WHAT IS NEUROBLASTOMA?

Part 2: Tumor Pathology and Genetics

NB is sometimes referred to as a "heterogeneous" disease because of the wide range in its behavior in different children—some NB tumors with favorable characteristics go away on their own (regress), some mature into a benign growth (ganglioneuroma), and some with unfavorable characteristics grow and spread rapidly. The pathologist's job is to try to identify which type of NB tumor your child has. This information, together with the child's age and the stage of his or her disease, is used to determine the degree of risk for the child's specific situation. The resulting risk assignment enables the oncologist to prescribe the right treatment for your child's disease—not too much, but not too little.

The scientific information used to determine risk assignment for NB is very technical in nature; understandably, some parents are content just knowing their child's risk assignment and the resulting treatment required. The various categories of "risk assignment" are described in Section 3 following. For those who wish to know more, this section summarizes the various types of pathology and genetic information used to determine the risk category of specific disease profiles. Each term used in the criteria for risk assignment is explained in more detail as well.

NB risk assignment is dependent on four distinct factors:

1. **age of the child;**
2. **stage of the disease;**
3. **pathology of the tumor; and**
4. **genetic make-up of the tumor.**

Each factor has significance (favorable or unfavorable) but no factor alone can determine prognosis. The *combination* of this information dictates the risk group assigned and the treatment your child will receive.

Since it takes some time to get the pathology and genetic analysis from the biopsy of the primary tumor, oncologists will often begin treating (surgery and/or chemo) very sick children before all of this information is obtained, rather than waiting for a final risk assignment, which can take a week or more.

1. Age of child.

Generally, the younger the patient is, the lower the risk assignment. For example, infants under 18 months with a certain pattern of metastatic disease are classified as low risk. Similarly, children aged 12-18 months with metastatic disease and other certain favorable tumor characteristics are classified as intermediate risk. In contrast, children over the age of 18 months with the same factors would be classified as high risk.

2. Stage.

The stage of the disease is one of the most important determinants of the child's risk group. Generally, localized disease is better (also called stage L1 or L2) than metastatic disease (called stage M), since getting rid of systemic disease can be more difficult.

3. Pathology of the tumor.

Another type of information used to determine risk classification is the pathology of the tumor after a sample (biopsy) is obtained. The pathologist determines whether the tumor has favorable or unfavorable "histology"--an analysis based on what the primary tumor cell structure looks like to the pathologist's eye and under a microscope. (Note that the "pathology," "histology" and "biology" of the tumor are often used as interchangeable terms.) Determination of histology as favorable or unfavorable is based on two factors: tumor grade and MKI.

Tumor Grade. NB is classified as one of the "peripheral neuroblastic tumors" or pNTs. Although they arise from the same tissue type, these tumors can behave very differently depending on the structure and genetics, and are graded accordingly. They range in character from highly malignant neuroblastoma to benign ganglioneuroma. Tumor grade is determined from a biopsy of the tumor obtained before treatment and based on the International Neuroblastoma Pathology Committee (INPC) developed in 1999[1] and revised in 2003.[2] The pathologist looks for the proportion of non-cancerous structural cells called "stroma" (also known as "Schwannian" cells) and the degree of maturity (differentiation) of neuroblastic cells, and assigns one of the following tumor grades:

- NB (Neuroblastoma): stroma-poor, undifferentiated, poorly differentiated, or differentiating;
- GNBi (Ganglioneuroblastoma intermixed): stroma-rich, intermixed with Neuroblasts;
- GNBn (Ganglioneuroblastoma nodular): stroma-rich, nodules of neuroblasts; or
- GN (Ganglioneuroma): stroma-dominant, benign.

Ganglioneuroma (GN) is a benign tumor. Ganglioneuroblastoma (GNB) with less than half cancerous cells mixed in (GNBi) is generally a low-risk tumor. Ganglioneuroblastoma with cancer cells in nodules (GNBn) behaves in a more aggressive manner. NB is similar but has less than half the proportion of benign stroma present in GNB, or none at all, and so is a malignant tumor.

MKI. In addition to tumor grade (NB, GNBi, GNBn, GN), information about cell division and activity is determined, referred to as the mitosis-karyorrhexis index (MKI). Dividing cells (mitosis) and cells with nuclear fragmentation (karyorrhexis) are counted and an MKI category is assigned (low, intermediate, or high MKI).

Histology. The above two factors--tumor grade and MKI--together with the child's age, allow INPC classification into two groups: favorable histology (FH) and unfavorable histology (UH):[3]

Favorable Histology

- all ganglioneuroma (GN) and ganglioneuroblastoma intermixed (GNBi);
- ganglioneuroblastoma nodular (GNBn) with 50% or more Schwannian cells;
- neuroblastoma (NB), poorly differentiated or differentiating, intermediate MKI, under 18 months old; or
- neuroblastoma (NB), under 5 years old, differentiating, low MKI.

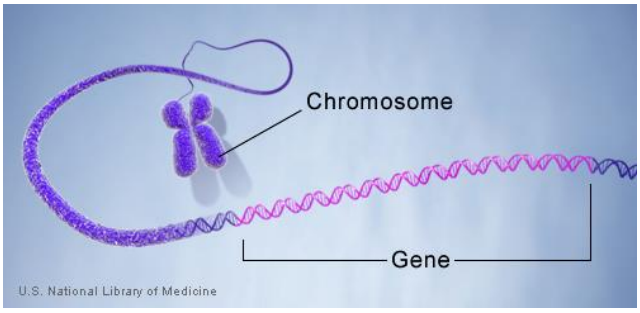
Unfavorable Histology

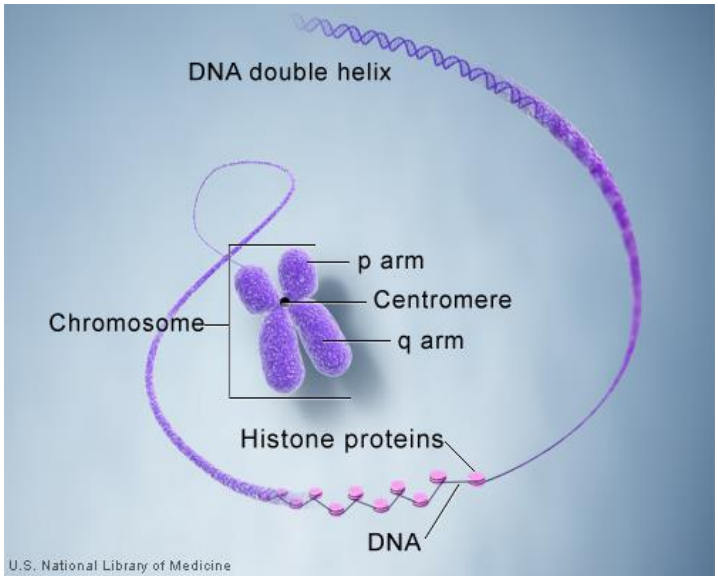
- ganglioneuroblastoma nodular (GNBn) with less than 50% Schwannian cells;
- neuroblastoma (NB), undifferentiated;
- neuroblastoma (NB), high MKI;
- neuroblastoma (NB), poorly differentiated or differentiating, intermediate MKI, over 18 months; or
- neuroblastoma (NB), differentiating, low MKI, over 5 years old.

This complex scheme enables pathologists to decide if the tumor has favorable or unfavorable characteristics, but this information *alone* does not determine prognosis or treatment intensity. It is used along with age, stage, and genetics to assign risk for treatment purposes. The next section, **"Risk Assignment,"** shows that favorable or unfavorable histology makes a difference in risk assignment in some situations, but not in others.

4. Genetic Make-up of the Tumor.

NB tumors act differently depending on genetic information coded inside the nucleus of the tumor cell. A cell has very long chains (about 5 feet) of compacted DNA within its nucleus. The DNA is wound up into strands like coiled rope and packaged in the chromosomes. Each chromosome has two short "p arms" and two longer "q arms," and hence is shaped like an X. Each place on a chromosome holds genetic information that pertains to the expression of a trait, and each piece of information on a chromosome is a gene. *See* illustrations below.





The presence or absence of certain genetic information in an NB tumor cell is another factor used to determine risk category. Two types of genetic information currently considered relevant are "ploidy" and "MYCN."

Ploidy. As noted, all dividing cells share genetic information through chromosomes, the "package" for DNA. Two copies of the DNA are normal in healthy cells and is called "diploidy" or a DNA index of 1.0. Diploidy is a poor prognostic factor for neuroblastoma and indicates higher risk disease. Three copies of DNA (DNA index 1.5 or DNA index > 1) in an NB cell is favorable and is called triploidy (or hyperdiploidy).

MYCN. Another genetic factor considered in risk assignment is MYCN (also written N-myc). MYCN is a type of oncogene--a gene with a DNA sequence that contributes to the growth of cancer. MYCN is an unfavorable factor—when there are more than 10 copies present, the NB tumor is referred to as MYCN amplified. MYCN is commonly multiplied, by 100 times, and has been found as high as 700 times in an NB cell. About 20% of all NB cases have MYCN amplification.[4] (Note: MYCN amplification is often found in other cancers such as retinoblastoma, medulloblastoma, rhabdomyosarcoma and small-cell lung cancer.[5])

MYCN is an important prognostic factor. Younger children and children with lower stage disease will be treated as high-risk (*see* the following section on risk assignment) if their tumor is MYCN amplified, but MYCN does not necessarily contribute to a poorer prognosis in high-risk cases because one or more unfavorable characteristics are present in all high-risk cases.[6]

Other genetic and molecular factors. Other genetic variables believed to have prognostic value for NB have been identified, but not all are currently used in risk assignment. For example, tumor suppressor genes are believed to be associated with 1p and 3p chromosomes, and deletion of either in the NB is considered an unfavorable prognostic factor, as well as loss of 11q or gain of 17q.[7] Currently 1p and 11q are used to further define treatment for intermediate risk.[8] The INRG (International Neuroblastoma Risk Group) will include 11q status in the new risk assignment schema.[9,10]

A host of potential prognostic factors have been studied over the past 25 years, and current consensus is that none add anything significant to current use of age, stage, pathology, ploidy, and

MYCN amplification. For example, lack of "trkA" and "CD44" expression on the NB cell surface are also considered unfavorable, but not independently prognostic.[11] TrkA is a high-affinity nerve growth factor receptor, and CD44 is a cell surface glycoprotein (antigen) involved in cellular interactions and homing to bone marrow. Overexpression of CD44 has been noted in the growth and spread in different types of malignancies, such as lymphomas. In neuroblastoma, however, unfavorable tumors often have low CD44 expression.[12]

Summary

The information involved in the diagnosis, staging, and prognosis of a rare disease like NB can be overwhelming This section identifies and introduces important factors used to determine the most critical treatment issue: risk assignment, which dictates treatment intensity. The next section, **"Risk Assignment,"** explains how these pieces fit together to determine whether a child receives treatment for low, intermediate, or high-risk NB. However, your child's oncologist is the definitive source for learning how all of this information relates to his or her particular case.

Please contact info@cncfhope.org with any comments

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