

Severe microcephaly with normal intellectual development: the Nijmegen breakage syndrome

A J Green, J R W Yates, A M R Taylor, P Biggs, G M McGuire, C M McConville, C J Billing, N D Barnes

Abstract

A brother and sister are described with severe microcephaly of prenatal onset, normal intellectual and motor development, chromosomal breakage and cellular immunodeficiency, which is characteristic of the autosomal recessive condition, Nijmegen breakage syndrome.

The proband was a girl who presented at 15 months, with normal developmental milestones and an extremely small head circumference of 36 cm. Twenty per cent of her lymphocytes showed spontaneous translocations involving chromosome 7p13, 7q35, 14q11, and 14q32. The lymphocytes also showed excessive x ray induced chromosome damage. She had T cell lymphopenia, but normal immunoglobulins, and a normal α fetoprotein. A brother was born shortly after her diagnosis was made. He also had extreme microcephaly of 28 cm, with similar spontaneous and x ray induced chromosomal breakage, and T cell lymphopenia. Neither child has clinical evidence of immunodeficiency.

To test the hypothesis that Nijmegen breakage syndrome and ataxia telangiectasia are allelic disorders, haplotype analysis was carried out in the family using DNA markers spanning the AT locus on chromosome 11q22. The affected boy had a different haplotype from his affected sister. Thus in this family, the Nijmegen breakage syndrome is not allelic to the ataxia telangiectasia locus on chromosome 11q, and the two conditions are genetically distinct. The normal intellect in these children raises questions about normal brain development in the presence of severe microcephaly.

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Microcephaly associated with developmental delay is a common presentation in paediatric practice. There are many causes, including perinatal and obstetric insults, chromosomal aneuploidy, and several genetic syndromes. About 50% of children with unexplained non-syndromal microcephaly have an autosomal recessive pattern of inheritance for the condition. Most children with microcephaly have serious intellectual impairment, and normal mental development is rare.

Nijmegen breakage syndrome is a recently described condition characterised by microcephaly, immunodeficiency, and typical chromosome breakage involving chromosomes 7 and 14.¹ It has been suggested that it may be an allelic variant of ataxia telangiectasia, in which there is identical chromosome breakage and immunodeficiency but a distinct clinical presentation.^{2,3} Paradoxically in most cases there has been severe microcephaly but normal intellectual development. We describe a sister and brother with these findings. They had chromosomal breakage characteristic of Nijmegen breakage syndrome and significant T cell lymphopenia but no clinical evidence of immunodeficiency. Haplotype analysis in this family, using DNA markers flanking the ataxia telangiectasia locus on chromosome 11q22, showed that in this family the condition is not an allelic form of ataxia telangiectasia.

Case description and investigations

A 15 month old girl was referred for assessment because of microcephaly of prenatal onset. She was the second child of healthy unrelated white English parents, the first child being a normal girl of 6 years. The pregnancy was complicated by hypertension and premature labour, and she was born by caesarean section at 36 weeks' gestation, with a weight of 1890 g, and a head circumference well below the third centile at 29 cm. After initial nasogastric feeding she fed well and gained weight.

At presentation, her motor and social development was normal for her age. She had not had any excess of infections, and had received diphtheria, pertussis, tetanus, and live polio vaccines without incident. Her length had followed the 3rd centile, with her weight slightly below the 3rd centile. Her head circumference was only 36 cm, being on the 50th centile for a term newborn (see fig 1). She was not dysmorphic. Her parents' and sister's head circumferences were normal. Investigations including skull radiography, computed tomography of the brain, blood count, electrolytes, liver enzymes, calcium, phosphate, thyroid function, and TORCH screen were all normal.

Her karyotype was 46,XX in the majority of lymphocytes. Structural rearrangements involving chromosomes 7 and 14 were present in 20% of cells. The karyotypes in these cells were 46,XX,inv(7)(p13;q35), 46,XX,t(7;14)(q35;q32), and 46,XX,t(14;14)(q11;q32). Studies of her lymphocyte chromosomes by x ray were performed as described.⁴ Compared with normal lymphocytes, there was a marked increase in x ray induced chromosome damage

Department of Clinical Genetics, Addenbrooke's NHS Trust, Cambridge and Department of Pathology, University of Cambridge
A J Green
J R W Yates

Department of Cancer Studies, University of Birmingham Medical School
A M R Taylor
P Biggs
G M McGuire
C M McConville

Department of Cytogenetics, Addenbrooke's NHS Trust, Cambridge
C J Billing

Department of Paediatrics, Addenbrooke's NHS Trust, Cambridge
N D Barnes

Correspondence to: Dr Andrew Green, Department of Clinical Genetics, Box 134, Addenbrooke's NHS Trust, Cambridge CB2 2QQ.

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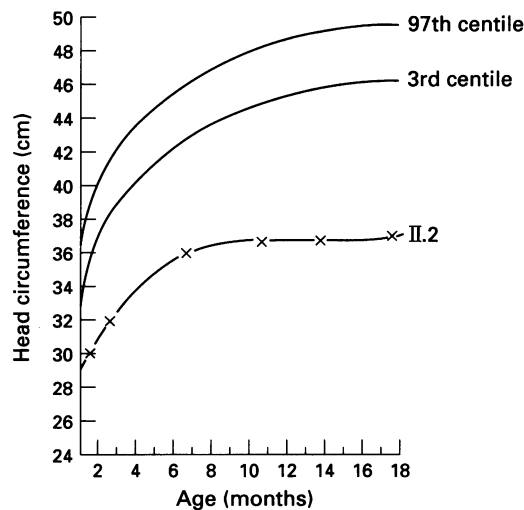


Figure 1 Graph of head circumference (cm) versus age in the proband (II.2), compared with 3rd and 97th centiles.

after exposure to 1 Gray at the G2 stage of the cell cycle (see fig 2). The specific spontaneous chromosome rearrangements and irradiation induced chromosome damage were typical of ataxia telangiectasia.

However, microcephaly is not a feature of ataxia telangiectasia, and her concentrations of α fetoprotein were normal. She had no signs of ataxia and no telangiectasia, although this would not be expected at 15 months of age in a child with ataxia telangiectasia. In view of the chromosome breakage, her immune system was assessed. She had low values of T lymphocytes, with a total lymphocyte count of $2.39 \times 10^9/l$, a T cell count of 0.96 (40%), a B cell count of 0.79 (33%), and relatively high natural killer cells of 0.48 (20%). The CD4/CD8 ratio was normal. There were no clonal rearrangements of her T cell receptor α or β genes on Southern blot analysis. She had normal immunoglobulin concentrations, including IgG subsets and IgE, and a normal antibody response to tetanus immunisation. In the light of the severe microcephaly, normal intelligence, T lymphopenia and chromosome breakage, a diagnosis of Nijmegen breakage syndrome was made.

Her parents' lymphocyte karyotypes, and that of her healthy sister showed neither chromosome 7:14 rearrangements, nor excess

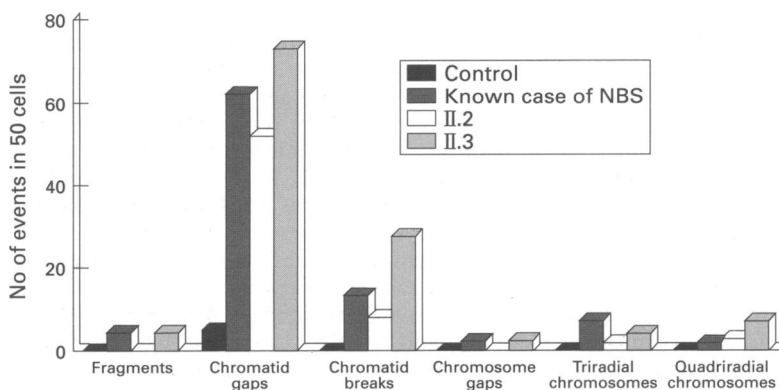


Figure 2 Excess chromosomal breakage in response to 1 Gray x irradiation at G2 in lymphocytes from both affected children (II.2 and II.3) and a known case of Nijmegen breakage syndrome (NBS; not UK).

x ray induced chromosome breakage. A brother was born shortly after the diagnosis was made. He was born at 38 weeks' gestation, with a birth weight of 2560 g. He had severe microcephaly of 28 cm at birth, T cell lymphopenia, and his lymphocytes showed similar rearrangements of chromosomes 7 and 14 in 20% of cells. The karyotypes in these cells were 46,XY,inv(7)(p13;q35), 46,XY,t(7;14)(p13;q11), 46,XY,t(7;14)(q35;q11), and 46,XY,t(7;7)(p13;q35). His lymphocytes showed excess chromosome breakage in response to x irradiation similar to his sister (see fig 2). A diagnosis of Nijmegen breakage syndrome was also made, consistent with the predicted autosomal recessive inheritance.

On review at age 3, the proband was developmentally normal, with a head circumference of 39.5 cm, with her height on the 3rd centile, and her weight just below the 3rd centile. She had not had any major infections. Her 14 month old affected brother was bottom shuffling, had a few words, and had not had any major infections. His head circumference was small at 40 cm, with his length and weight on the 10th centile.

Haplotype analysis was performed in the family, using previously described polymorphic DNA markers flanking the ataxia telangiectasia locus on chromosome 11q22-23 (see fig 3).⁵ If the Nijmegen breakage syndrome were allelic with ataxia telangiectasia, then both affected children should have had identical parental haplotypes in the region of the ataxia telangiectasia locus. However, each affected child had inherited a different paternal haplotype in the region of chromosome 11q22 to which ataxia telangiectasia maps, between the markers D11S1343 and D11S1897. Thus there was no common combined haplotype between the affected siblings, as they had different copies of their father's ataxia telangiectasia genes on chromosome 11q22. It follows that in this family the Nijmegen breakage syndrome is not allelic to ataxia telangiectasia on chromosome 11q22, contrary to previous suggestions.^{2,3}

Discussion

Nijmegen breakage syndrome, which has also been called Seemanova's syndrome, is a rare autosomal recessive condition characterised by microcephaly, severe immunodeficiency, and excess chromosome breakage involving chromosomes 7 and 14. Weemaes *et al* first described the disorder in two affected siblings, the children of consanguineous parents, and named it the Nijmegen breakage syndrome.¹ Seemanova *et al* described eight children of Czech origin, all with microcephaly and severe humoral and cellular immunodeficiency.⁶ Three of the Czech children have been shown subsequently to have excess chromosome breakage, and the two conditions appear to be the same entity.² To date, a total of 30 patients with probable Nijmegen breakage syndrome have been described in 21 families, almost all of eastern European origin.⁷

Seventeen confirmed cases, all with 7:14

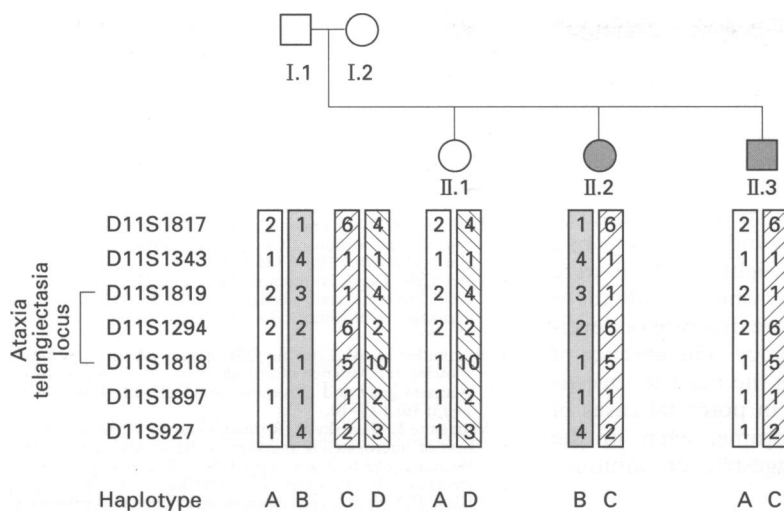


Figure 3 Haplotype analysis in the region of ataxia telangiectasia locus on chromosome 11q22. Between the DNA markers D11S1343 and D11S1897, the affected daughter (II.2) has inherited haplotype B from her father, and haplotype C from her mother. In the same region her affected brother (II.3) has inherited haplotype A from his father, and haplotype C from his mother. These data exclude a gene in this region as a cause of Nijmegen breakage syndrome in this family.

chromosome breakage, microcephaly and immunodeficiency, have been described.^{1,2,6-12} Twelve of the cases were described as having a bird-like facies, and five had unusual skin pigmentation. Two sisters also had anal atresia or stenosis, and mild finger syndactyly.¹¹ Another child had congenital dysplasia of the hips, hydronephrosis and hydrocephalus, in addition to features of the Nijmegen breakage syndrome.² Four children died, three from pneumonia, and one from a lymphosarcoma. Thirteen of the 14 cases had significant recurrent infections. The immunodeficiency ranged from selective immunoglobulin deficiency to severe combined immunodeficiency. T cell lymphopenia was also common and lymphocytes were often slow to grow and failed to proliferate in response to mitogens. Four children were reported to have mental retardation, but the parents of two of these children were also said to have mild mental retardation. It is remarkable that the other 13 children were reported to have normal intelligence, despite often severe microcephaly. This was also a striking feature of the siblings described here.

There are also 13 cases described, which strongly resemble Nijmegen breakage syndrome, but have not had the characteristic chromosome breakage demonstrated. Three of those described by Seemanova *et al* had unsuccessful chromosome analysis, but had microcephaly and recurrent infections.⁶ Two of these died of lymphoreticular malignancy. An Italian woman of 31 was reported with primary amenorrhoea, microcephaly, normal intelligence, a bird-like facies, and mild immunodeficiency.¹³ She had the karyotype 46,XX,t(8q;21q) in 59% of her lymphocytes and a small number of cells had 7:14 translocations. Her sister, who had a similar facies, had died of lymphoma at the age of 20, but no karyotype was performed. A large consanguineous Kuwaiti family with eight affected members, all of whom had microcephaly, normal intelligence and immunodeficiency, was described.¹⁴ Chromosomal analysis in this

family was reported as normal. Two Pakistani girls, the offspring of a first cousin marriage, were described with microcephaly, areas of skin depigmentation, 'bird-like' facies, and normal intelligence. One sister had acute lymphoblastic leukaemia, but showed no spontaneous or induced chromosomal breakage.¹⁵ These cases may reflect genotypic or phenotypic heterogeneity within a broad clinical classification of Nijmegen breakage syndrome.

It has been suggested that the condition may be allelic with ataxia telangiectasia, a DNA repair disorder which has identical cytogenetic findings and similar immunodeficiency but distinct clinical findings.² Jaspers *et al* described two complementation groups of Nijmegen breakage syndrome, V₁ and V₂, which did not complement any of the known ataxia telangiectasia groups.¹⁶ Those families in the V₂ group appeared to have congenital abnormalities not seen in the V₁ group. Curry *et al* described Mexican twin sisters with microcephaly, mental retardation, immunodeficiency, ataxia, scleral telangiectasia, a raised α fetoprotein, and chromosomal breakage involving chromosomes 7 and 14.³ These are features of ataxia telangiectasia and Nijmegen breakage syndrome, and the findings suggest that there is clinical overlap between the two conditions. This overlap condition was named AT_{Fresno}. Complementation analysis showed these sisters to fall into the V₁ complementation group.¹⁶ Haplotype analysis in this family supported linkage at AT_{Fresno} to DNA markers in the region of the AT locus on chromosome 11q22.¹⁷

In almost all families with ataxia telangiectasia, the condition is linked to markers on chromosome 11q22.¹⁸ Occasional families may not show linkage to chromosome 11q22.¹⁷ We therefore analysed the family we describe for linkage to DNA markers on chromosome 11q22 and were able to exclude this locus as a cause of the condition. The Nijmegen breakage syndrome is thus not allelic with ataxia telangiectasia, at least in this family. These data do not exclude the possibility of genetic heterogeneity in Nijmegen breakage syndrome, with some other cases linked to chromosome 11q22.

Haplotype studies and complementation studies have been performed in Nijmegen breakage syndrome families with the V₂ complementation group. These have shown that the condition is not linked to the ataxia telangiectasia gene region on chromosome 11q22.¹⁷ Children in the V₂ group show various congenital anomalies not seen in the V₁ group. It is not clear at present whether there is a consistent relationship between complementation group and the level of congenital anomalies in Nijmegen breakage syndrome (C M R Weemaes, personal communication). If this family is more likely to be in the V₁ complementation group on the basis of the absence of any associated anomalies, then haplotype analysis would indicate that the V₁ complementation group of Nijmegen breakage syndrome is also not linked to the ataxia telangiectasia gene region on chromosome 11q22.

A further concern is the degree of immunodeficiency in the children we describe, neither of whom has had serious infection. Live vaccines have been avoided, however the proband had received live polio vaccine before diagnosis with no sequelae. Death from infection occurred in three of the other confirmed cases. Of 30 definite or probable children with Nijmegen breakage syndrome, nine had developed a malignancy, eight of which were lymphomas.⁷ This is a risk, which is difficult to quantify, for the children we describe of developing a lymphoid malignancy. The absence of serious infection indicates the need to investigate the immune system in potential cases of Nijmegen breakage syndrome, even in the absence of a history suggestive of immunodeficiency.

The striking clinical feature of the condition is the preservation of intellectual development despite severe microcephaly. This is in contrast to the mental impairment commonly seen in isolated or autosomal recessive non-syndromal microcephaly. It is difficult to provide a biological explanation for normal functional brain development without normal brain growth. Discovery of the gene responsible for Nijmegen breakage syndrome may give a clue to such development. The finding of normal intelligence in the presence of profound microcephaly should prompt close analysis of the karyotype and assessment of the immune system.

Nijmegen breakage syndrome is a rare cause of microcephaly, and the diagnosis is important because of the immune deficit, and also for the recurrence risk of an autosomal recessive disorder. The condition does not appear to be allelic with ataxia telangiectasia. The marked discrepancy between profound microcephaly and normal intellectual development is characteristic.

Addendum

The gene for ataxia telangiectasia on chromosome 11q22 has recently been published, and encodes a protein resembling phosphatidylinositol-3' kinases involved in signal transduction,

meiotic recombination, and cell cycle control (Savitsky *et al*, *Science* 1995; 268: 1749-53).

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