



## Ataxia-Telangiectasia in Twins Presenting as Autosomal Recessive Hyper-Immunoglobulin M Syndrome

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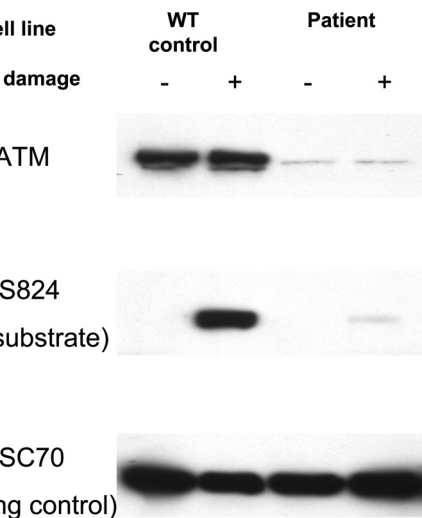
Ataxia-telangiectasia is a rare autosomal recessive multisystem disorder characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia, recurrent sinopulmonary infection – all due to immune defects, and a high incidence of mainly B lymphoid malignancy [1]. Ataxia-telangiectasia results from mutations in a single gene, ataxia telangiectasia mutated (*ATM*). The protein product of the *ATM* gene is a serine-threonine kinase involved in cell cycle control, gene regulation, intracellular signaling and DNA repair. Recently, investigators partly clarified its role in the immune system by showing its importance in class-switch recombination, an essential step in the production of immunoglobulin A, G and E but not M [2]. While this explains the hypogammaglobulinemia observed in A-T, the exact mechanism that leads to the cellular immune defect in this disease is not yet understood.

Progressive cerebellar ataxia is the presenting symptom in most cases, and in 70% telangiectasia appeared before the diagnosis was established. While recurrent bacterial infections due to immunodeficiency are common features, hypogammaglobulinemia as the only symptom of A-T is very rare. In the present study we report twin girls who were diagnosed as suffering from hyper-IgM syndrome without any

neurological problems and were subsequently found to have A-T when one of them developed Hodgkin's lymphoma.

### Patient Description

Twin girls, aged 3, were admitted for evaluation of recurrent pneumonias. They were born to healthy parents who were first cousins. Although there were several consanguinity marriages in the family, no genetic disorder was observed. Both girls were in the 10th percentile for weight and height, and apart from some rales in both lungs the physical examination was completely normal. No telangiectasias were observed. Complete blood count was normal in both girls, but both had low levels of IgG (242 mg/dl and 198 mg/dl respectively) and IgA (below 5 mg/dl in both) and very high IgM levels (467 and 825 mg/dl respectively). While isohemagglutinin levels were normal, no specific antibodies to recall antigens were detected. Aside from a low normal CD4 count (40%), lymphocyte subsets were all within the normal range as was the expression of CD40 on B cells. Since no mutations in AID (activation-induced cytidine deaminase) or UNG (uracil N glycosylase) were found, the twins were diagnosed as suffering from autosomal



Western blotting showing only a trace amount of *ATM* in the patients' fibroblast lysate.

recessive hyper-IgM syndrome, most probably type 4 [3].

Treatment with intravenous gammaglobulin 400 g/kg for 3 weeks was started with good clinical results. Eighteen months later one of the sisters was found to have a thoracic mass which was diagnosed as Hodgkin's lymphoma. Further investigation disclosed high levels of alpha-fetoprotein in both girls and Western blotting showed only a trace amount of *ATM* [Figure]. Six months later the girl with the lymphoma died; her sister continues with the intravenous gammaglobulin therapy. Recently some gait disturbance was noted.

A-T = ataxia-telangiectasia  
 Ig = immunoglobulin

## Further investigations

In order to understand the primary defect in this family we performed several more studies. Class-switch recombination was evaluated by measuring IgE production. Peripheral blood mononuclear cells were incubated with soluble CD40L (500 ng/ml) and recombinant interleukin-4 (100 U/ml) for 12 days. A marked defect in class-switch recombination was observed. While IgE production in the control rose from 70 to 922 pg/ml after 12 days, no increase in the patients' cells was observed – 202 pg/ml versus 147 pg/ml.

Somatic hypermutation in the *VH3-23* gene in CD19+ CD27+ B cells was assessed as described earlier [3]. Normal frequency (2.4%) was observed (age-matched control 2.6%–6.3%).

Ionizing radiation sensitivity was analyzed by clonogenic assays upon exposure of primary fibroblasts to gamma rays. A marked decrease in cell survival was observed after irradiation, similar to the one seen in other patients with A-T.

## Comment

A-T is considered a primary immunodeficiency disease. While several defects in the immune system have been reported, hypogammaglobulinemia is the most frequent and is associated with recurrent sinopulmonary bacterial infection [4]. Low levels of IgG, IgA and IgE are observed in more than 80% of the patients, while very high IgM occurs in approximately 1%. Once IgM + B cells engage antigen, two genetic alterations can occur to improve antibody function, mainly increasing binding affinity for antigen. Somatic hypermutation alters the antigen-binding specificity of antibodies by introducing point mutations in the immunoglobulin variable region.

Class-switch recombination allows the previously rearranged immunoglobulin heavy chain V domain to be expressed in association with a different constant (C) region, leading to production of diverse isotypes. In order for this recombination reaction to occur, three successive events must take place: firstly, transcription of the targeted DNA sequences; then the AID-induced lesion and cleavage of the DNA occur; and finally, a DNA repair process will permit the joining of the downstream C region in its new position.

Immunodeficiency with hyper-IgM comprises a group of genetically heterogeneous defects of class-switch recombination, variably associated with defects of somatic hypermutation [5]. The most common defect is due to mutation in the CD40 ligand and is transmitted in an X-linked manner, ruling out our girl twins.

Several autosomal recessive rare mutations can also cause the hyper-IgM syndrome. Defects in CD40, AID and UNG were not found in our cases, who were therefore diagnosed as having the hyper-IgM syndrome type 4 [3]. Indeed, in this type of hyper-IgM syndrome, somatic hypermutation is normal, as seen in our case, and the defect(s) in class-switch recombination are postulated to be in the DNA repair machinery.

The appearance of malignancy in one of the twins, a complication that has not been reported in hyper-IgM syndrome type 4, led us to conduct further studies, although no clinical characteristic of A-T was observed. Indeed it was found that *ATM*, the gene mutated in A-T, is essential for the class-switch recombination process, but not for somatic hypermutation. Although in most cases of A-T no *ATM* molecule is detected, the trace amount

that was seen in our case may point to a partial *ATM* kinase activity that would explain the milder clinical phenotype observed in our patients.

In summary, we believe that A-T should be considered in the rare cases of children presenting with autosomal recessive hyper-IgM syndrome type 4.

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*There was never a genius without a tincture of madness*

Aristotle (384-322 BCE)

*The mind commands the body and the body obeys. The mind commands itself and finds resistance*

St. Augustine (354-430 CE), one of the most important figures in the development of Western Christianity