 55%) and the near-diploid (-tetraploid) (45%) tumour subgroups.

Near-triploid (-penta, hexaploid) neuroblastomas

The majority of near-triploid tumours exhibit only numerical gains and losses (a rather specific pattern including over-representation of 7 and 17 and under-representation of chromosomes 3, 4, 11 and 14, amongst others). Patients showing this genomic pattern in their tumours frequently have an excellent survival expectation (near 100%). In infants spontaneous regression either without surgical intervention (stage MS) or after surgical intervention but even with tumour residuum is frequently observed. In older children with this genomic profile of the tumour cells, spontaneous maturation can be found in a substantial number of patients. However, this group of patients was frequently assigned to the diploid group as the DNA Index (D.I.) displays a diploid peak while less frequently a minor triploid peak was observed. This diploid peak usually represents a population of normal cells, mainly Schwann cells, which 'invade' the tumour from the outside and most likely trigger the maturation process. Only the ganglionic cell population, which can be as low as 1% or even less, displays a near-triploid genotype whereas the majority of cells are diploid.

Interestingly, also structural chromosome aberrations like MYCN amplifications, deletions at the chromosomal regions 1p36.3, or 11q, gains of long arms of chromosome 17, can be found in near-triploid tumours. However, the frequency of these aberrations is much lower than in the di-/tetraploid tumours. Although the majority of near-triploid tumours are clinically favourable, it is important to know that the discussed structural chromosome aberrations can turn the biological behaviour of near-triploid tumours into an unfavourable one. The question which structural aberrations can render the biological behaviour into an aggressive one has not been completely understood so far. Therefore, data on a large cohort of patients generated with pan- or multigenomic techniques like array CGH or MLPA are needed to clarify the biological impact of certain genetic aberrations.

di-/tetraploid tumours

Diploid/tetraploid tumours usually have a dismal prognosis. The majority of these tumours have unbalanced structural chromosome rearrangements.

Of these genomic imbalances, MYCN oncogene amplification has been known for a long time to infer poor prognosis and has been implemented in clinical decision making processes. This ampli-fication is predominantly found in the form of double minute chromosomes (dmin) and rarely appears as homogenously staining regions (hsr). In addition, as already indicated, MYCN amplification can be found independent of the ploidy of the tumour. Other neighbouring genes such as NAG and DDX1 can be co-amplified but their impact on prognosis is controversial. Other amplicons can be implicated in addition to MYCN such as regions including ALK, CCND1 and MDM2. MYCN amplification is often accompanied by 1p deletion and 17q gain.

A second genomic subgroup of 2n/4n NB shows no MYCN amplification but presents with 11q deletion

and 17q gain and often in association with 3p deletion. Thus, MYCN amplification and loss of 11q, define two major different genetic subtypes of the disease with vastly different global gene expression profiles. Therefore, the INRG will recommend, besides MYCN amplification, deletions of 11q and diploidy as decision making features in certain clinical subgroups.

Heredity: Linkage analysis using 10 families with neuroblastoma mapped the hereditary neuro-blastoma locus at 16p12-p13. Furthermore, heterozygote germline alterations in PHOX2B have recently been identified in patients with familiar neuroblastoma. However, these germ line aberra-tions are only rarely associated with the onset of neuroblastomas.

Genes involved and proteins

MYCN

Location

2p24

Protein

Nuclear protein; helix-loop-helix and a leucine zipper domain; transcription factor. Amplification of the MYCN oncogene is found in 20-25% of neuroblastomas. The term amplification was defined by the ENQUA (European Neuroblastoma Quality Assessment) Group i.e. Greater than four-fold increase of the signal number as compared with the reference probe located on the same chromosome. The oncogene is either amplified in form of acentric double minute chromosomes (dmin) or chromosomally integrated as homo-geneously staining regions (hsr).

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