Ataxia-Telangiectasia in a Patient Presenting With Hyper-immunoglobulin M Syndrome

A Aghamohammadi,1,2 K Imai,3 K Moazzami,1 H Abolhassani,1 M Tabatabaeiyan,1 N Parvaneh,1,2 R Nasiri Kalmarzi,2 N Nakagawa,3 K Oshima,4 O Ohara,4,5 S Nonoyama,3 N Rezaei1,2,6

1Research Center for Immunodeficiencies, Tehran University of Medical Sciences, Tehran, Iran
2Department of Pediatrics, Pediatrics Center of Excellence, Children’s Medical Center, Tehran University of Medical Sciences, Tehran, Iran
3Department of Pediatrics, National Defense Medical College, Saitama, Japan
4Laboratory for Immunogenomics, Research Center for Allergy and Immunology, RIKEN, Yokohama Institute, Kanagawa, Japan
5Department of Human Genome Research, Kazusa DNA Research Institute, Chiba, Japan
6Molecular Immunology Research Center and Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Abstract
Ataxia-telangiectasia (AT) and hyper-immunoglobulin M (HIGM) syndrome are both primary immunodeficiency diseases caused by different genetic defects. While a small proportion of AT patients have increased serum immunoglobulin (Ig) M concentrations during the course of a disease, a high level of IgM at onset is rare. We report the case of an 8-year-old girl who had experienced recurrent respiratory infection, cutaneous abscesses, and hepatosplenomegaly since the age of 2 years. She was diagnosed with HIGM based on the results of immunological studies, including low IgG and IgA levels and raised serum IgM concentrations. However, at the age of 4 years, a neurological examination revealed gait disturbance and telangiectatic lesions on the conjunctiva; therefore, a diagnosis of AT was suggested. In spite of regular intravenous immunoglobulin infusions and antimicrobial prophylaxis, the patient experienced several episodes of respiratory infection and eventually died of respiratory failure at the age of 8 years. Further molecular analysis revealed a novel homozygous missense mutation in exon 53 (c.8250C>T, p.2622Ala>Val) of the \( \text{ATM} \) gene.

Patients with AT and the HIGM phenotype may not develop clinical characteristics of AT for some time. While patients with AT and increased serum IgM levels could have a considerably more severe disease course and a shorter survival, IgM levels could be considered a prognostic factor.

Key words: Ataxia-telangiectasia. Hyper-IgM syndrome. Mutation. IgM

Resumen
La ataxia telangiectasia (AT) y el síndrome de hiperinmunoglobulina M (HIGM) son enfermedades de inmunodeficiencia primaria causadas por diferentes defectos genéticos. Si bien una pequeña proporción de pacientes con AT presentan concentraciones séricas elevadas de inmunoglobulina (Ig) M durante el curso de la enfermedad, es poco frecuente observar niveles elevados de IgM al inicio. En este artículo se recoge el caso de una niña de 8 años de edad que experimentó infección respiratoria, abscesos cutáneos y hepatosplenomegalia recurrentes desde los 2 años de edad. Se le diagnosticó HIGM basándose en los resultados de los estudios inmunológicos, que incluyeron niveles bajos de IgG e IgA y concentraciones séricas elevadas de IgM. No obstante, a los 4 años, una exploración neurológica reveló alteración de la marcha y lesiones telangiectásicas en la conjuntiva; por ello, se sugirió un diagnóstico de AT. A pesar de las perfusiones regulares de inmunoglobulina intravenosa y la profilaxis antibiótica, la paciente experimentó varios episodios de infección respiratoria y finalmente murió por insuficiencia respiratoria a los 8 años de edad. Análisis moleculares adicionales revelaron una nueva mutación de sentido erróneo homocigótica en el exón 53 (c.8250C>T, p.2622Ala>Val) del gen ATM.

Los pacientes con AT y el fenotipo HIGM pueden no desarrollar las características clínicas de AT durante algún tiempo. Puesto que los pacientes con AT y niveles séricos elevados de IgM pueden tener un curso considerablemente más grave de la enfermedad y una menor supervivencia, los niveles de IgM pueden considerarse un factor pronóstico.

Palabras clave: Ataxia-telangiectasia. Síndrome de hiper IgM. Mutación. IgM.
Introduction

Ataxia-telangiectasia (AT) is a rare autosomal recessive primary immunodeficiency disease (PID) that can affect several organs. Cerebellar ataxia and oculocutaneous telangiectasia are the most common forms of this syndrome, although there have also been reports of increased susceptibility to sinopulmonary infections, hypersensitivity to radiation, and predisposition to malignancy [1,2].

Hyper-immunoglobulin M (HIGM) syndrome, also known as immunoglobulin class switch recombination (CSR) deficiency, comprises a heterogeneous group of PIDs characterized by recurrent infections associated with decreased serum immunoglobulin (Ig) G, IgA, and IgE levels, and normal to increased IgM levels [3-5]. Whereas several genetic defects account for this syndrome [6-9], other PIDs can also present with Ig levels suggestive of HIGM [10].

While about 10% of patients with AT show raised serum IgM concentrations during the course of the disease [11], it is unusual to find a high level of IgM at onset. Infants with AT may initially present with recurrent infections, whilst neurodegenerative conditions and ocular telangiectasia may not be apparent at this stage. Consequently, the clinical picture may lead to misdiagnosis of HIGM. However, most patients develop the typical symptoms of AT with advancing age.

We report the case of a child who presented with HIGM syndrome and in whom the diagnosis of AT was subsequently confirmed.

Case Description

The patient was an 8-year-old girl, the fourth child of consanguineous parents (first cousins). Her mother had an 8-year history of infertility followed by 2 miscarriages and 1 stillbirth. There was no family history of immunodeficiency or cancer (Figure 1).

The patient was fully immunized with no complications and was in good health until the age of 2 years, when she was admitted to hospital because of lower respiratory tract infection associated with anemia, leukopenia, and splenomegaly. She received antibiotic therapy and recovered.

One month later, she experienced high fever and cutaneous abscesses. Physical examination revealed generalized lymphadenopathy and hepatosplenomegaly. As there were several differential diagnoses for these clinical manifestations, a number of laboratory tests were performed. Blood cell count analysis revealed severe neutropenia (white blood cells, 3900/mm³; polymorphonuclear leukocytes, 9%; lymphocytes, 62%) with an absolute neutrophil count of 374/mm³. The immunologic workup revealed the following values: IgG, 200 mg/dL (reference range, 656-1350); IgA, 5 mg/dL (reference range, 86-320); and IgM, 470 mg/dL (reference range, 120-320). The proportions of lymphocyte subtypes were 61% CD3, 40% CD4, 12% CD8, and 17% CD19.

Based on low IgG and IgA levels and raised serum IgM concentrations, a diagnosis of HIGM was suspected. The patient started monthly intravenous immunoglobulin infusion (400 mg/kg) and daily oral antimicrobial prophylaxis. However, during follow-up, she experienced several episodes of upper and lower respiratory tract infections and urinary tract infections. The results of further immunological workups were also compatible with this diagnosis, although reduced IgG and IgA and increased IgM levels were detected after 2.5 years (IgG, 460 mg/dL; IgA <10 mg/dL; and IgM >400 mg/dL). A low response to the polysaccharide pneumococcal vaccine was documented (from 70 U/mL before vaccination to 150 U/mL after vaccination), and functional assay of antibody response to meningococcal vaccine also confirmed that the patient did not respond to polysaccharide antigens. Stimulation of peripheral blood mononuclear cells with phytohemagglutinin revealed a low stimulation index, compared with a matched control. The percentage of class-switched (IgM IgD CD27⁺) memory B cells was below the lower limit of normal (<0.4% of peripheral blood mononuclear cells).

The neurological examination showed mild gait disturbance, although no progression of neurological symptoms was noted. At the age of 4 years, telangiectatic lesions developed on the patient’s conjunctiva. The presence of unsteady gait and the development of ocular telangiectasis led us to make a clinical diagnosis of AT. α-fetoprotein level at this stage was 46.8 ng/mL (reference range, <11).

At the age of 8 years, the patient was admitted to our hospital with fever and respiratory distress due to severe pneumonia. Although antibiotic therapy and intravenous immunoglobulin were started, she eventually died of respiratory failure.

Further analyses were performed to understand the primary
defect in this patient. Genetic studies of the DNA extracted from the patient’s Epstein-Barr virus–transformed B-cell line revealed the coding regions of CD40L, CD40, AID, and UNG to be normal. ATM gene sequence analysis showed a novel missense mutation in exon 53 (c.8250C>T) leading to an amino acid change (p.2622Ala>Val) in the ATM protein. Neither of the 2 Internet databases that update the mutations of ATM—RAPID (Resource of Primary Immunodeficiency Diseases; http://rapid.rcai.riken.jp/) and HGMD (Human Gene Mutation Database; http://www.hgmd.cf.ac.uk)—has yet documented a similarly altered ATM sequence. Moreover, a search of the Ensemble genome browser (www.ensembl.org) and NCBI (www.ncbi.nlm.nih.gov/snp) revealed no reported single-nucleotide polymorphism at codon 2622. Sequence alignment showed that the amino acid A2622 of the ATM protein is conserved in several species (Figure 2).

Discussion

AT is an autosomal recessive PID characterized by progressive cerebellar ataxia, ocular telangiectasia, and radiation hypersensitivity [1,2]. Hypogammaglobulinemia is the most frequent immune disorder: low levels of IgG, IgA, and IgE are observed in most patients [12]. IgM level may be normal or mildly elevated in AT. However, very high IgM is observed in approximately 1% of these patients [13]. Diagnosis of AT in infancy may be difficult, as cerebellar ataxia and ocular telangiectasia are difficult to recognize at this age and recurrent sinopulmonary infections are often the only presenting symptom. Consequently, AT patients who present with elevated IgM serum levels may be misdiagnosed as HIGM syndrome. Moreover, a search of the Ensemble genome browser (www.ensembl.org) and NCBI (www.ncbi.nlm.nih.gov/snp) revealed no reported single-nucleotide polymorphism at codon 2622. Sequence alignment showed that the amino acid A2622 of the ATM protein is conserved in several species (Figure 2).

References

A. Aghamohammadi, et al


Manuscript received October 13, 2009; accepted for publication February 24, 2010.

Asghar Aghamohammadi, MD, PhD

Children's Medical Center Hospital
62 Qarib St.
Keshavarz Blvd.
Tehran 14194, Iran
E-mail: aghamohammadi@sina.tums.ac.ir