

## Original Article

# Clinical Presentation of Ataxia-Telangiectasia

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**Introduction**

Ataxia-telangiectasia (A-T) is a rare autosomal recessive disorder that exhibits progressive neurological dysfunction, immunological impairment, telangiectasia, chromosome instability, radio-sensitivity, infection susceptibility and cancer predisposition.<sup>1</sup> Other abnormalities such as growth retardation, diabetes, sterility, absence of thymus or thymus atrophy and premature aging have been observed, as well. Movement disorders include both cerebellar ataxia and extra-pyramidal presentations (tremor, chorea, dystonia, myoclonus, parkinsonism).<sup>2</sup> Neurological symptoms include: abnormalities in eye movement (apraxia, abnormal gaze and nystagmus), neuropathy, dysarthria, dysphagia and cognitive decline.<sup>3</sup>

In lab data, elevated alpha fetoprotein (AFP) is usually noted. Immune dysfunction can present in clinical manifestations (recurrent infections), or in lab data (lymphopenia, decreased levels of IgA, IgG2 and CD markers).<sup>4</sup>

Biallelic mutation in the A-T mutated (*ATM*) gene, which encodes a serine/threonine protein kinase (found on chromosome 11q22-23), results in A-T complications.

This gene is involved in the repair of DNA double-strand breakage and cell cycle control. Its impaired function results in genome instability which manifests as neurodegeneration, radio-sensitivity and neoplasm susceptibility in A-T patients.<sup>5</sup>

Cerebellar ataxia appears as the first symptom at the age of 1–5 years in A-T patients; the patients require wheelchair due to progression in movement disorders in the second decade of their life. They might survive to the third decade of their life; however, there have been patients who lived to their 40s and 50s.<sup>6</sup> Treatment is only symptomatic and protective and most of the patients die following decline in pulmonary function or malignancy (mostly lymphoma and leukemia).<sup>7</sup>

A-T has been reported to be more prevalent in Iran, which might be due to higher degree of inbreeding in Iranian families. There are studies which have addressed the patients with A-T.<sup>8,9</sup> However, long-term follow-up of patients with immune deficiency disorders is of importance due to the complications which might appear along with the disease progression.<sup>10</sup> On the other hand, the knowledge about the clinical and immunological

features would help with early diagnosis of A-T and the selection of the appropriate treatment procedure. So, in the present study, the clinical and immunological features of patients with A-T were assessed in a long-term follow-up period.

## Patients and Methods

### Patients

This study reports a case series of 18 patients who were referred to the immunology tertiary center of Shiraz University of Medical Sciences, Shiraz, Iran, in the period of 2008-2018. Patients who fulfilled the A-T, were followed for clinical presentations during this time.

### Inclusion Criteria

Diagnosis was confirmed based on the documented medical data, patient history, lab data, physical examination, and genetic analysis as needed. According to the European Society for Immune Deficiency Disorders (ESID),<sup>11</sup> the diagnostic criteria for A-T include increased chromosomal breakage due to radiation, progressive cerebellar ataxia, oculocutaneous telangiectasia, elevated levels of serum  $\alpha$ -fetoprotein and immunoglobulin disorders.

In this study, the clinical symptoms of movement disorders, neurologic symptoms, systemic features and lab data were considered.

### Exclusion Criteria

We excluded patients with other types of ataxia (ataxia without telangiectasia, Friedreich's ataxia, Marie's ataxia, Charcot-Marie-Tooth hereditary neuropathies, hereditary olivopontocerebellar atrophy, Nijmegen breakage syndrome, Bloom syndrome, cerebral palsy, Cogan oculomotor apraxia, AT-like disorder), brain mass and presentations of other immune system disorders.

### Data Collection

Data were collected over a 10-year period of follow-up. Data were recorded in data gathering sheets, based on the medical records. History was taken; clinical presentations (cerebellar ataxia, apraxia of eye movement, chromatosis, parkinsonism, tremor, epilepsy, failure to thrive, dysarthria, dysphagia, cutaneous and conjunctival telangiectasia, infections, metabolic disorders, characteristic face or posture and malignancy), lab data ( $\alpha$ -fetoprotein level, immunoglobulin level and CD markers) and demographic features (age, sex, family history, consanguinity, age at the first clinical symptoms and diagnosis) were considered. Data are presented descriptively and compared with previous studies. Valid percents are considered for data presentation.

## Results

### Demographic Features

The demographic data are shown in Table S1 (see online

Supplementary file 1). Eleven (61.1%) female and seven (38.9%) male patients from 18 families were followed. Consanguinity was recorded in 13 (72.2%) families: 11 parents were first cousins and two parents were beyond second cousins. Two patients were cousins and A-T was observed in the families of two other patients (uncle and cousin). Miscarriage was observed in four (22.2%) mothers and two (11.1%) patients reported early death in siblings. The mean age of the patients was  $10.92 \pm 3.24$  years (5–16 years).

### Clinical Presentations

The onset of clinical manifestations was at  $2.56 \pm 2.55$  years of age while the mean age of diagnosis was  $6.46 \pm 2.67$  years. Balance problem was reported by parents as the first clinical presentation. The mean age of the ataxia presentation was  $2.83 \pm 2.45$  years and telangiectasia was observed at the mean age of  $4.37 \pm 1.92$  years.

The most frequent clinical presentation was ataxia which was present in all of the patients (100%). Dysarthria and dysphagia were seen in 13 (76.5%) and 7 (38.9%) patients, respectively. The frequencies of apraxia in eye movement, choreatic movement, parkinsonism, tremor and epilepsy presentations are reported in Table 1. Reflex was reduced in 9 (50%) patients and 7 (38.9%) patients were wheelchair-bound.

Six (33.3%) patients were not educated in schools; however, the other patients (except for one patient who attended special needs school) were studying in normal schools (one patient was not at school age). No patient seemed to be mentally retarded.

The presentation of conjunctival telangiectasia [in 14 (77.8%) patients] was higher than cutaneous telangiectasia [10 (55.96%) patients].

Characteristic face and failure to thrive were recorded

**Table 1.** Frequency of Clinical Presentations in This Study in Comparison with Two Previous Studies

Clinical Manifestations	Present Study	Moin et al <sup>8</sup> (2007)	Levy et al <sup>16</sup> (2018)
Cerebellar ataxia	100	100	96
Apraxia of eye movement	72.2	80.6	82
Dysarthria	76.5	100	99
Epilepsy	16.7	8.7	—
Conjunctival telangiectasia	77.8	83.8	84
Cutaneous telangiectasia	55.6	70.2	60
Failure to thrive	28.6	37.5	—
Choreoathetosis	44.4	87.1	89
Recurrent sinopulmonary infection	64.3	75.0	—
Parkinsonism	44.4	—	41
Tremor	77.8	—	74
Malignancy	16.7	—	22
Elevated alpha fetoprotein level	100	—	98

in eight (44.4%) and four (22.2%) patients, respectively. Thrombocytopenia was observed in three (16.7%) patients and one (5.5%) patient was admitted with hemolytic anemia. AFP level was raised in all of the patients (mean: 261.85 for 14 patients).

Malignancy was reported in three (16.7%) patients. One patient was diagnosed with acute lymphoblastic leukemia (ALL) at the age of 6 years; this patient is alive and receiving chemotherapy. Two other patients were diagnosed with ALL at the age of 11 and 14 years, and expired subsequently.

#### Immune Function and Infections

Lymphopenia was recorded in three (27.3%) patients. IgM and IgE levels were normal in all of the patients; however, reduced levels of IgG and IgA were observed in five (33.3%) and six (40.0%) patients, respectively.

The number of T-cells (CD3<sup>+</sup>, CD4<sup>+</sup> and CD8<sup>+</sup> cells) was reduced in 11 (73.3%) patients. Reduced number of B-cells was observed in seven (46.7%) patients (lab data are shown in Table S2, online Supplementary file 1).

Infections (pneumonia, otitis media, sinusitis) were observed in 12 (70.6%) patients, and 11 (73.3%) patients were admitted to hospital due to infections or for other reasons.

#### Medication and Treatment

Six (33.3%) patients received IVIG. The patients received antibiotics as prophylaxis and antioxidants (vitamin C and E), as needed.<sup>12</sup> The patients were followed every 6 months for any possible changes in immune system presentations or blood cell counts. No patient received bone marrow transplantation.

#### Mortality

Two of the patients (11.1%, both males) expired following ALL at the age of 11 and 16 years. One of them refused receiving chemotherapy. Pneumonia and renal failure coexisted with ALL in one of the patients.

#### Discussion

The complications of A-T appear in the first years of life and result in movement and neurological disorders. A-T is a debilitating disease with poor prognosis and imposes several limitations in daily activities. The patients need wheelchair in the second decade of their lives. A-T eventually causes death in the third decade of life, mostly due to lung diseases or malignancies.<sup>13</sup>

The incidence of A-T varies from 1:40 000 to 1:100 000. It is more prevalent in Iranians maybe because of the high prevalence of consanguinity in Iranian families. Based on the previous reports, consanguinity was observed in 81.1% of patients with A-T in Iran.<sup>8</sup> In this study, 13 (72.2%) patients were from consanguineous families.

Due to allelic heterogeneity of the *ATM* gene and

mutations, there is heterogeneity in clinical manifestations. As described in a study by Taylor et al, atypical forms of A-T have been observed with slower progression rate or adulthood onset. Several mutations have been identified in the *ATM* gene. There are mutations which result in complete loss of function. However, missense mutations and leaky splice site have been observed in patients with retained *ATM* activity, resulting in milder forms of A-T.<sup>14</sup> In a study by Staples et al, the correlation between genetic and immunodeficiency was determined. It was reported that immunological phenotype is more severe in patients with no activity of *ATM* compared to the patients with little activity.<sup>15</sup> In the present study, late onset of the disease symptoms was noted in two patients.

As A-T has been defined since 1957, the clinical manifestations are well described. As shown in Table 1, the results described here are compared to a recent review by Levy and Lang<sup>16</sup> and a previous study of Iranian patients by Moin et al,<sup>8</sup> which includes the combined results with the studies conducted by Woods and Taylor<sup>9</sup> and Boder and Sedgwick.<sup>17</sup>

Neurodegeneration in A-T patients presents as cerebellar symptoms, as well as peripheral neuropathy, extra-pyramidal impairments and cognitive disorders. Brain stem nuclei and nerve tracts are also affected.<sup>18</sup> To find out more about the connectivity of cerebrum and cerebellum, Sahama et al have suggested further studies focusing on diffusion magnetic resonance imaging.<sup>19</sup>

In the present work, ataxia, tremor and conjunctival telangiectasia were the most frequently observed clinical presentations, respectively. Ataxia was observed in all of the patients, in consistence with other studies which have reported ataxia in 100% of the patients.<sup>9</sup> Telangiectasia usually appears at 5-8 years of age. However, it might not be present in every patient.<sup>6</sup> In the study by Moin et al, conjunctival and cutaneous telangiectasia were observed in 83.8% and 70.2% of the patients, respectively.<sup>8</sup> In the present study, conjunctival and cutaneous telangiectasia were reported in 14 (77.8%) and 10 (55.6%) patients, respectively.

Dysphagia appears in the second decade of life of A-T patients which might result in malnutrition, aspiration and lung problems.<sup>6</sup> Krauthammer et al have reported malnutrition in 61.4% of patients that was more prominent in the patients with dysphagia. Failure to thrive was observed in A-T patients; however, the observed failure to thrive was not secondary to nutritional problems. In the previous studies, 40-80% of A-T patients were observed to have failure to thrive,<sup>20</sup> while in the present study, failure to thrive was observed in four (22.2%) patients. Growth retardation progresses over time in A-T patients. Percutaneous endoscopic gastrostomy was suggested by Stewart et al for children above the age of 8 years.<sup>21</sup>

Endocrine abnormalities were studied by Nissenkorn et al<sup>22</sup> Impairments in gonadal function and sexual hormones

were observed. Also, decreased levels of 25-hydroxy vitamin D and insulin-like growth factor-1 were reported. Diabetes was observed in patients with A-T, due to impaired glucose metabolism; however, thyroid dysfunction was not observed. Adrenal and pituitary glands were normal in function. In the present study, none of the patients were observed to have diabetes or thyroid dysfunction.

Along with the clinical presentations, AFP level, immunoglobulin levels (IgA, IgG2), CD markers, ATM protein expression level or *ATM* gene mutation investigations are considered for A-T patients.

Immunological defects might be observed in A-T patients in the cellular and/or humoral immune system.<sup>15</sup> Although infections are expected due to the immune dysfunction, the clinical observations are not in favor of susceptibility to infections. In a study by Nowak et al, viral infections were uncommon and infections with *Candida* were not frequently observed. In our study, there were two patients with low B-cell numbers, while no manifestation of infections was observed. According to previous studies, the level and pattern of immune dysfunction are variable among different patients. Although reduction in B-cell lymphocytes was reported in 73% of the patients in the study by Nowak et al,<sup>4</sup> the number of B lymphocytes has been reported to be normal or elevated in other studies.<sup>23</sup> Reduced levels of T-cells, IgA, IgG and IgE have been also observed in other studies. In the present study, 11 (73.3%) and 7 (46.7%) patients were observed with reduced number of T-cell and B-cells, respectively. There were also six (40.0%) and five (33.3%) patients with reduced IgA and IgG levels, respectively.

Immunodeficiency may result in chronic inflammatory and auto-immune diseases such as immune thrombocytopenia, vitiligo and arthritis.<sup>6</sup> In the present study, thrombocytopenia was noted in five (27.8%) patients. Two (11.1%) patients were recorded to have anemia and hemolytic anemia.

Malignancy occurrence rate has been reported to be 22–24% in different studies.<sup>6,16,24</sup> Leukemia and lymphoma were mostly present at younger age, while at older age (>20), solid tumors were also observed. In a study by Suarez et al, lymphoid malignancies were reported with the highest incidence. They reported an association between immune deficiency and the risk of cancer, and IgA deficiency was found to be associated with lymphoid malignancies.<sup>25</sup> In the present study, three (16.7%) cases were observed with ALL. ALL was diagnosed for one of the patients, prior to the diagnosis of A-T.

Pulmonary dysfunction and cancer have been reported as the main causes of death in A-T patients. Morrel et al studied 263 A-T cases for mortality rates. They reported an elevated mortality rate, peaking at the age of 15 years. Lymphoma was the main type of cancer observed. Higher mortality rates and cancer manifestations were observed in black patients compared to white patients.<sup>26</sup> An increased

survival rate was observed in patients who received treatment for cancer.<sup>25</sup>

Although there is not any established therapy for A-T patients, steroids and dopaminergic drugs have been found effective in improving neurological symptoms, along with antioxidants as neuroprotective. Antibiotic prophylaxis and IVIG are beneficial in decreasing the severity and frequency of infections. Supportive therapy is also effective. Considering future therapies, gene therapy approaches seem promising.<sup>24</sup>

Since A-T patients are radio-sensitive, X-ray exposure and radiotherapy must be limited to urgent situations. Expert oncologists should be consulted to choose the suitable drugs for chemotherapy in A-T patients. Live vaccines must be avoided.<sup>18</sup>

The lifespan for patients with A-T is 25 years. The only available therapeutic approach is symptomatic and supportive therapy. Education, genetic consultation and regular examinations are suggested for A-T patients. Further investigations on genetic determinants can facilitate finding targets for therapy.

Although this study was conducted in an area with high rate of consanguinity and genetic disorders,<sup>27-29</sup> the number of patients was limited due to the rarity of this disease and the limited geographic area of the study. A-T is a progressive disease with clinical presentations which appear over time. So, follow-up of the patients is of importance to observe the clinical presentations in the course of the disease. The data presented here may facilitate the diagnostic procedure and consequently, disease management.

#### Authors' Contribution

SA, HE, NE, SHN and HN have contributed to the design and conception of the study. NE and SHN contributed to data acquisition and manuscript drafting. SA, HE and HN contributed to data acquisition and interpretation; and critically revised the manuscript. All the authors have approved the manuscript. The study was supervised by HE.

#### Conflict of Interest Disclosures

There is no conflict of interest.

#### Ethical Statement

This study was approved by ethics committee of Shiraz University of Medical Sciences (Ethics No. IR.sums.med.rec.1397.584).

#### Supplementary Materials

Supplementary file 1 contains Table S1 and S2.

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