Ataxia telangiectasia in Turkey: multisystem involvement of 91 patients

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Background: **Ataxia telangiectasia (AT) is a genetically based multisystemic disorder. We aimed to make a comprehensive evaluation of multisystem involvement in AT by describing clinical features and outcome of 91 patients.**

Methods: **Medical records of the patients who were diagnosed and followed by a multidisciplinary approach during a 27-year period (1988-2015) were reviewed retrospectively.**

Results: **Forty six female and 45 male patients with a mean follow-up period of 39.13±4.28 months were evaluated. The mean age at the time of symptom onset and diagnosis were 15.4±1.09 months and 73.61±4.11 months, respectively. Neurological abnormalities were progressive truncal ataxia, nystagmus, dysarthria, oculomotor apraxia and choreoathetosis. Thirty one patients (34.1%) became dependent on wheelchair at a mean age of 12.1±2.8 years. Eleven patients (12.1%) became bedridden by a mean age of 14.7±1.8 years. Cranial magnetic resonance imaging revealed pathological findings in 47/66 patients. Abnormal immunological parameters were determined in 51/91 patients: immunoglobulin (Ig)A deficiency (*n*=38), lymphopenia (*n*=30), IgG (*n*=15) and IgG_2 (*n*=11) deficiency. Occurrence of recurrent sinopulmonary infections (*n*=45) and bronchiectasis (*n*=22) were found to be more common in patients with impaired immunological parameters (*P*=0.029 and *P*=0.023, respectively). Malignancy developed in 5 patients, being mostly lymphoreticular in origin and resulted in death of 4 patients.**

Conclusions: **AT is a long lasting disease with multisystem involvement necessitating multidisciplinary follow up, as described in our cohort. Early diagnosis of malignancy and supportive treatments regarding pulmonary and neurological health may prolong survival and increase the quality of life.**

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Key words: **ataxia telangiectasia; immunodeficiency; malignancies; neurological impairment**

Original article

Introduction

Ataxia telangiectasia (AT) is a rare genetic disorder caused by a defective DNA damage response. It is inherited in an autosomal recessive manner with the incidence of 1:40 000-300 000 live births in the USA.[1] Ataxia telangiectasia mutated (*ATM*) is the gene responsible for this disorder and has been mapped to band 11q22-23.[2] ATM protein, the product of the *ATM* gene, is a serine/threonine protein kinase involved in many critical pathways of cellular cycle including DNA damage response, cell cycle regulation and cellular response to oxidative damage.[3] In the absence of ATM protein, neither repair nor the apoptosis of the cells with damaged DNA can be achieved. This phenomenon leads to cerebellar neurodegeneration, progressive cerebellar atrophy and ataxia.

AT is a chronic childhood illness, which may influence multiple organ systems and appear with a wide range of signs and symptoms. The disease is mainly characterized by progressive neurologic impairment beginning commonly with ataxia, ocular telangiectasia, variable immune deficiency and increased risk of malignancy. The objective of the present study is to comprehensively evaluate multisystem involvement in AT by describing the clinical features and outcomes.

Methods

The study population included 91 patients with AT, who

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had been diagnosed and treated with a multidisciplinary approach (Departments of Pediatric Infectious Diseases and Clinical Immunology, Pediatric Neurology and Genetics) during a 27-year period (1988-2015). Medical records of these patients were reviewed retrospectively. Patients were considered to have AT if they displayed characteristic neurologic features (ataxia, oculomotor abnormalities and dysarthria) together with elevated serum alpha-fetoprotein level (AFP) more than twice the upper limit of the normal and ocular telangiectasia. Retrospective confirmation of the diagnoses was made according to clinical diagnostic criteria defined by European Society for Immunodeficiencies (ESID).[4]

Patients' medical records in different clinics were reviewed to gather data regarding demographic features, family history of AT and malignancy, presenting age and clinical features, age at diagnosis, clinical history of infections, features of neurologic and other system involvements, cranial magnetic resonance imaging (MRI) findings, AFP levels, occurrence of malignancy and mortality. Immunological parameters including immunoglobulin (Ig) levels, lymphocyte subgroup analysis (CD3+, CD3+CD4+, CD3+CD8+, CD3+, CD3+CD19+, CD3+CD20+, CD3+CD16+CD56+) were recorded. Serum IgG, A, M and IgG subgroups were analysed nephelometrically by Beckman Coulter Immage 800 (Beckman Coulter Inc, Fullerton, CA, USA). Values that were two standard deviation below the age-controlled average were considered as low.[5] Alpha-feto protein levels were analysed by Beckman Coulter Unicel DXI 800 (Beckman Coulter Inc, Fullerton, CA, USA) and concentrations >13.6 ng/mL were accepted as high.

Chromosomal analysis was performed in 7 patients at the Molecular Pathology Laboratory in the Department of Pathology and the Medical Laboratory, David Geffen Medical School, California University. Radiosensitivity assay and evaluation of ATM protein kinase activity were analysed in 24 patients. Patients with a mutation in the *ATM* gene consistent with AT, patients with negative ATM protein detected by western blotting analyses and patients with low radiosensitivity indexes (2%-20% for AT, 33%-68% for normal individuals) were defined as definitive AT.

This study was approved by the Ethical Committee of Istanbul Medical Faculty.

Statistical analysis

Statistical analysis of data was performed with statistical package for social science (SPSS) for Windows version 21.0 (SPSS 21.0, SPSS Inc. USA). Categorical and numerical variables between groups were compared by using Fisher Chi-squared test and independent sample *t* tests, respectively. Statistical significance limit were accepted as $P<0.05$.

Results

Ninety one AT patients (46 female, 50.5%) with a mean follow-up period of 39.13±4.28 months were evaluated (Table 1). The mean age at the time of symptom onset and diagnosis were 15.4±1.09 months and 73.61±4.11

Table 1. Clinical and laboratory features of the patients with ataxia telangiectasia (continuous variables)

Variables	Mean±standard deviation
Age of symptom onset (mon)	15.40±1.09
Age of diagnosis (mon)	73.61±4.11
White blood cell (/mm^3)	8811.36±401.18
Absolute lymphocyte count (/mm^3)	2892.42±194.53
IgG (mg/dL)	971.62±44.01
IgG_2 (mg/dL)	145.11±58.33
IgM (mg/dL)	219.90±15.49
IgA (mg/dL)	63.04±7.99
IgE (kU/L)	29.18±11.67
CD3 (/mm^3)	1702.43±164.73
CD4 (/mm^3)	947.25±135.43
CD8 (/mm^3)	769.75±77.97
CD19 (/mm^3)	370.58±67.31
CD16+56+ (/mm^3)	556.14±60.35

Ig: immunoglobulin; CD: cluster of differentiation.

Table 2. Clinical and laboratory features of the patients with ataxia telangiectasia (categorical variables) (*n*=91)

Variables	*n* (%)
Gender (male)	45 (49.5)
Paternal consanguinity	53 (58.2)
Family history of ataxia telangiectasia	27 (29.7)
Family history of malignancy	25 (27.5)
Presenting symptom	
Only ataxia	53 (58.2)
Only telangiectasia	2 (2.2)
Only recurrent infections	8 (8.8)
Oculocutaneous telangiectasia	84 (92.3)
Ataxia	91 (100)
Intellectual disability	22 (24.2)
Neurological outcome	
Able to walk independently	49 (53.8)
Wheelchair dependent	31 (34.1)
Bedridden	11 (12.1)
Dermatological findings	46 (50.5)
Presence of immunologic disorder	51 (56.0)
Recurrent sinopulmonary infections	40 (43.9)
Development of bronchiectasis	22 (24.2)
Malignancy	5 (5.5)
Intravenous immunglobulin treatment	14 (15.4)
Antibiotic prophylaxis	31 (34.1)
Lymphopenia	30 (33.0)
Low IgG level	11 (12.1)
Low IgG_2 level	15 (16.5)
Low IgA level	38 (41.8)
High IgM level	32 (35.2)
High IgE level	6 (6.6)
Low CD3 count	24 (26.4)
Low CD4 count	32 (35.2)
Low CD8 count	31 (34.1)
Low CD19 count	38 (41.8)
Low CD16+56+ count	3 (3.3)

Ig: immunoglobulin; CD: cluster of differentiation.

months, respectively. Elevated serum alpha-fetoprotein level (mean value: 203.6±178.9) was present in 95.8% of the patients (92 out of 96). Mean diagnostic delay was found as 56.16±33.97 months with a range of 0-156 months. Paternal consanguinity was present in 53 patients (58.2%, Table 2). Nine sibling pairs with AT were identified. An overall positive family history for AT were reported in 27 patients (29.7%). Genetic mutations were studied in 7 patients, all of whom had biallelic mutations in *ATM* gene: homozygous c.27delT in two siblings; homozygous c.4973del; homozygous c.20+1G>A in two siblings, homozygous c.3576G>A and compound heterozygous c.6047A>G/c.887ins. Deficiency of ATM protein was identified in 24 patients, including 7 patients with positive genetic analysis. Furthermore, one patient had ATM protein but lacked kinase activity. The rest of the patients (*n*=66) had probable diagnosis of AT based on clinical features.

Ataxia was the sole presenting symptom in 53 patients (58.2%) at a mean age of 17.8±11.2 months (median: 15 months; min-max: 9-72 months). Eight patients (8.8%) were admitted with recurrent infections at a mean age of 7.7±2.6 months (median: 6.5 months; min-max: 7.7-2.6 months). Both were observed in 28 patients (30.8%) at the time of presentation, the mean of which was 18.6±12.3 months (median: 14.5 months; min-max: 11-72 months). Although all patients had ocular telangiectasia, only two patients were presented with oculocutaneous telangiectasia alone, at the ages of 62 months and 36 months, respectively. Both patients had a history of late walking and repated falls that the parents did not perceive as a serious problem.

When clinical features of 9 sibling pairs with AT were analyzed, it was detected that neurological outcome was similar in 6 sibling pairs, all had to use wheel chair at similar ages. In 7 sibling pairs, immunological dysfunction was detected in both siblings. In one sibling pair, similar dermatologic manifestations, which were hypopigmented macules, were observed. Malignancy developed in one of the affected sibling pair, but not in the other.

Neurological manifestations

Progressive truncal ataxia was observed in all patients (Table 1). The median age for onset of ataxia was 15 months (range: 9-72 months) with a mean of 17.69±1.17 months. Other neurological abnormalities were reported as nystagmus (*n*=49, 52.7%), dysarthria (*n*=60, 64.5%), oculomotor apraxia (*n*=49, 52.7%) and choreoathetosis (*n*=35, 37.6%). Recurrent convulsions were observed in 3 patients (3.2%). Variable levels of intellectual disability were recorded in 22 patients (24.2%). During the follow-up period, 31 patients (34.1%) became dependent on wheelchair at a mean age of 12.1±2.8 years. Eleven patients (12.1%) became bedridden by a mean age of 14.7±1.8 years. Cranial MRI was performed in 66 patients. Pathological findings were determined in 47 patients (72.5%) as follows: cerebellar atrophy (*n*=28, 59.5%), cerebellar vermis hypoplasia (*n*=13, 27.6%), and increased hyperintense signals on cerebral white matter (*n*=6, 12.7%).

Immunological and infectious manifestations

Forty six patients (50.5%) experienced normal range and frequency of infections as expected for their age. The predominant type of infections was sinopulmonary in the rest of the patients. Of the 45 patients, 40 patients (88.8%) had a history of recurrent upper respiratory tract infections more than 8 episodes/year and 31 patients (68.8%) suffered from more than one episode of lower respiratory tract infection including pneumonia, acute bronchitis or bronchiolitis. Bronchiectasis developed in 22 patients (24.2%). Recurrent gastroenteritis, urinary tract infections and skin abscess were rare type of infections that were encountered in 7.6%, 3.2% and 2.1% of the patients, respectively. Immunological parameters of the study patients are summarized in Tables 1 and 2. Forty (44%) patients displayed no abnormalitiy in their immunologic evaluation. IgA deficiency (<10 mg/dL) was the most common humoral abnormality (*n*=38, 41.8%), followed by IgG_2 and IgG deficiency (*n*=11, 12.1% and *n*=15, 16.5%, respectively). Concomitantly low levels of IgA and IgG_2 were determined in 9 patients (9.9%). Increased levels of IgM were found in 32 patients (35.2%). Lymphopenia was observed in 30 patients (33%). CD4+ lymphopenia was evident in 32 patients (35.2%). Decreased B cell counts were present in 38 patients (41.8%). Occurrence of recurrent sinopulmonary infections and bronchiectasis were found to be more common in patients with impaired immunological parameters than those without (61.8% *vs*. 36%, *P*=0.029; 84.6% *vs*. 50%, *P*=0.023, respectively). Intravenous Ig replacement therapy was given to 14 patients (15.4%), who had impaired immunity together with recurrent infections and/or bronchiectasis. The patients, who were mostly suffering from recurrent upper respiratory infection without an overt immunological dysfunction, were followed up with antimicrobial prophylaxis (*n*=31, 34.1%).

The patients who had immunological dysfunction were compared with those who did not, regarding other clinical features such as neurological presentation and course, age at onset, initial presentation, infections and malignancy. No differences were found other than recurrent infections,

which were more frequently detected in patients with immunological dysfunction, as expected (P=0.018).

Malignancy

Malignancy developed in 5 patients (3 girls) at a mean age and duration of follow up of 9.9±2.4 years and 27.6±6.06 months, respectively. All of these patients also had a positive family history of malignancy. Overall 25 patients (27.5%) had a positive family history of malignancy, which included hepatocellular carcinoma as the most common, followed by gastrointestinal system tumors, primary lung cancer and breast cancer. Types of malignancies included Hodgkin lymphoma (n=2), Burkitt lymphoma (n=1), acute lymphoblastic leukemia (n=1) and adenocarcinoma of the large bowel (n=1). Four of these patients died secondary to complications of their malignancies including infections. The patient with adenocarcinoma of the bowel is a 15 year old girl, who is still on chemotherapy and in clinical remission.

Other clinical findings

Forty six patients (50.5%) had dermatologic manifestations like hyperpigmentation (n=6), cafe au lait spots (n=15), hypopigmentation (n=14), grey hair (n=7), acanthosis nigricans (n=1), eczematous skin lesions (n=1), multiple nevi (n=1). One patient had chronic generalized squamous papular rash which were more intense on face and extremities. The pathological examination of punch biopsy revealed nodular granulomatous dermatitis. Hydroxychloroquine has been initated recently to this patient, whose response to treatment is not yet known.

Growth retardation was encountered in 41 (45%) patients. The percentage of immune deficient patients with growth retardation was significantly higher than those without (54.9% *vs*. 32.5%, P=0.033).

Outcome

Among the 67 patients who were followed-up, 8 (5 female/3 male) died at the mean age of 103.4±50.6 months (median: 89.5 months; range: 42-150 months). The median disease duration was 58 months (range: 12-108 months) for the patients who had died, and 17 months (range: 16-180 months) for the patients who were still alive at the time of research. Mortality occurred in two patients with Hodgkin lymphoma, one patient with Burkitt lymphoma and one patient with acute lymphoblastic leukemia due to the complications of malignancy. The other four patients died of chronic lung disease and bronchopulmonary infections. An immunological dysfunction was present more frequently in the patients who had died, compared to those who had not (87.5% *vs*. 12.5%, P=0.054)

Discussion

The present report describes the clinical and laboratory features of 91 patients with AT, diagnosed and followed up in a single center during a 27-year period. The first cases in the literature consistent with AT were published in 1926 by Syllaba and Henner,[6] who described three adolescent Czech siblings with progressive chorea, dystonia and ocular telangiectasia. Following different designations for the similar cases, the term ataxia telangiectasia was first used by Boder and Sedgwick in 1957.[7] High levels of serum AFP was described in patients with AT in 1972 by Waldmann and McIntire.[8] Immunological affection and predisposition to malignancy were further defined in subsequent reports.[9,10] After the discovery of the *ATM* gene, atypical clinical pictures were defined in genetically proven cases with unusual findings like absence of telangiectasia or mild neurological involvement.[10-12]

Consanguineous marriages which are known to increase the risk of autosomal recessive disorders are common in Turkey.[13] Although we do not have a national registry of AT and most other autosomal recessive disorders, it could be argued that they are more frequently seen in our country compared with western countries due to high rate of paternal consanguinity, which was present in more than half of our patient group (58.2%). Presence of AT in nine and 18 sibling pairs in the current and the Moin's study[14], respectively, indicates the importance of determining genetic analysis of the patients and prenatal diagnosis in the subsequent pregnancies. Unfortunately, genetic mutations could be studied in a minority of our patients. Although genetic analysis is increasingly made in AT patients, it is still unsatisfactory due to rarity of the laboratories equipped for this and the high cost of the procedure.

Our study population showed an overall expected spectrum of clinical findings in AT. The vast majority of our patients presented with ataxia approximately at the age of independent walking. It is the most important diagnostic hallmark of the disease and may also appear at later ages.[14] Due to the progressive nature of ataxia, 46% of our cases became unable to walk in the follow up period, similar to other studies.[14-16] Dysarthria, oculomotor apraxia and choreoathetosis are among other commonly recorded clinical signs of spinocerebellar degeneration, as also previously reported.[14-16] In consistence with these clinical findings, cerebellar atrophy and cerebellar vermis hypoplasia were common pathologies in cranial MRI of our cases. Intellectual disability was reported to be found in 33% of the Boder and Sedgwick's cohort in 1963.[17] Our retrospective analysis revealed that intellectual disability was recorded in 24% of the patients' files. However, which formal tests had been used in defining the intellectual disability was

not clear. Thus, our data was not certain in terms of defining neurocognitive status of the patients with AT. A recent work reported that cognitive impairments in AT present early in the disease and, widespread and deeper cognitive deficits manifest in later stages.[18]

Immunological aspects of AT show great variability among patients; some have no abnormal immunological parameters or increased rate of infection, while some may have varying degrees of immunological dysfunction. Generally, immune deficiency is seen in about half of AT patients.[14,16,19] As consistent with the literature, 56% of our cases had an abnormality in their immunological evaluation. When present, immune deficiency mostly affects both the cellular and humoral immune system, in a combined form. Low Ig levels (mostly IgG/IgA), low IgG_2, impaired antibody responses and lymphopenia affecting mostly CD4 cells and reduced B cell numbers can be seen.[19-21] A similar pattern of immunological impairments were detected in our cases as well. High IgM levels can be detected in AT patients in varying rates from <1% to 60% in different studies and the rate was 35.2% in the present study.[19,21-23] When high IgM level is present together with low IgG/IgA, AT can be misdiagnosed as hyper IgM syndrome.[24] In this study, increased IgM levels were determined in 6 patients with IgG deficiency (18.2%) and in 14 patients with IgA deficiency (42.4%). Staples et al[19] suggested that the known role of ATM in Ig class-switch recombination might play a role in high IgM levels seen in 17% of their cohort. They also found that AT patients with mutations resulting in complete loss of ATM kinase activity had a markedly more severe immunological phenotype than those with mutations resulting in residual kinase activity.[19] Thus, they suggested that, by determining the genetic characteristics, it can be predicted which patients with AT will suffer from severe immune deficiency and resulting infections.[19] Another important finding regarding immune dysfunction in AT was reported by Chopra et al,[21] who found that for the majority of patients with AT, the severity of immune deficiency did not deteriorate significantly with time. Certainly, it should be remembered that due to progressive neurological dysfunction, all patients with AT, irrespective of their immune status, may experience recurrent pulmonary infections as a result of aspiration in later stages of the disease.

Although 44% of patients with AT had normal immunological parameters in our cohort, 50.5% of the patients experienced normal range and frequency of infections, meaning that some patients with laboratory abnormalities in immunological evaluation did not suffer from an excess of infections. This discrepancy between the clinic and laboratory was indicated by other studies as well.[19,20] Although there is no clear explanation, Staples et al[19] suggested that differences in innate immune mechanism may contribute to this finding. The majority of infections experienced by our patients were sinopulmonary in origin, as consistent with the literature.[13,18,19] Intravenous Ig replacement was needed at a similar rate to other reports (15.4% *vs*. 12.5% and 13%).[19,20] Bronchiectasis developed in about one fourth of our patients. Sinopulmonary infections and bronchiectasis occurred more frequently in patients with impaired immunological parameters. Schroeder et al[22] evaluated pulmonary disease in a large cohort of patients with AT. They indicated that a combination of multiple factors such as increased susceptibility to infections, inability to clear infections, recurrent aspiration, ineffective airway clearence and an abnormal immune response may play a role in the etiology of chronic pulmonary disease and bronchiectasis.[22] They emphasized the point that early recognition and aggressive treatment is very important because of the irreversible nature of late manifestations of chronic pulmonary disease.

Patients with AT have about 100-fold increased risk of developing malignancy than the population.[25] Cancer is the second most common cause of death in AT patients, following pulmonary disease.[14] Lymphoma, leukemia and tumors of the gastrointestinal tract are the predominant malignancies determined in these patients.[25,26] In a recently published large retrospective cohort, 24.5% of 279 patients with AT developed a cancer.[26] The authors determined that B-cell non-Hodgkin lymphoma, Hodgkin lymphoma and acute lymphoblastic leukemia occured at a high rate and earlier age than carcinomas.[26] Overall survival was found to be significantly shorter in AT patients who developed cancer compared with those who did not (15 *vs*. 24 years).[26] In our cohort, 5.5% of the patients (5/91) with AT developed a malignancy, most of which were lymphoreticular in origin. All except one patient with adenocarcinoma of the gastrointestinal tract died due to complications of malignancy. In the present cohort, a positive family history of malignancy including hepatocellular carcinoma, gastrointestinal system tumors, primary lung cancer and breast cancer were present in 27.5% of all patients with AT and 100% of the patients with AT who developed malignancy. This finding is consistent with other studies which also found increased rate of malignancies in the families of AT patients.[27] However, tumor spectrum was observed to be different in AT patients and their parents, similar to our findings.[27] Therefore, it is uncertain that if the increased rate of malignancy in families of AT patients is a manifestation of carrying heterozygote AT gene or not.

Ocular telangiectasia is a cardinal feature of AT and was described in the first reports of the disease.[17] Other cutaneous manifestations include abnormalities of pigmentation, poikiloderma, seborrheic dermatitis,

acanthosis nigricans, hirsutism and cutaneous granulomas.[28-30] In our cohort, all patients had ocular telangiectasia and half of the patients had a cutaneous manifestation other than oculocutaneous telangiectasia, most of which were abnormalities of pigmentation. Nodular granulomatous dermatitis was determined in one patient. Noninfectious cutaneous granulomas, which are thought to be a manifestation of immune dysregulation, are rarely seen in AT.[29,31] Immunosuppressive agents like topical and systemic steroids were used in treatment.[29,31] Although not used in a patient with AT yet, hydroxychloroquine has been shown to have immunomodulatory, anti-inflammatory, anti-proliferative and photoprotective effects.[32-34] It has been recently used with success in a patient with primary immune deficiency presented with rash consistent with cutaneous lupus erythematosus.[35] Since nodular granular dermatitis, although not the same as the aforementioned case, is an autoimmune skin manifestation, we have started hydroxychloroquine in this patient recently based on its proven actions on the immune system in order to avoid the immunosupressive effects of systemic steroids.

Chronic childhood disorders can adversely affect nutritional status and growth of the patients. Forty-five percent of our cases showed retardation of growth. It was significantly more common in patients with immunological dysfunction. In the literature, failure to thrive has been reported in 38%-72% of children with AT.[14,16,17] Several causes may underlie this condition including oropharyngeal dysphagia, aspiration, chronic catabolic state due to recurrent infections and pulmonary complications.[20,36-39] Nutritional intervention like tube feeding from an early age was recommended for these patients.[36,38] On the other hand, neurodegenerative process may affect the hypothalamic-pituitary axis leading to endocrine dysfunction. Correspondingly, Voss et al[39] found that a disturbance was present in the growth hormone–insulin like growth factor-I axis in 58.3% of AT patients in their study and low levels of growth hormone were the result of reduced central growth hormone secretion.

There are some limitations of this report. First, it is a retrospective study which covers a long period of time. Data were retrieved from patients' files. Therefore, all details about their clinical course and outcome could not be obtained. Second, molecular genetic confirmation could be made in a small number of patients due to lack of laboratory facilities for genetic analysis of AT covered by health insurance in our country. Therefore, in this cohort, diagnosis of AT was mostly based on clinical diagnostic criteria defined by ESID.[4]

Ataxia telangiectasia is a rarely seen genetic disorder, which is possibly more common in countries where consanguineous marriages are common. It is a syndrome with multisystemic involvement, which can be variable in severity from patient to patient due to presence of different mutations ending with different phenotypes. Here, we reviewed the multisystemic involvement of AT by describing the clinical and laboratory features of a 91-patient cohort. Multidisciplinary follow up and supportive care should be provided for these patients. Since chronic lung disease and malignancy are the most important issues in survival of these patients, every effort should be made to maintain pulmonary health and to provide early diagnosis and treatment of malignancy.

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