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Original Article

Clinical Manifestations of Ataxia-Telangiectasia with Class Switch Recombination Defect

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Abstract

Background: Elevated serum levels of IgM and recurrent infections, mainly respiratory tract infections, could be the presenting features in some ataxia-telangiectasia (AT) patients, and may initially be misdiagnosed as hyper-IgM (HIgM) syndrome. Class switch recombination (CSR), which is defective in HIgM syndrome, is an important mechanism in the maturation of B lymphocytes to produce different isotypes of antibodies in response to antigen stimulation.

Methods: The clinical manifestations and laboratory findings of 16 cases with low IgA and IgG levels, and normal to elevated IgM levels with CSR defect are reported.

Results: In 16 cases, the median age at onset of the diseases, and median age at the time of the diagnosis were 1 year (interquartile range [IQR] = 1.6), and 4 years (IQR = 3.1), respectively. Two of the patients (12.5 %) died due to respiratory infection. In this study, Out of the studied population, four were male (25%), and 12 were female (75%). Most of the patients had consanguineous parents (81.3 %). All of the patients had ataxia, and 15 patients had telangiectasia (93.8 %), and one of the cases had malignancy (dermatofibroma). Also, 15 patients presented infections (93.8 %). Autoimmunity was seen in three patients (18.8 %). In addition, some of the patients manifested hepatosplenomegaly (31.3 %) and thrombocytopenia (18.8 %). Neurological manifestations, such as visual impairment (12.5 %), epilepsy (6.3 %), and tremor (12.5 %), were also present.

Conclusion: AT patients with HIgM phenotype and CSR defect, compared to other AT patients, may present different clinical manifestations, such as various infections. Considering their manifestations, the management and treatment of these patients are necessary.

Keywords: Ataxia-Telangiectasia; Case Series; Class Switch Recombination Defect; Hyper-IgM

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Introduction

Ataxia-telangiectasia, is an autosomal recessive disease due to mutations in the ataxia-telangiectasia mutated (ATM) gene that codes ATM kinase (1). ATM is responsible for regulating some processes in cells, including the cell cycle and DNA repair (2). AT affects approximately one in 40,000 to 100,000 people worldwide (3). Its clinical manifestations are characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia, different levels of immunodeficiency, radiosensivity, and a high prevalence of malignancies (4). However, depending on the activity of ATM kinase, a variety of manifestations can be seen, so that mild AT presents with milder manifestations and a longer lifespan in comparison with the classic AT (5).

HIgM syndrome is a rare disorder, which is characterized by low levels of IgG, IgA and IgE with normal or high serum levels of IgM. This disorder is a heterogeneous form of primary immunodeficiencies that is caused by defective CSR (6). It is characterized by recurrent infections, especially respiratory tract infections (7). The prevalence of CSR defects, is approximately one in 500,000 births (8).

About 10% of the AT cases, could be misdiagnosed as HIgM syndrome, because of the low levels of IgG and IgA, and also normal to elevated serum levels of IgM (9). Some studies reported that elevated serum levels of IgM in the AT patients, should be considered as a prognostic parameter, because of its probable worse prognosis (10). In addition, the effects of ATM proteins on CSR, have been demonstrated in the literature (11). The AT patients with HIgM phenotype and CSR defect, cannot produce any type of class-switched Ig; therefore, they have normal to elevated IgM levels. So, although the AT patients with this defect usually present with infections, others present with neurological symptoms (12). In the present study, we gathered 16 AT patients with low IgA and IgG levels, and normal to elevated IgM levels with CSR defect, and evaluated their clinical manifestations and laboratory findings.

Materials and Methods

Patients

Sixteen patients with AT along with immunodeficiency, were gathered for the present study, and were referred to Children's Medical Center in Tehran, Iran. They had low IgA and IgG levels, and normal to elevated IgM levels with CSR defect. The diagnosis of AT was based on the guidelines of the European Society of Immunodeficiency (ESID) (13); having cerebellar ataxia and at least two of the following symptoms: oculocutaneous telangiectasia, high alpha-fetoprotein, 7;14 translocation in lymphocyte AT karyotype, and cerebellar hypoplasia on magnetic resonance imaging (14). Their Ig levels were compared to the age-matched reference [IgG: 500–1300 (mg/dL), IgA: <1 month: 7–94; 1 month to 12 months: 10–131; 1 year to 3 years: 19–220; 4 years to 5 years: 48–345; 6 years to 7 years: 41–297; 8 years to 10 years: 51–297; 11 years to 13 years: 44–395, Adults: 70–400 (mg/dL), IgM: 1 month to 3 months: 12–87; 4 months to 6 months: 25–120; 7 months to 12 months: 36–104; 1 year to 11 years: 55–210; Adults: 40–230 (mg/dL)]. The CSR was evaluated by peripheral blood mononuclear cell production of IgE. Afterwards, the cells were cultured for 12 days at 37 C, in humidified air with 5% CO2 in the presence of IL-4 (IL-4, 200 U/ml; R&D, USA), and CD40L (CD40L, 300 ng/ml, MiltenyiBiotec, Germany). Defective CSR was defined when the IgE production was lower than 0.35 IU/ml (2 standard deviations below the normal population of Iran) (15). Whereas, serum IgE was within the normal range in all cases.

Data collection

The patients' demographic information, clinical manifestations, and laboratory findings were recorded through an appropriate questionnaire. Demographic information includes sex, age at the onset of the disease, age at the diagnosis of the disease, life status, and parental consanguinity. For laboratory findings, alpha-fetoprotein levels were also measured.

Ethical approval

Approval has been obtained from the ethical committee of the Tehran University of Medical Sciences. Also, a written consent was obtained from the parent(s) or guardians of every participant of the study.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, Version 26.0. Armonk, NY. The Kolmogorov-Smirnov test was used to test the normality of data distribution. A P-value lower than 0.05 was considered statistically significant.

Results

In our study, from 16 Iranian AT patients, ranging from 5 to 20 years old, four were male (25 %), and 12 were female (75 %). Median age at onset of the diseases, and the median age at the time of the diagnosis were 1 year (interquartile

Table 1. Demographic data of the cases

Variable	Patients (n = 16)
Sex (male, female) %	25 %, 75 %
Median age at onset of the disease; years (IQR)	1.0 (1.6)
Median age at diagnosis; years (IQR)	4.0 (3.1)
Life status (alive, dead) %	87.5 %, 12.5 %
Parental consanguinity (consanguineous, nonconsanguineous) %	81.3 %, 18.7 %

IQR, interquartile range

Table 2. Types of infection, skin lesion, autoimmunity, malignancy, and other manifestations in our 16 cases

Patients	Type of infection	Type of skin lesion	Type of autoimmunity	Type of malignancy	Other manifestations
P 1	Pneumonia, otitis media	Albinism			Abdominal pain, gastrointestinal disorder, failure to thrive
P 2	Pneumonia	Rash			
P 3	Sinusitis, pneumonia, otitis media	Petechiae	Immune thrombocytopenic purpura		Cardiac impairment, tonsil loss
P 4	Pneumonia, sepsis	Rash			
P 5	Pneumonia				Growth retardation (failure to thrive)
P 6	Pharyngitis, pneumonia, otitis media				Tremor, recurrent epistaxis
P 7	Pneumonia, otitis media				
P 8	Sinopulmonary				
P 9	Sinopulmonary, otitis media	Eczema			Tremor, vomiting
P 10	Pneumonia				
P 11		Rash			Lymphocytopenia
P 12	Pneumonia				Hair loss*
P 13	Eye, nail, skin, tooth, otitis media, nail fungal lesions	Granulomatous	Immune thrombocytopenic purpura	Dermatofibroma	Hearing loss, failure to thrive
P 14	Pneumonia, tooth, otitis media				Dizziness, recurrent epistaxis, hair loss*
P 15	Pneumonia, tooth, otitis media				
P 16	Respiratory infection, otitis media		Inflammatory bowel disease		

range [IQR] = 1.6), and 4 years (IQR = 3.1), respectively. Two of the patients died (12.5 %), while 14 patients (87.5 %) were alive at the time of the study. Both deceased cases, died because of respiratory infection, one at the age of 12 and the other at 14 years of age. Most of the patients had consanguineous parents (81.3 %) (**Table 1**).

All of the patients had ataxia, and 15 patients had telangiectasia (93.8 %). 15 patients presented with infection (93.8 %). **Table 2**, shows the types of infections in our cases. In addition, it shows types of skin lesions, autoimmunity, malignancy, and other clinical manifestations, which are not reported in **Table 3**. There were more patients with a lower respiratory infection (75 %), in comparison to the patients with an upper respiratory infection (62.5 %). Also, two of the cases had respiratory distress (12.5 %). Otitis

Table 3. Clinical manifestations in the cases

Variable	Patients (n = 16)
Ataxia frequency (%)	100 %
Median age at onset; years (IQR) (n = 16)	1.0 (0.5)
Telangiectasia frequency (%)	93.8 %
Mean age at onset; years (SD) (n = 15)	3.2 (1.9)
Infection frequency (%)	93.8 %
Median age at onset; years (IQR) (n = 14)	2.5 (3.5)
Upper respiratory infection frequency (%)	62.5 %
Mean age at onset; years (SD) (n = 9)	4.3 (3.9)
Lower respiratory infection frequency (%)	75 %
Mean age at onset; years (SD) (n = 12)	2.3 (1.6)
Otitis media frequency (%)	56.3 %
Mean age at onset; years (SD) (n = 9)	4.6 (3.8)
Thrombocytopenia frequency (%)	18.8 %
Mean age at onset; years (SD) (n = 3)	2.7 (0.6)
Fever frequency (%)	87.5 %
Median age at onset; years (IQR) (n = 14)	2.5 (3.5)
Common cold frequency (%)	81.3 %
Mean age at onset; years (SD) (n = 13)	4.1 (2.4)
Repeated coughs frequency (%)	68.8 %
Median age at onset; years (IQR) (n = 11)	3.0 (4.0)
Diarrhea frequency (%)	56.3 %
Mean age at onset; years (SD) (n = 9)	4.0 (2.3)
Skin lesion frequency (%)	43.8 %
Mean age at onset; years (SD) (n = 6)	4.2 (1.5)
Oral thrush frequency (%)	6.3 %
Age at onset (years) (n = 1)	2.0
Respiratory distress frequency (%)	12.5 %
Mean age at onset; years (SD) (n = 2)	3.0 (2.8)
Epilepsy frequency (%)	6.3 %
Age at onset (years) (n = 1)	1.0
Visual impairment frequency (%)	12.5 %
Mean age at onset; years (SD) (n = 2)	6.5 (0.7)
Speech impairment frequency (%)	0.0 %
Hepatosplenomegaly frequency (%)	31.3 %
Autoimmunity frequency (%)	18.8 %
Mean age at onset; years (SD) (n = 3)	2.7 (0.6)
Malignancy frequency (%)	6.3 %
Age at onset (years) (n = 1)	7.0

IQR, interquartile range; SD, standard deviation

Table 4. Laboratory data in the cases

Variable	Patients (n = 16)
Median alpha-fetoprotein level (ng/mL) (IQR) (n = 16)	114.0 (77.5)
Normal (< 20 ng/mL) %	0 %
High (20 – 100 ng/mL) %	43.8 % (n = 7)
Very high (> 100 ng/mL) %	56.2 % (n = 9)
Mean IgG level (mg/dL) (SD) (n = 14)	115.8 (102.5)
Normal %	0 %
Decreased %	100 % (n = 16)
Increased %	0 %
Mean IgA level (mg/dL) (SD) (n = 13)	5.3 (4.4)
Normal %	0 %
Decreased %	100 % (n = 16)
Increased %	0 %
Median IgM level (mg/dL) (IQR) (n = 16)	435.0 (500.0)
Normal %	43.8 % (n = 7)
Decreased %	0 %
Increased %	56.2 % (n = 9)
Median IgE level (IU/mL) (IQR) (n = 16)	1.0 (0.0)
Normal %	100 % (n = 16)
Decreased %	0 %
Increased %	0 %

IQR, interquartile range; SD, standard deviation

media, fever, common cold, repeated coughs, diarrhea, and oral thrush were presented in nine (56.3 %), 14 (87.5 %), 13 (81.3 %), 11 (68.8 %), nine (56.3 %), and one (6.3 %) of the cases, respectively. Thrombocytopenia and splenomegaly were seen respectively in two (18.8 %) and five (31.3 %) of the patients. In addition to ataxia, which was seen in all of the patients, neurological manifestations, including visual impairment, epilepsy, and tremor, were presented by respectively two (12.5 %), one (6.3 %), and two of the patients (12.5 %). Seven patients manifested skin lesions (43.8 %), even though three of them were diagnosed with skin rashes. Autoimmunity and malignancy were seen in three patients (18.8 %), two of them had immune thrombocytopenic purpura, and one patient (6.3 %) had dermatofibroma. None of the patients had speech impairment.

Laboratory findings in patients were alpha-fetoprotein, IgG, IgA, IgM, and IgE. As mentioned, these 16 patients were cases with decreased IgG and IgA, and normal to elevated IgM levels with CSR defect. All patients had normal IgE, and high or very high alpha-fetoprotein (**Table 4**).

Discussion

AT, as an immunodeficiency syndrome, has an association with malignancies and infections (16). In a study by Alyasin et al. (17), reporting the clinical features of 18 AT patients, two of them were expired due to acute lymphoblastic leukemia; however, in our study, two patients died as a result of a respiratory infection.

Most of the cases were the results of a consanguineous marriage, this finding was in line with previous studies performed in Iran (18). Although various neurologic presentations, such as dysarthria, dysmetria, bradykinesia, hypomimia, etc., can be found on AT (19), in our group of patients, the only neurological manifestation of the disease was ataxia, seen in all of the patients, and tremor, in two patients, as well as epilepsy, in one patient.

It was believed that AT cannot deteriorate the visual acuity (20); however, in our study, two patients presented with blurred vision. Moreover, hepatosplenomegaly was so rare in AT, that a few case reports had been published on this matter (21, 22), but, in our study, about 31.3% of the

patients had hepatosplenomegaly.

In a previous study by Aucouturier et al., (23), the IgG4 and IgG2 were found to be decreased in almost every patient, with only 12.5% of them having low levels of total IgG. In our study, however, all of the patients had a low IgG level. Furthermore, in a study by Polmar et al., (24), 80% of the AT patients had low IgE levels, 66% had lower than normal levels of IgA, and 57% of AT patients had a combined deficiency of IgE and IgA. In our study, on the other hand, all of the patients had low levels of IgA and normal levels of IgE.

Previously, it was shown that the level of alpha-fetoprotein is increased in AT, and it has a linear correlation with age (25, 26). Although high levels of alpha-fetoprotein were observed in all of our patients, the correlation with age was not researched.

In a previous study by Amirifar et al., (14) conducted on 41 patients in Iran, the authors found that the rate of various infections and noninfectious complications in AT patients with CSR defect, were significantly higher. Furthermore, Pereira et al. has reported that the defect in humoral immunity of AT patients, might be due to alterations in the CSR gene (27).

Conclusion

In conclusion, in this study 16 AT patients with CSR defect were analyzed, concerning clinical features and laboratory data. The most common signs and symptoms of this group of patients were ataxia, telangiectasia, and various infections. All of them had higher than normal alpha-fetoprotein levels, low IgG and IgA levels, and normal IgE levels. 56.2% of the patients had high IgM levels, while others had normal levels. It is best for physicians all around the world to know about this disease, its presentations, and clinical features in order to be able to manage the patients properly.

Conflict of interest

The authors declare no conflicts of interest.

Ethical approval

Approval has been obtained from the Ethical Committee at the Tehran University of Medical Sciences.

Informed consent

A written consent form was obtained from the parent(s) or guardians of every case that participated in the study.

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