

Clinical Manifestations in Iranian Ataxia Telangiectasia Patients

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Abstract

Background/objectives: AT is an autosomal recessive primary immunodeficiency (PID) disease with multisystem involvement caused by biallelic mutations in the *ataxia telangiectasia mutated (ATM)* gene. The patients with AT represent a broad range of clinical manifestations including progressive cerebellar ataxia, oculocutaneous telangiectasia, immunodeficiency, and susceptibility to malignancies. We aimed to determine different clinical features of the AT patients to identify their key diagnostic or prognostic characteristics.

Methods: In the present study, 120 patients with the confirmed diagnosis of AT were enrolled from Iranian immunodeficiency registry center. A demographic information, clinical complications, and laboratory data were obtained from all the patients to evaluate the clinical manifestations.

Results: In this study, we found that in the AT patients, the frequency of total infection, respiratory infection, gastrointestinal infection, urinary tract infection, chronic fever, lymphadenopathy, and hepatosplenomegaly were 83.3%, 68.3%, 18%, 6.7%, 26.7%, 7.5%, and 20%, respectively.

Conclusions: The AT patients present different types of infections and noninfectious complications; therefore, early detection and careful management is *necessary* for these patients.

Keywords: ataxia telangiectasia, autosomal recessive, primary immunodeficiency disorders, ataxia telangiectasia mutated

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Introduction

AT (OMIM #208900) is a rare autosomal recessive multifaceted disorder with a complex phenotype including progressive cerebellar atrophy and ataxia, oculocutaneous telangiectasia, radiosensitivity, the increased serum alpha fetoprotein levels, immune deficiency, recurrent sinopulmonary infections, and the increased risk of malignancies especially those with lymphoid origin (1, 2). In some AT patients, different types of abnormalities including growth failure, poor pubertal development, insulin resistant diabetes, gonadal atrophy, lung disease, cutaneous abnormality, and cardiovascular disease have been observed (3).

AT is caused by germline mutations in the ATM gene encoding a serine/threonine protein kinase, which is located at 11q22.3-23. ATM is a large protein (~350 KDa) involved in many critical pathways of cellular cycle including DNA double strand breaks (DSBs) repairing, genomic stability, cell cycle regulation, and cell survival (4-7). The classic form of A-T is attributed to the presence of two truncating ATM mutations, which result in total loss of the ATM protein function, also on the other hand, milder forms are characterized by a leaky splice site ATM mutation or the presence of missense mutation (8, 9).

Ataxia Telangiectasia is reported with the incidence of 1:40,000 to 1:100,000 newborns worldwide (10). AT patients are generally suffering from poor prognosis, delay in diagnosis or in misdiagnosis based on its breadth of clinical heterogeneity. The affected children are normal at the time of birth; however, they become wheelchair-bound early in their second decade and do not survive beyond the age of 30 years old. (11, 12). Chronic pulmonary diseases and malignancy are the most common causes of mortality among these patients (13, 14). Primary immunodeficiency is observed in approximately 70-80% of the AT patients (15). Immunodeficiency phenotype in AT is variable; with some patients with the lack of infections and normal immunological profile. Whereas sometimes the immunodeficiency may elicit the humoral immune system, cellular immune system or maybe both of them.

Usually, it is manifested as low immunoglobulin (Ig) A, low IgG2, defective polysaccharide antibody responses, and lymphopenia, especially of the naive CD4 cells (15-20). The immunologic abnormalities remain unchanged by passing the time in majority of the AT individuals (15, 21).

Because there is no information on the clinical classification in the AT patients, we aimed to describe different clinical manifestations of the AT patients to identify their key diagnostic or prognostic characteristics.

Materials and methods

Study population

Based on data from the group of the unrelated AT patients who were referred to Iranian Immunodeficiency Registry Center at Children's Medical Center hospital in Tehran, Iran (22), the clinical and laboratory findings of these patients were retrospectively evaluated.

In terms of the European Society for Immunodeficiencies (ESID) guideline (23), diagnosis of AT was performed, in which the ataxia and at least two of the followings were included: elevated alpha-fetoprotein (AFP), oculocutaneous telangiectasia, lymphocyte AT karyotype with translocation chromosome 7:14, and cerebellar hypoplasia on magnetic resonance imaging (MRI).

Data collection

With the aim of recording clinical and demographic information containing age, sex, consanguinity of parents, first clinical appearance, age at the onset of different AT symptoms, age at the period of diagnosis, and record of infectious and noninfectious complications, a proper questionnaire was established. Furthermore, for each individual, the laboratory results including serum alpha-fetoprotein (AFP) level and the initial immunophenotyping were recorded. It is worth mentioning that, The Ethics Committee of the Tehran University of Medical Sciences have been approved the study, and the written in-

formed consents were collected prior to the study inclusion from the cases or their parent(s).

Local *reference ranges* of *immunoglobulins* are needed for clinical interpretation. In this study, serum levels of IgA, IgG, and IgM in all the patients have been adjusted to age [IgG: 500- 1300 (mg/dl), IgA: <1 m: 7-94; 1 m to 12 m: 10-131; 1 y to 3 y: 19-220; 4 y to 5 y: 48-345; 6 y to 7 y: 41-297; 8 y to 10 y: 51-297; 11 y to 13 y: 44-395, Adults: 70-400 (mg/dl), IgM: 1 m to 3 m: 12-87; 4m to 6 m: 25-120; 7 m to 12 m: 36- 104; 1 y to 11 y: 55-210; Adults: 40-230 (mg/dl)].

Statistical analysis

A commercially available software package (SPSS Statistics 17.0.0, SPSS, Chicago, Illinois) was used to perform the Statistical analysis. In order to estimate whether the data were normally distributed, the one-sample Kolmogorov-Smirnov test was applied. Furthermore, based on the finding of this evaluation, Parametric and nonparametric analyses were performed. It is noteworthy that, a *p*-value of 0.05 or less was considered as statistically significant in this study.

Results

A total of 120 patients (59 males and 61 females) with median (IQR) age of 13 years old (9.5-22.6) at the time of the study were included in the pres-

ent study .Among these 120 individuals, in 57 patients, biallelic ATM mutations were detected and remaining 63 patients had probable diagnosis in terms of the ESID criteria. The median age of the diagnosed patients was 6 (4-8) years old and the median of the diagnostic delay was 4 (2- 6) years old. All the patients were suffering from ataxia and the prevalence of parental consanguinity was noted in 91 (75.8%) of the patients. The prevalence of AT in men and women is almost similar. Demographic characteristics of all the AT patients are shown in **Table 1**.

The first presentations were ataxia, infections, and telangiectasia with median (IQR) date of the presentations 1.3(1.0-2.3), 2(1.0-4.0), and 4(2.0-6.0), respectively. 91.6 % of the patients were suffering from telangiectasia, and overall, the other common manifestation in the AT patients was infection (83.3%).

The frequency of the respiratory infection was higher among other infections in our patients. Pneumonia and lower respiratory tract infections were reported in 45.8% and 49.1% of the patients followed by upper respiratory tract infections (URTI) 55 % patients, otitis media 25% patients, sinopulmonary 16.6%, and sinusitis 33.3%.

Table 1. Demographic data of AT patients

Parameter	Total patients (n=120)
Age at the study time, years (IQR)	13 (9.5-22.6)
Age at diagnosis, years (IQR)	6 (4-8)
Age at onset of ataxia, years (IQR)	1.3 (1.0-2.3)
Age at onset of Infection, years (IQR)	2.0 (1.0-4.0)
Age at onset of telangiectasia, years (IQR)	4.0 (2.0-6.0)
Delay diagnosis, years (IQR)	4 (2-6)
Follow up, years (IQR)	3(1-5)
Sex, N (%)	
Male	59(49.2)
Female	61(50.8)
Consanguinity, N (%)	91(75.8)
Mortality, N (%)	
Alive	32(28.3)
Dead	14(12.4)
Unknown	67(59.3)

Abbreviations: N, Count; For quantities data the median is shown [with IQR, 25th and 75th percentiles]

Moreover, gastrointestinal infection and urinary tract infection were reported in 18.3% and 6.7% patients, respectively. Among non-infectious manifestations; splenomegally, hepatomegally, allergy, and FTT were observed in 10.8%, 9.2%, 9.2%, and 23.3% of the patients, respectively. The detailed information on clinical manifestations and organ involvement are presented in **Figure 1**.

Based on laboratory data, the median serum AFP levels were 140 (88-275) ng/dL, and it increased in all the AT patients. At the time of diagnosis and before initial Ig replacement therapy, the median serum IgG level was 800 (470-1170) mg/dL and that of other serum Ig levels were 10 (0-66.5) mg/dL for IgA and 207 (119 - 400) mg/dL for IgM (**Table 2**). The decreased serum levels were observed in 98 patients (81.6%) for IgA, and 35 patients (29.2%) for IgG whereas we observed the increased serum levels in 37 patients (30.8%) for IgM in our patients (**Table 3**).

Table 2. Laboratory and immunological data of AT patients

Parameter	Total patients (n=120)
AFP, ng/dL (IQR)	140 (88-275)
IgG, mg/dl (IQR)	800 (470-1170)
IgA, mg/dl (IQR)	10 (0 - 66.5)
IgM, mg/dl (IQR)	207 (119 - 400)
IgE, IU/ml (IQR)	4 (1-10)

Abbreviations: Ig, Immunoglobulins; n, Count; Note. For quantities data the median is shown [with IQR, 25th and 75th percentiles

Table 3. Qualitative laboratory and immunologic data of AT patients

Parameter	Total patients (n=120)
AFP	Normal
Frequency (%)	Increased 120 (100%)
IgG	Decreased 35 (29.2%)
Frequency (%)	Normal 85(70.8%)
IgA	Decreased 98 (81.6%)
Frequency (%)	Normal 22 (18.3%)
IgM	Decreased -
Frequency (%)	
IgE	Normal 120 (100%)
Frequency (%)	Increased

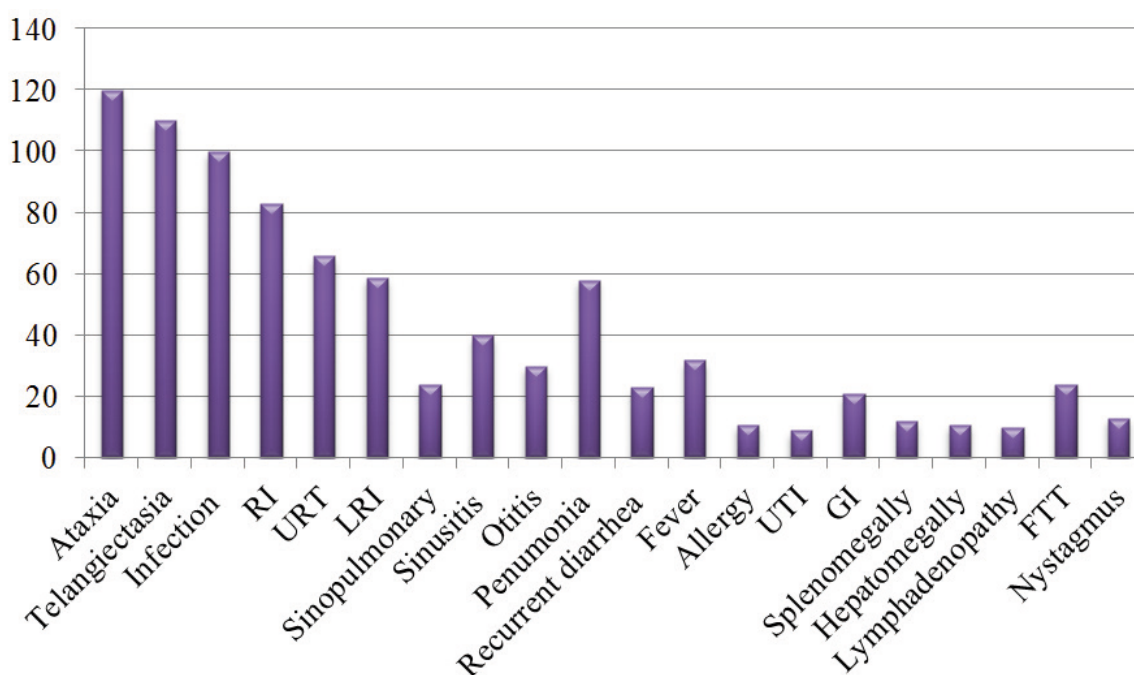


Figure 1. Clinical Manifestations of AT patients

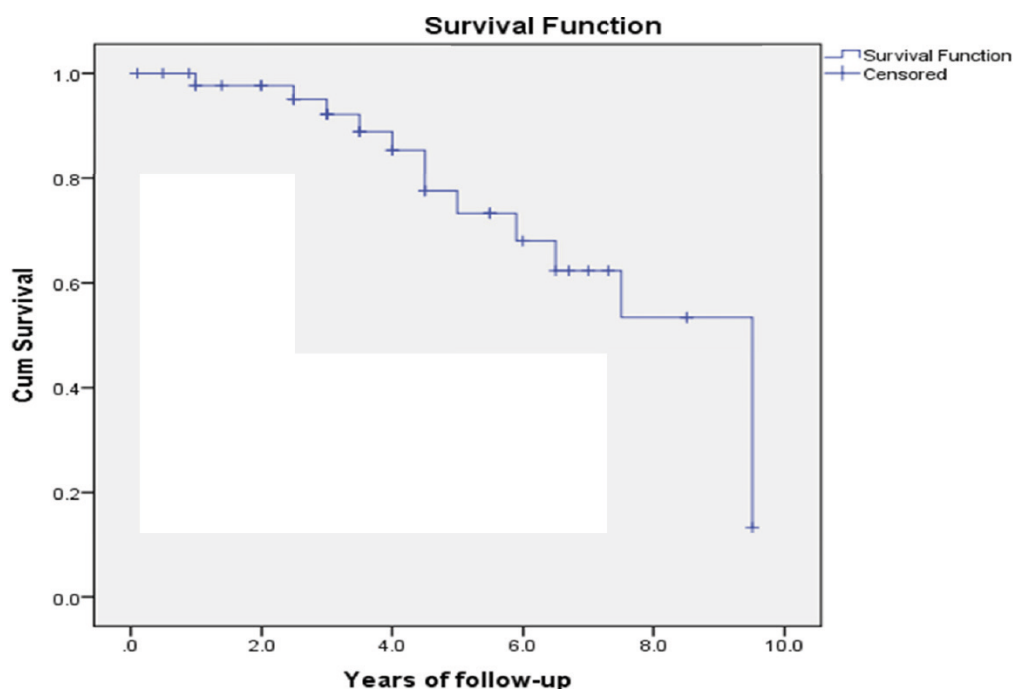


Figure 2. Survival analysis of 120 patients with ataxia telangiectasia using Kaplan–Meier overall survival curve (log-rank test)

During the follow-up period, 14 (12.4%) patients were deceased due to the AT-related complications, accounting for the median of overall survival of 10 years with the age at the time of death extended over a wide range (**Figure 2**).

Discussion

Herein, we described 120 unrelated AT patients from the Iranian immunodeficiency registry center. Due to its autosomal recessive inheritance, AT frequency varies with the degree of consanguinity in different regions of the world. Generally, consanguineous marriages can increase the risk of autosomal recessive disorders such as AT in Iran and other Middle Eastern countries (24, 25). In this study, the prevalence of parental consanguinity was determined to be about 76% of the patients. The clinical features of AT are intricate and are characterized by cerebellar degeneration, immunodeficiencies, recurrent infections, susceptibility to malignancies, and cutaneous abnormalities (26). The AT patients manifest hallmarks of progressive spinocerebellar neurodegeneration such as truncal

swaying, gait ataxia, and muscle hypotonia (27). Ataxia is usually the first diagnostic sign, appearing in the toddler years when children begin to sit and walk. Between the age of 8–12 years old, the movement disability cause a child to be confined to a wheelchair (28). In our study, gait abnormality was the first presentation and all the AT patients were suffering from ataxia. In addition to ataxia, telangiectasia is the main clinical feature that its onset is commonly after the age of 3 years old (29). In the AT patients, the ocular telangiectasia become more prominent by age increasing as well as other ocular manifestations such as strabismus and nystagmus (30). Approximately 92% of our AT patients were involved with telangiectasia at the age of 4 years old. Measurement of serum AFP concentration is another main diagnostic marker in AT, as it is elevated in more than 90% of patients (31). All of our patients had the increased level of AFP at the time of initial diagnosis.

Recurrent infections are observed in approximately 80% of the AT patients due to impaired antigen receptor recombination and class

switching recombination (CSR) infections (32-34). Generally, lymphopenia, decreased CD4+ and/or CD8+ T cells, impaired antibody production, hypogammaglobulinemia, selective IgA deficiency, and IgG subclass deficiency are abundant findings in the individuals with AT (35). The most prevalent manifestation of immunodeficiency in AT is respiratory infection that often appeared early in the life and is often progressed by age increasing and neurological deterioration (15, 36). Based on the findings of this study, it can be concluded that, more than 80% of the AT cohort are suffering from recurrent infections, especially respiratory tract infections (*upper respiratory tract infections; URTI and lower respiratory tract infections; LRTI*). Moreover, the other type of infections including gastrointestinal and urinary infections rarely occur in our cohort.

The most common symptoms of respiratory infections in AT are a recurrent or persistent productive cough, wheezing, and chest congestion. These serious symptoms may occur in the lack of other systemic signs, which lead to delayed treatment. If pulmonary symptoms are not considered, severe manifestations of the respiratory disease such as recurrent pneumonia, bronchiectasis, and lung fibrosis can appear (3). Therefore, administration of prophylactic antibiotics should be considered for the treatment of the prolonged respiratory infections (9).

In addition, the AT patients may suffer from noninfectious complications including organomegaly, growth failure, poor pubertal development, gonadal atrophy, insulin resistant diabetes, cutaneous abnormality, and cardiovascular diseases (26, 36-38).

Hepatosplenomegaly is a lymphoproliferative complication that often occur in the PID patients due to immune system impairment. Massive hepatosplenomegaly with mild organ dysfunction and

enzyme abnormalities may contribute to the severity of the AT patients (39-43). Our results showed that, about 20% of patients were involved with hepatosplenomegaly.

Growth failure can be observed in genomic instability syndromes such as Nijmegen Breakage syndrome (NBS), Fanconi anemia, Cockayne syndrome, and AT (44). Generally, growth delay and small stature are common features of AT. Also, in more than 20% of our patients, apparent failure to thrive was present. This was often correlated with the impaired immune system or neurologic disability. It seems that, nutritional problems, oropharyngeal dysphagia, infections, and reduced growth factor and hormone levels are related to this growth impairment (45, 46). A recent study showed that, the concentrations of Insulin-like growth factor-1 (IGF-1) and IGF binding protein 3 (IGF-BP3) were low in the majority of the AT individuals (45).

Other noninfectious complications associated with AT include the impaired eye movements and visual impairment. Visual disturbances due to degeneration of the cerebellar cortex manifest in the AT patients including oculomotor apraxia, nystagmus, strabismus, and vestibulo-ocular (VOR) abnormalities (47-49). In our patients, nystagmus was the common visual impairment.

Heterogeneity of immunoglobulin profiles is a common feature of the AT patients and paying attention to it may be beneficial for clinical prognosis prediction (40). Based on serum Ig profile, the AT patients can be classified into normal Ig level, selective IgA deficiency, hypogammaglobulinemia, and hyper IgM phenotype (50-52). In the AT patients, the most prevalent humoral immune defect was IgA deficiency; however, approximately 10-20% present with HIgM phenotype (40). We observed the decreased serum levels of IgG and IgA compared to the age-matched controls, which were about 30% and 81% of the patients, respectively. The Increased serum level

of IgM was also observed in about 31% of the patients. It seems that, in our AT patients with immunodeficiency, the most common humoral immune defect was the IgA deficiency.

Conclusions

Generally, the quality of life and survival in the AT patients reduced due to the infectious complications. The infectious complications are a common cause of morbidity and mortality in AT (36, 53), as about 50% of the patients die in early age mainly due to respiratory failure (54). The life span of these patients could be prolonged by the immunoglobulin replacement therapy and antibiotic treatment, as well as vaccination against common bacterial respiratory pathogens such as hemophilus influenzae and pneumococci (15). Follow up evaluation of immune system in our patients indicated that, antibiotic and IVIG replacement therapy can decrease the severity of infections.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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