

Ataxia, ocular telangiectasia, chromosome instability, and Langerhans cell histiocytosis in a patient with an unknown breakage syndrome

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Abstract

An 8 year old boy who had Langerhans cell histiocytosis when he was 15 months old showed psychomotor regression from the age of 2 years. Microcephaly, severe growth deficiency, and ocular telangiectasia were also evident. Magnetic nuclear resonance imaging showed cerebellar atrophy. Alphafetoprotein was increased. Chromosome instability after x irradiation and rearrangements involving chromosome 7 were found. Molecular study failed to show mutations involving the ataxia-telangiectasia gene. This patient has a clinical picture which is difficult to relate to a known breakage syndrome. Also, the relationship between the clinical phenotype and histiocytosis is unclear.

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Ataxia and various neurological disorders associated with chromosomal instability have been described previously. Classical ataxia-telangiectasia (AT) is an autosomal recessive disorder characterised by variable immunodeficiency, oculocutaneous telangiectasia, neurological symptoms, DNA instability, and increased incidence of cancer. The gene for ataxia-telangiectasia (ATM) has recently been identified.^{1,2}

Nijmegen breakage syndrome (NBS) is characterised by microcephaly, inconstant mental retardation, typical facial features, short stature, immunodeficiency, and chromosomal instability.³ Recently, the gene for NBS has been mapped on chromosome 8q21.⁴

Here we describe a child with a clinical picture resembling AT and NBS in whom molecular genetic studies failed to show mutations related to the AT gene.

The proband is an 8 year old boy, the only child of healthy, unrelated parents. For the first year of life psychomotor development was reported to be normal and at the age of 12 months he was able to walk alone.

At the age of 15 months a Langerhans cell histiocytosis was diagnosed. The child received treatment with VP16 for a year with complete remission of the disease.

At the age of 2 years psychomotor regression began; ataxia and dysarthria were the first symptoms. Now at the age of 8 years he has severe muscle atrophy, arthrogyposis, areflexia, dystonic posture, apraxic eye move-

ments, and dysarthria. He is unable to walk, sit, or to grasp objects. Microcephaly (head circumference 47 cm), severe height and weight deficiency, and ocular telangiectasias are also evident (figs 1 and 2). Normal values were found for leucocyte N-acetylglucosaminidase, β galactosidase, β exosaminidase, plasma lactate, pyruvate, amino acids, and caeruloplasmin, urinary organic acids, mucopolysaccharides, and oligosaccharides. Magnetic nuclear resonance imaging showed cerebellar atrophy. The lymphocyte subset was normal; IgA ranged between 776 and 553 mg/dl, IgM was 453 mg/dl, and IgG 1470 mg/dl. Alphafetoprotein was repeatedly abnormal (up to 100 ng/ml).

In order to identify chromosome aberrations such as breaks, deletions, ring formations, and translocations, 87 mitotic cells were examined from peripheral blood slides. The karyotype was 46,XY,inv(9)(p11q13); structural chromosome rearrangements were present in 23.7% of metaphases and occurred preferentially in chromosome 7. After x ray (100 rad in Go phase), rearrangements were present in 55.1% (table 1).

The ATM transcript was scanned for mutations using restriction endonuclease fingerprinting (REF). The open reading frame was



Figure 1 The patient at the age of 7 years; note the severe dystrophy and arthrogyposis.

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Figure 2 Ocular telangiectasias.

Table 1 Chromosome abnormalities in lymphocytes of our patient; 87 metaphases were analysed

	Without Rx	After Rx* (1 Gy/Go)
Normal metaphases	29 (76%)	22 (45%)
Abnormal metaphases	9 (24%)†	27 (55%)†
Rearrangement/cell	0.34	1.51
Rearrangement/abnormal cell	1.44	2.74

*Structural rearrangements (chromosome break, inversion, translocation, dicentric, triradius, unidentified marker, small acentric chromosomal fragment, ring, deletion).

Four clones showed rearrangements involving chromosome 7: t(X;7)(p11.2;q11.2), inv(7)(p22;q11.2), del(7)(p22), t(3;7)(p13;q22).

†For this dose in normal cells abnormal metaphases are less than 5% (only break and gap).

divided into eight partly overlapping fragments, which were amplified using reverse transcription PCR and subjected to REF analysis, as described by Gilad *et al*⁶; no mutation was found.

Our patient has an unusual phenotype, intermediate between AT and NBS, characterised by early onset cerebellar ataxia, unusually rapid psychomotor regression, microcephaly, ocular telangiectasia, normal immunoglobulins and normal lymphocyte subset, increased alpha-fetoprotein, radiosensitivity, rearrangements primarily involving chromosome 7, and no demonstrable mutations in the AT gene.

In 1989, Curry *et al*⁷ reported twin patients with shared features of both classical AT (ataxia, telangiectasia, characteristic chromosomal rearrangements, increased alpha-fetoprotein, and radioresistant DNA synthesis) and NBS (microcephaly, mental retardation) and they called this AT variant AT Fresno. Other clinical variants of AT have also been reported.⁸

Our patient probably has an AT variant, even though it is difficult to compare him to other published cases, except for the patient reported by Curry *et al*⁷ who had an ATM mutation, which was not found in our patient.

Histiocytosis is not a known complication in patients with chromosomal instability, but they are usually prone to lymphoreticular or epithelial malignancies.¹ In some patients with Langerhans cell histiocytosis, progressive ataxia, dysarthria, and cranial nerve disorders may develop years after the original diagnosis of Langerhans cell histiocytosis has been made.⁹ These patients show abnormal white matter areas on magnetic nuclear resonance imaging but not cerebellar atrophy as in our patient. Furthermore, increased alpha-fetoprotein and chromosomal instability have not been reported in patients with central nervous system sequelae of Langerhans cell histiocytosis.

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- Shiloh Y. Ataxia-telangiectasia: closer to unraveling the mystery. *Eur J Hum Genet* 1995;3:116-38.
- Savitsky P, Bar-Shira A, Gilad S, *et al*. A single ataxia-telangiectasia gene with a product similar to PI-3-kinase. *Science* 1995;268:1749-53.
- Van der Burgt I, Chrzanowska KH, Smeets D, Weemaes C. Nijmegen breakage syndrome. *J Med Genet* 1996;33:153-6.
- Saar K, Chrzanowska KH, Stumm M, *et al*. The gene for the ataxia-telangiectasia variant, Nijmegen breakage syndrome, maps to a 1-cM interval on chromosome 8q21. *Am J Hum Genet* 1997;60:605-10.
- Gilad S, Khosravi R, Uziel R, *et al*. Predominance of null mutations in ataxia-telangiectasia. *Hum Mol Genet* 1996;5:433-9.
- Gilad S, Khosravi R, Harnik R, *et al*. Identification of ATM mutations using extended RT-PCR and restriction endonuclease fingerprinting and elucidation of the repertoire of A-T mutations in Israel. *Hum Mutat* (in press).
- Curry CJR, Tsai J, Hutchinson HT, Jaspers NGJ, Wara D, Gatti RA. AT Fresno, a phenotype linking ataxia telangiectasia with the Nijmegen breakage syndrome. *Am J Hum Genet* 1989;45:270-5.
- Willems P, Van Roy BC, Kleijer WJ, Van der Kraan M, Martin JJ. Atypical clinical presentation of ataxia telangiectasia. *Am J Med Genet* 1993;45:777-82.
- Egeler RM, D'Angio GJ. Langerhans cell histiocytosis. *J Pediatr* 1995;127:1-11.