CASE REPORT

Unusual T cell clones in a patient with Nijmegen breakage syndrome

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Abstract

The rare autosomal recessive Nijmegen breakage syndrome is characterised by severe immunodeficiency, microcephaly associated with mental retardation, and typical chromosomal rearrangements in peripheral T lymphocytes. This syndrome, though similar to ataxia telangiectasia, does not exhibit the neurological and cutaneous signs of this disorder. We report here the first patient with Nijmegen breakage syndrome ascertained in France. Chromosome analysis detected, in addition to the specific aberrations, two clonal T cell proliferations which do not involve the usual bands 14q11.2 and 14q32.1.

The Nijmegen breakage syndrome (NBS) is an inherited disorder similar to ataxia telangiectasia (AT).[1 2] Common clinical features to NBS and AT are immunodeficiency, chromosomal rearrangements involving chromosomes 7 and 14, increased risk of cancer, and radiation sensitivity. However, patients with NBS exhibit neither the neurocutaneous signs of AT (ataxia, oculocutaneous telangiectasia, progeric skin changes) nor the increased serum α fetoprotein level, but have microcephaly associated with mental retardation. Complementation group analyses have shown that NBS could be related to two different mutations and that this disorder represents an entity genetically distinct from AT.[2-4] We report here on the first NBS patient observed in France.

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Case report

The proband is a male born in 1978 to unrelated parents of east European ancestry. There is no relevant family history. After an uncomplicated pregnancy and delivery, birth weight was 2890 g, length was 54 cm, and head circumference was 34 cm. The patient was referred for repeated respiratory tract infections and mental retardation (IQ 45). At the age of 11 years, the head circumference is 48 cm (−4 SD) and there is moderate growth failure (−1·5 SD). There are no severe dysmorphic features (fig 1), but slight microgenia and brachymesophalangism of the fifth fingers

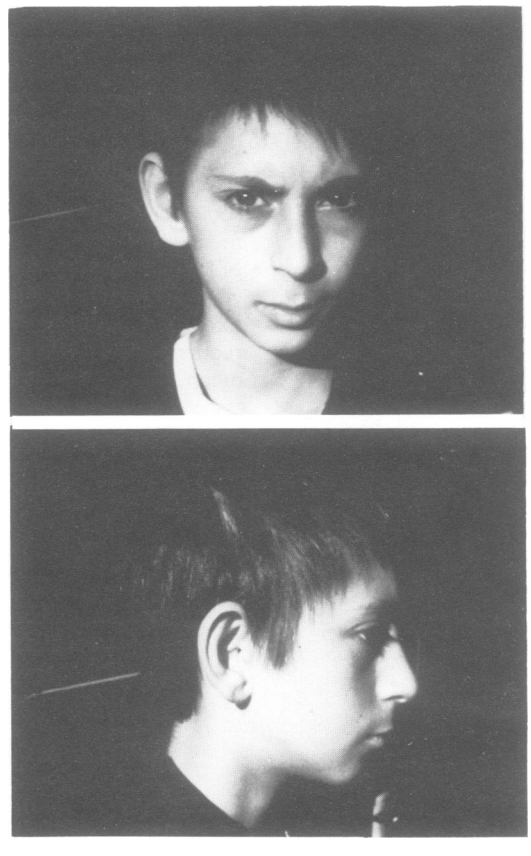

Figure 1 The patient aged 11 years.

are present. Despite normal neurological status, including EEG, cerebral CT scan showed a very large parieto-occipital cystic cavity. There are no cutaneous signs of AT, apart from a few areas with decreased pigmentation.

LABORATORY INVESTIGATIONS

The serum α fetoprotein level and blood lymphocyte count (2300/mm^3) were normal. The lymphocyte subpopulation analysis showed a decrease of T cell populations owing to CD4$^+$ cell deficiency (CD3$^+$ 46%, CD4$^+$ 22%, CD8$^+$ 26%). T lymphocyte response to PHA stimulation was normal but there was no proliferation after antigen stimulation (tetanus, tuberculin, candidin). Very low serum levels of gammaglobulins were observed (IgG 0·83 g/l, IgA 0·14 g/l, normal IgM 1·28 g/l). No antibodies against vaccinal antigens were observed.

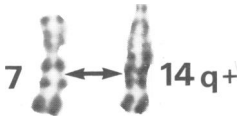

Figure 2 R banded chromosomes. The abnormal chromosome 14 is compared to chromosome 7.

CYTOGENETIC STUDIES

Chromosome preparations were obtained after four days' culture of PHA stimulated lymphocytes. Metaphases were analysed after R banding. In the 75 mitoses studied, 26 rearrangements were scored, 23 of them involving chromosomes 7 and 14 only (table). In 11 metaphases, derivative chromosomes 14 were observed. All these 14q+ appeared identical and probably correspond to a clonal rearrangement. The segment translocated to band 14q32.3 is of unknown origin but could correspond to a part of the long arm of a chromosome 7 (fig 2). Three cells exhibited a translocation t(7;7)(p14;q35) associated with a translocation t(3;14)(p24;q11.2) (fig 3). The independent occurrence of these two rare rearrangements in different cells is very unlikely and we can assume that these cells are also of clonal origin.

The proband's chromosomes were also studied with high resolution banding after synchronisation with thymidine and BrdU incorporation. No microdeletion was observed and, in particular, chromosome 11, where the AT genes are located,[5] was normal at the cytogenetic level.

The 26 rearrangements observed in 75 mitoses.

Rearrangements	No of metaphases
inv(7)(p14q35)	2
t(7;7)(p14;q35)	1
t(7;7)(p14;q35), t(3;14)(p24;q11.2)	3
t(7;14)(p14;q11.2)	6
der(14), t(14;?)(q32.3;?)	11
t(14;16)(q11.2;qter)	1
r(17)	1
i(21)	1

Discussion

The patient in this report clearly represents a variant form of ataxia telangiectasia. The clinical, biological, and cytogenetic findings led us to conclude that the patient's disorder corresponds to the rare Nijmegen breakage syndrome. Up to now, the reported cytogenetic findings in NBS have been similar to those of AT[1 2 6] and, in agreement with these previous reports, some of the aberrations detected in our patient are inv(7), t(7;7), and t(7;14). However, it is striking that two independent and unusual clones were also found. One of these clonal rearrangements was an unbalanced translocation of band 14q32.3; the other was a balanced translocation between bands 3p24 and 14q11.2. In normal AT clones, aberrations always involve bands 14q11.2 and 14q32.1 and correspond to an illegitimate rearrangement between the TCRA gene and the putative TCL1 oncogene.[7] From our preliminary results, we suggest that the selective advantage of the T cell proliferation in NBS can also be obtained through recombinatory events involving other genes.

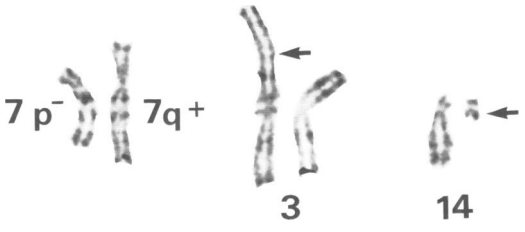

Figure 3 Partial R banded karyotype showing the t(7;7) translocation associated with the t(3;14) translocation. Arrows point to the postulated breakpoints.

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