

The Assessment of a Patient with Ataxia-Telangiectasia (A-T): A Case Report Study

Marziyeh Heidarzadeh¹, Reza ArefNezhad², Javad Fathgharib¹, Asghar Aghamohammadi³, and Hossein Motedayyen⁴

¹Kashan University of Medical Sciences

²Shiraz University of Medical Sciences

³Tehran University of Medical Sciences

⁴Affiliation not available

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Abstract

Ataxia-telangiectasia (A-T) is a multi-system disorder, resulted from the mutation in the ATM gene. Its mortality is largely related to some other disorders. Therefore, the management of its complications significantly improves patient quality of life. We studied a pediatric patient with A-T who one of his relatives had A-T.

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Authors

Marzieh Heidarzadeh Arani¹, Reza ArefNezhad², Javad Fathgharib¹, Asghar Aghamohammadi³, Hossein Motedayyen^{4,*}

Affiliations

¹ Department of Pediatrics, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran.

² Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran.

³ Research Center for Immunodeficiency, Tehran University of medical Sciences, Tehran, Iran.

⁴ Autoimmune Diseases Research Center, Kashan University of Medical Sciences, Kashan, Iran.

*Corresponding author: Dr. Hossein Motedayyen, Autoimmune Diseases Research Center, Shahid Beheshti Hospital, Kashan University of Medical Sciences, 5th Kilometer of Ravand Road, Kashan, Iran, Fax: 00983155578011, e-mail: hmotedayyen@gmail.com.

Key clinical message

Ataxia-telangiectasia (A-T) is a multi-system disorder, resulted from the mutation in the *ATM* gene. Its mortality is largely related to some other disorders. Therefore, the management of its complications significantly improves patient quality of life.. We studied a pediatric patient with A-T who one of his relatives had A-T.

Key words: Ataxia-telangiectasia, Hyper IgM syndrome, Recurrent pneumonia.

Introduction

Ataxia-telangiectasia (A-T) is known as an uncommon autosomal recessive disorder related to the nervous system which involves several systems. It is described by telangiectases, immunodeficiency, ataxia, radiosensitivity and susceptibility to hematologic malignancies (1). A-T resulted from mutations in the *ataxia-telangiectasia mutated (ATM)* gene (2, 3). A-T affects 1 or 2 per 100 000 subjects globally and its prevalence in men is similar to women (4, 5). The morbidity of A-T can be contributed to pulmonary disease, immune deficiency, and dysphagia (2). Moreover, it is reported that various infections are mainly responsible for its morbidity and mortality (6). *ATM*, a checkpoint gene of the cell cycle, has a pivotal role in the reconstruction of fractured DNA during B and T cell differentiation, lymphocyte development, and support genetic status (7, 8). Furthermore, changed *ATM* gene can lead to cancer such as lymphoma and breast cancer (7, 9). In spite of there is not yet notable advance in the treatment, the management of A-T complications can be useful (10). Recent studies have reported some disorders in association with A-T, for example, hyper immunoglobulin (HIgM) syndrome and dystonia (11) but whether other disorders are associated with A-T is not clearly defined. In addition, there are few studies about the association of the inflammatory disease with A-T. The line with this, we evaluated a pediatric patient with A-T for better diagnosis and subsequently for better management of A-T.

Subject description

Our case is an 8-year-old pediatric patient who had been studied due to recurrent respiratory infections and other health problems. He was born via elective cesarean section from a mother who delivered at 41-week gestation. His birth weight was 3250 grams. Our pediatric patient suffered from different manifestations of infections during years, including pneumonia, otitis, parotiditis, chickenpox, zona, etc. At first, HIgM syndrome was diagnosed but after it, other manifestations of A-T appeared. His parents had consanguinity. His umbilical cord dropped at 11 days of age. The routine vaccination was done and he was nourished with mother milk. Thus, growth and weight gaining were normal. In family history, there was A-T in his mother's uncle's children. The patient had several experiences of mouth aphthous during the first year of age and was hospitalized in Kashan Shahid Beheshti hospital owing to pneumonia for one week. At 15 months of age, magnetic resonance imaging (MRI) was carried out because of ataxia while seating. The result of MRI was normal. Afterwards, ataxia occurred in walking in the form of waddling gait. Ataxia was treated by behavioral therapy. The patient was hospitalized due to severe fever and neutropenia at 18 months of age and discharged after recovery. During these years, our case was also admitted to Kashan Shahid Beheshti hospital three times because of fever and suppurative rhinitis. When the patient was three years old, he suffered from petechial, thrombocytopenia, and mouth bleeding. Idiopathic thrombocytopenic purpura (ITP) was considered and he was treated with intravenous immunoglobulin (IVIG). However, patient had petechial all over the body after ten days. Bone marrow aspiration (BMA) was done to detect the cause(s) of thrombocytopenia. The result was normal. Having considered that thrombocytopenia may be associated with splenomegaly, sonography was performed. In his sonography, mild splenomegaly was reported which was normal in later follow up. Thrombocytopenia was treated with IVIG and corticosteroids and the clinical symptoms were gradually disappeared. At 3.5 years of age, our case experienced acute otitis media, which was treated with antibiotic therapy (meropenem and vancomycin) and ventilation tube (VT). During these years, he also had several episodes of respiratory infections (pneumonia and otitis) and acute gastroenteritis which were treated out-patiently with co-amoxiclav, azithromycin, and tavanex. At four years of age, the patient suffered from herpetic gingivostomatitis and chickenpox. Moreover, he had otitis and neutropenia again. Therefore, he was hospitalized in Kashan Shahid Beheshti hospital for one week. Immunological situation of patient was investigated (Table. 1). Based on laboratory data, HIgM syndrome was suggested. Antibiotic therapy and IVIG were employed to treat patient and then discharged. When our case was six years ago, he had ocular nystagmus accompanied by severe telangiectasia and ataxia. Regarding the fact that the patient's family history was positive for A-T, he was genetically studied to determine a defect in the *ATM* gene. The genetic analysis revealed that our case suffered from A-T (Table. 2). After certain diagnosis of A-T, antibiotic prophylaxes, IVIG administration, and different food regimes were considered as a suitable approach to control health condition of patient. However, the patient had zona and parotiditis after one year. He was hospitalized in Kashan Shahid Beheshti hospital for two weeks and received acyclovir.

The patient is currently alive and in good health condition.

Discussion

Ataxia-telangiectasia (A-T) is a genetic neurodegenerative disorder described by several problems such as ataxia, telangiectasis, failure in motor ability, unusual eye movement, immune deficiency, pulmonary disorder, and susceptibility to hematologic malignancies due to the mutation in the *ATM* gene on the chromosome 11q22.23 (1, 2, 12). Infectious complications play indispensable role in the morbidity and mortality of the disease (6). The etiology of some hematologic disorders in A-T patients may be related to immune disorders such as thrombocytopenia. Furthermore, inflammation participates in the pathogenesis of the disease. It is demonstrated that inflammatory cytokines had the increased levels in A-T patients (13). These increased levels can be involved in inflammatory diseases such as suppurative rhinitis, gastroenteritis, acute otitis media, and parotiditis which were observed in our case. One of the characterizations of A-T is cerebellar neurodegeneration (14). In our patient, nervous system disorders were included ataxia and ocular nystagmus. In this respect, it is stated that the neurogenesis kinetics in A-T are changed. The *ATM* gene encodes a protein kinase which participates in the activation of cellular responses to DNA double-strand breaks and neural stability (15, 16). Hence, it is likely that these functions are disrupted by *ATM* mutation. The majority of A-T patients have immune problems such as defects in the productions and/or functions of IgA, IgG, and reduction in the number of CD4+ T cells. Moreover, it is reported that few A-T patients have HIgM syndrome or different viral and opportunistic infections (2). However, our case has chickenpox, zona, and HIgM syndrome with a significant frequency of CD4+ cells which the reason of this occurrence is not clearly known. Others have indicated that pulmonary disorders in A-T may be contributed to neurological disorders, regressive infectious, and lung disorder (2).

Conclusion

Based on our results, it is thought that some inflammatory diseases such as suppurative rhinitis, acute otitis media, parotiditis, and gastroenteritis are mediated by the defects occurred in A-T. Moreover, our findings indicated that a pediatric patient with A-T, who one of his relatives also had A-T, can have various manifestations of infections, for example, pneumonia, chickenpox, zona, etc. In addition, HIgM syndrome can be accompanied by A-T which may be appeared before other manifestation. Among immune and hematological disorders, our patient revealed neutropenia, HIgM syndrome, and thrombocytopenia. The nervous system signs were ataxia and ocular nystagmus. Flow cytometry findings showed that CD3+, CD4+ and CD8+ are more frequent, respectively.

Conflict of interest

The authors report no conflict of interest.

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Authors' contributions

Marzieh Heidarzadeh carried out some of the experiments. Reza ArefNezhad participated in the design of the experiments. Javad Fathgharib collected the laboratory findings and performed some experiments. Asghar Aghamohammadi participated in the design of the experiments. Hossein Motedayyen drafted the manuscript and participated in the study design. All authors read and approved the final manuscript.

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Table. 1) Laboratory findings of patients

Biochemistry	Biochemistry	IgE 0	NR: 1.53- 11.4 mg/dl
ALT 75	Normal range (NR): up to 41	IgG 27	NR: 386-1470 mg/dl
AST 78	NR: up to 37	CD3+ cell population	69%
ALP 573	NR: 98-279	CD4+ cell population	40%
GGT 26	NR: 100-500	CD8+ cell population	19%
AFP 275.7	NR: 0.1 – 10	CD19+ cell population	10%
Immunology	Immunology	CD20+ cell population	10%
Anti-tetanus Ab <0.1	NR: <0.1 basic immunization recommended	CD56+ cell population	10%
Anti-diphtheria Ab <0.1	NR: <0.1 basic immunization recommended	CD16+ cell population	10%
Anti-HCV Ab Negative	Anti-HCV Ab Negative	Stool examination	Stool examination
Anti-HAV Ab Negative	Anti-HAV Ab Negative	RBC 0-1	RBC 0-1

Biochemistry	Biochemistry	IgE 0	NR: 1.53- 11.4 mg/dl
Anti-HBS Ab 94.2	NR: 10-100 weakly positive	WBC 4-6	WBC 4-6
IgM 724	NR: 37-224 mg/dl	Fat drop Not seen	Fat drop Not seen
IgA 2	NR: 25-154 mg/dl	Cryptosporidium Positive	Cryptosporidium Pos

Alanine aminotransferase: ALP; Aspartate Aminotransferase : AST; Alkaline phosphatase: ALP; Gamma-glutamyltransferase: GGT; Antibody: Ab; Alpha feto protein: AFP; Hepatitis C virus: HCV; Hepatitis A virus: HAV; Hepatitis B surface antigen: H

Table. 2) Genetic analysis of *ATX* gene

Gene/transcript (RefSeq)	Variant location	Variant	Chromosome position	Zygosity	Related phenotypes	OMIM number	Inheritance pattern	Variant classification	Re
ATM NM_-000051.3	Exon 26	c.3895delG p.A1299Pfs*50	Chr11:108,155,160	1/1	Ataxia-telangiectasia	208900	AR	Pathogenic	1
					Susceptibility to breast cancer	114480	SMu, AD		
					Lymphoma, B cell non-Hodgkin, somatic	-	-		
					Lymphoma, mantle cell, somatic	-	-		
					T-cell pro-lymphocytic leukemia, somatic	-	-		