

## How can NBS diagnosis be confirmed?

When NBS is suspected on the basis of the clinical phenotype, a prompt confirmation of the diagnosis, through laboratory investigations, must follow.

**Cytogenetic analysis** and **cellular radiosensitivity assay** are performed in order to evaluate the presence of spontaneous and induced chromosome instability.

All disease-causing mutations of the NBS1 gene identified to date are located within exons 6-10 and result in premature truncation of the nibrin protein. In such circumstances, **immunoblotting assay**, with antibodies directed against nibrin, fails to detect the protein in cell lines from NBS patients, and can be used for a first confirmation of the diagnosis.

**Molecular testing** enables definitive confirmation of the diagnosis, with the demonstration of disease-causing mutations in both alleles of the NBS1 gene.

When NBS diagnosis is confirmed a clinical follow-up of the patient must be established and genetic counselling can be offered to the family.



**Refer to the NBS website for more information about the disease:**

<http://www.nijmegenbreakagesyndrome.net>

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## Nijmegen Breakage Syndrome

Nijmegen Breakage Syndrome (NBS) is a genetic autosomal recessive disease. Its full clinical phenotype is characterized by growth deficiency, microcephaly, distinct facial appearance, developmental delay, immunodeficiency, recurrent infections, high incidence of malignancies, particularly lymphoproliferative disorders, and ovarian dysgenesis in females. NBS patients' cells show a high number of chromosome breaks and rearrangements, increased sensitivity to ionising radiation and aberrant cell cycle checkpoint control. The disease is caused by mutations in the NBS1 gene (located on chromosome 8q21) which encodes nibrin (or p95), a component of a protein complex (hMre11/hRad50/p95) involved in cellular response to DNA damage.

Due to the increased radiosensitivity of NBS patients, **ionising radiation must be avoided for therapeutic uses and, if not strictly necessary, also for diagnostic uses.** The use of conventional radio- and chemotherapy protocols, in these patients who are at high risk of developing malignancies, can lead to severe toxic complications (even death) and/or second tumour. This implies that:

**EARLY RECOGNITION AND CERTAIN DIAGNOSIS ARE ESSENTIAL FOR NBS PATIENTS.**

# Nijmegen Breakage Syndrome

## When does the diagnosis of NBS have to be considered?

The diagnosis of NBS must be taken into account in all patients with severe **microcephaly** (OFC below the 3<sup>rd</sup> percentile) of unknown origin.

[Notes: OFC is the head circumference as measured around the glabella and occipital protuberance. When proportions among head dimensions (length and breadth) are not retained, the OFC does not correlate with microcephaly.]



Microcephaly is congenital in about 75% of NBS patients and the remainder develop it during the first months of life. Microcephaly can be the only apparent symptom of the disease in very young children.

Despite its severity, in NBS patients microcephaly is usually associated with normal neuromotor development during the first year of life. This is in sharp contrast to the profound mental impairment commonly

seen in autosomal recessive non-syndromal microcephaly. Moreover in NBS patients MRI of the brain can often reveal the presence of frontal lobe hypoplasia and corpus callosum posterior part agenesis.

[Please note that even if severe psychomotor delay, major structural malformations of the brain and severe epilepsy with onset in early infancy seem not to be associated with NBS, their presence is not a sufficient criterion to exclude NBS diagnosis.]

In NBS patients microcephaly, being associated with normal or mildly retarded psychomotor development, can be overlooked and **recurrent respiratory infections/ immunodeficiency** may be the most striking symptoms.

In NBS disturbances of the immune system are very common and may be profound. However, they tend to worsen over time and very young patients can have completely normal immunological parameters. The most characteristic defects are: combined IgG and IgA deficiency with normal levels of IgM; low levels of IgG2 and IgG4 (that, in some cases, can be masked by normal concentrations of total serum IgG); reduced number of CD3<sup>+</sup> T lymphocytes with low CD4<sup>+</sup> cells and decreased CD4<sup>+</sup>/CD8<sup>+</sup> ratio;

increased number of NK cells; reduced proliferative response of T-lymphocytes to mitogens.

A **lymphoproliferative disorder**, mainly a B-cell non-Hodgkin lymphoma (B-NHL) or acute lymphoblastic leukaemia (ALL), may be the presenting finding of NBS, that leads to medical attention.

Therefore, the diagnosis of NBS should be carefully considered before radio-chemotherapy is initiated in patients with lymphoproliferative disorders, especially of very young age. Moreover, the presence of a chromosome instability disorder, including NBS, must be suspected in any patient who develops severe adverse reactions to radio-chemotherapy.

**Impaired sexual maturation** (primary amenorrhoea, poor development of secondary sex characteristics) and short stature may lead to clinical evaluation and chromosome analysis if Turner syndrome is suspected. However, they can also be prominent symptoms of female NBS patients who reach pubertal age.

Please remember that **with NBS patients, ionising radiation must be avoided for therapeutic uses and, if not strictly necessary, also for diagnostic uses**