Nijmegen breakage syndrome in a Dutch patient not resulting from a defect in NBS1

J A P Hiel, C M R Weemaes, B G M van Engelen, D Smeets, M Ligtenberg, I van der Burgt, L P W J van den Heuvel, K M Cerosaletti, F J M Gabreëls, P Concannon

EDITOR—Nijmegen breakage syndrome (NBS) is a rare autosomal recessive chromosomal instability disorder characterised by microcephaly, immunodeficiency, x-ray hypersensitivity, and predisposition to malignancy. The gene responsible for NBS, NBS1, is located on chromosome 8q21 and encodes a protein called nibrin. This protein is a component of the hMre11/hRad50 protein complex, suggesting defective DNA double strand break (DSB) repair or cell cycle checkpoint function in NBS.1–7 In this report we describe a patient with the NBS phenotype, typical cytogenetic presentation with aberrations in chromosomes 7 and 14, and increased x-ray sensitivity. Our index patient had deafness unlike all the other NBS patients reported so far. Mutation detection did not show a mutation in NBS1 and the protein nibrin was normally expressed.

Case report
The boy is the second child of non-consanguineous parents. His older sister is healthy. From the sixth month of pregnancy microcephaly and growth retardation were noted. Amniocentesis was performed followed by a cytogenetic study which showed a normal male karyotype. He was born in 1997 at 39 weeks of gestation. Birth weight was 1915 g, length 42 cm, and head circumference 28.5 cm (all below the 3rd centile). The neonatal period was complicated by mild hypoglycaemia. During the first year of life he suffered from feeding difficulties and vomiting for which no specific cause was found. Developmental milestones were markedly delayed in language skills because of a severe hearing deficit. Motor skills were reached within the normal range. Head circumference remained below the 3rd centile.

At 20 months of age he was examined in our hospital. On examination, he was a small, microcephalic boy with hearing aids on both sides. Head circumference was 40.2 cm, weight 8.2 kg, and height 77 cm. He had large ears, epicanthic folds, and a receding mandible (fig 1). On his back two hyperpigmented spots were noted. Apart from speech delay, neurological examination was normal. EEG showed no abnormalities. A CT scan of the os petrosum showed severe dysplasia of the cochlea. Cerebral MRI showed no structural lesions. The extent of myelinisation was considered normal for age. Routine blood tests were normal, as were endocrinological studies and amino acid levels.

Immunological studies showed IgG4 deficiency, but the immunoglobulins were otherwise normal: IgG 7.41 g/l, IgG1 6.38 g/l, IgG2...
Table 1 Clinical and laboratory data

<table>
<thead>
<tr>
<th></th>
<th>Our patient</th>
<th>Cerosaletti et al</th>
<th>NBS reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcephaly</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Typical facial appearance</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Skin abnormalities</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Deafness</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>Cataract</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>IgG (g/l)</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased</td>
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<tr>
<td>IgA (g/l)</td>
<td>Normal</td>
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<tr>
<td>IgM (g/l)</td>
<td>Normal</td>
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<tr>
<td>CD3 cells</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>CD4 cells</td>
<td>Normal</td>
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</tr>
<tr>
<td>CD8 cells</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>NK cells</td>
<td>Normal</td>
<td>Not determined</td>
<td>Increased</td>
</tr>
<tr>
<td>Chromosomal instability</td>
<td>7/14</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>7/14 rearrangements</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Radiation hypersensitivity</td>
<td>+</td>
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Discussion

NBS belongs to the family of DNA repair disorders. Other members are Bloom syndrome (BS) and ataxia telangiectasia (AT). All of these disorders show chromosomal instability, immunodeficiency, and predisposition to cancer, but are genetically heterogeneous, involved in different pathways of DNA repair. The gene for NBS1 has been identified on chromosome 8q21, the gene for BS (BLM) on chromosome 15, and the gene for AT (ATM) on chromosome 11.\(^2\)\(^*\) Apparently, different proteins encoded by different genes play a role in cell cycle control. Although identification of the genes has been very helpful, the specific pathophysiological mechanisms have still to be elucidated.

The patient described here fulfills the criteria for NBS, namely microcephaly, growth retardation, immunodeficiency (although very mild), typical chromosome 7 and 14 aberrations, and x-ray hypersensitivity (table 1). His face with receding mandible and epicantlic folds is in keeping with the typical appearance, which usually becomes more obvious with age. At the molecular and protein level, however, the patient shows completely normal results and thus does not fit into the NBS spectrum as described previously. This strongly suggests the presence of another gene, a NBS-like gene. Another family with the NBS phenotype, but without linkage to chromosome 8 has been described by Cerosaletti et al.\(^2\) (table 1). The proband had microcephaly, growth retardation, unusual facial features, mild radial cataracts, and diffuse, abnormal skin pigmentation. Deafness was not mentioned. Immunoglobulin levels and B and T cells were normal as in our patient. In NBS nearly all patients have disturbances of serum immunoglobulins and T cell subpopulations.

Hearing loss is seen in many syndromes with microcephaly, but until now it has not been reported in NBS.\(^3\) Many congenital disorders have been found in some, but not all patients of the group with the Slavic mutation.\(^3\) The absence of hearing loss may be coincidental. However, specific congenital anomalies such as hearing loss in our patient and cataract in the patient of Cerosaletti et al.\(^2\) may be symptoms of other NBS disorders. Identification of the gene involved (NBS2) will be an important step forward in unravelling these questions.


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