ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALERJİ İMMÜNOLOJİ

doi: 10.21911/aai.006
Asthma Allergy Immunol 2023;21:3-10

RESEARCH ARTICLE

Received: 04.04.2022 • Accepted: 18.08.2022
Online Published: 13.01.2023

Evaluation of Clinical and Laboratory Features of Patients with Ataxia-Telangiectasia

Mehmet KILIC[1], Omer GUNBEY[2], Erdal TASKIN[3], Bunyamin DAG[2], Elif KUCUK[2], Fatma Betul GUNBEY[2], Askin SEN[4]

[1]Department of Pediatrics, Division of Allergy and Immunology, Firat University Faculty of Medicine, Elazig, Turkey
[2]Department of Pediatrics, Firat University Faculty of Medicine, Elazig, Turkey
[3]Department of Pediatrics, Division of Neonatology, Firat University Faculty of Medicine, Elazig, Turkey
[4]Department of Medical Genetics, Firat University Faculty of Medicine, Elazig, Turkey

Corresponding Author: Mehmet Kilic ✉ drmkilic@gmail.com

ABSTRACT

Objective: Ataxia-telangiectasia is a rare genetically inherited disease with multisystem involvement. We evaluated the clinical and laboratory features of patients diagnosed in our clinic with ataxia-telangiectasia.

Materials and Methods: The files of children diagnosed with ataxia-telangiectasia in our clinic between 2008 and 2021 were evaluated retrospectively.

Results: Twelve children diagnosed with ataxia-telangiectasia were included in the study. Fifty percent of our patients were boys, and 50% were girls. There was a family history of ataxia-telangiectasia in seven patients and consanguineous marriage between the parents of 11 patients. The mean age at diagnosis of the patients was 5.5 years. Our cases had telangiectasia in the conjunctiva (n=8), a nevus (n=5), cafe-au-lait spots (n=5), hypopigmentation (n=4), and skin telangiectasia (n=3). Eosinophilia (n=1), lymphopenia (n=7), and neutropenia (n=1) were also found. Our patients were determined to be below -2 SD for age in terms of IgE levels in 25%, IgA levels in 58.3%, and IgG levels in 8.3%. Antibody responses were negative for anti-hepatitis B surface (HBs) IgG (n=5), anti-measles IgG (n=7), anti-mumps IgG (n=6), anti-VZV IgG (n=6), anti-tetanus IgG (n=6), and anti-hepatitis A virus IgG (n=3). Seven patients had homozygous ataxia-telangiectasia gene (ATM) mutations.

We most commonly detected homozygous c.4940T>G (p.L1647R) and homozygous c.6047A>G (p.D2016) mutations. Alpha-fetoprotein (AFP) levels were elevated in all patients. We started intravenous immunoglobulin (IVIG) therapy for 10 patients.

Conclusion: Ataxia and telangiectasia were the most common findings of the disease, followed by immunological findings, growth retardation, and pigmentation abnormalities.

Keywords: Ataxia-telangiectasia, immunodeficiency, sinopulmonary infection, childhood, complication

INTRODUCTION

Ataxia-telangiectasia (AT) is characterized by progressive cerebellar ataxia, dysarthria, ocular apraxia, cutaneous and conjunctival telangiectasia, immunodeficiency, recurrent sinopulmonary infections, hair and skin changes, endocrine abnormalities, growth retardation, infertility, chromosomal instability, hypersensitivity to ionizing radiation, and elevated serum AFP levels. The defective gene function results in chromosome breaks and increases cancer risk (especially leukemia and lymphoma). The disease frequency is estimated to be 1-4:100.000. Ataxia-telangiectasia is rarely seen and is caused by a mutation/mutations in the *ATM* serine/threonine kinase gene. *ATM* (MIM, * 607585) has an autosomal recessive inheritance pattern for AT (1).

ORCID Mehmet Kilic / 0000-0002-1089-1316, Omer Gunbey / 0000-0002-8888-2954, Erdal Taskin / 0000-0001-6387-1741, Bunyamin Dag / 0000-0002-6949-0111, Elif Kucuk / 0000-0003-1011-9905, Fatma Betul Gunbey / 0000-0001-7057-8623, Askin Sen / 0000-0002-3534-5477

The gene that causes the disease is localized on the long arm of chromosome 11 (11p22-23). The gene encodes an *ATM* serine/threonine kinase associated with phosphatidylinositol 3-kinase, which provides familial mitogenic signal transduction, deoxyribonucleic acid (DNA) recombination and stability, intracellular protein transport, and cell cycle control (2). Without *ATM* serine/threonine kinase, DNA breaks cannot be repaired, and a signal transduction pathway disorder occurs. As a result, patients experience hypersensitivity to ionizing radiation, immune deficiency, and infertility (3).

The first sign of the disease is ataxia, which usually occurs when the child starts walking. Neurological symptoms including intentional tremors, oculomotor apraxia, and nystagmus may also be seen concurrently with the disease. Generally, telangiectasias begin to appear on the conjunctiva and earlobe around two years of age, and telangiectasias can also be seen, including pigmentation anomalies (hyperpigmentation, hypopigmentation, cafe-au-lait spots, albinism), papulosquamous facial eruptions, and hypertrichosis (4,5). Immunodeficiency findings also occur in patients with AT. Defects in humoral and cellular immunity may develop in varying degrees. IgA deficiency is the most common, and IgE deficiency is also detected. IgG deficiency and IgG subgroup deficiency are less common. In addition, 71% of patients respond poorly to pneumococcal vaccines (6).

In the study, we evaluated the clinical, immunological, and laboratory features and socio-demographics of patients with ataxia-telangiectasia.

MATERIALS and METHODS

The files of the patients who were followed up with an AT diagnosis at our hospital's Pediatric Allergy and Immunology Clinic were reviewed retrospectively. We diagnosed AT in patients who presented to our clinics according to the diagnostic criteria determined by the European Society for Immunodeficiencies (ESID) (7). We checked the complete blood count, serum AFP, blood immunoglobulin (Ig) (IgA, IgM, IgG, IgE) levels, IgG subgroup analysis, flow cytometry analysis of lymphocyte subgroups (CD3+, CD4+, CD8+, CD19+) CD20+, CD16+56+, CD45 RA+, CD45 RO+, HLA DR+), IgG response to vaccinations and previous infections; complement (C) 3, C4, CH50 levels; brain magnetic resonance imaging (MRI), and sequence analysis of the *ATM* gene in patients with AT.

The immunological tests of the patients were measured twice. The values of lymphocyte subgroups, serum Ig levels, and IgG subgroups were compared with normal limits adjusted for age. A defect in the humoral immunity was defined based on immunoglobulin values lower than -2 standard deviation (SD) for age, and impairment in cellular immunity was defined as a low absolute lymphocyte count or CD4+ T lymphocyte value adjusted for age. We defined lymphopenia if the absolute lymphocyte count was less than 3000/mm3 under one year of age and less than 1500/mm3 over one year of age. Neutropenia was considered if the neutrophil count was less than 1500/mm3 and eosinophilia if the eosinophil count was equal to or more than 450/mm3 in the peripheral blood. An alpha-fetoprotein level above 8 ng/mL over two years of age was considered high. We administered intravenous immunoglobulin therapy and prophylaxis with trimethoprim-sulfamethoxazole to patients with immunoglobulin levels below -2 SD for age and frequent sinopulmonary infections. The local ethics committee of our university approved the study with decision number 15755 dated 16.02.2021.

Statistical Analysis

For the data analysis, we used the Statistical Package for Social Sciences (SSPS) for Windows (version 22.0). The categorical variables in descriptive statistics were expressed as numbers and percentages, and continuous variables were expressed as median (minimum–maximum) values.

RESULTS

Twelve patients with a diagnosis of AT were included in the study. Fifty percent of our patients were male (n=6) and 50% were female (n=6). We detected median (range) values for the patients' ages as 10.5 (3.5–20) years, the age at the onset of complaints as 5.5 (0.5–9) years, and the age at diagnosis as 5.5 (1.5–10) years. There was a history of A-T disease in their families in 58.3% (n=7) of our patients and consanguineous marriage between parents in 91.7% (n=11) of our patients. The first findings noticed by the families were ataxic gait in 75% (n=9) and frequent infection in 25% (n=3) of the patients. We detected conjunctival telangiectasia in 66.6% (n=8), granulomatous skin lesions in 41.6% (n=5), a nevus in 41.6% (n=5), café-au-lait spots in 41.6% (n=5), hypopigmentation in 33.3% (n=4), and skin telangiectasia in 25% (n=3) of the patients with AT. No malignancy developed in our cases. The aunt of one of our patients developed colon cancer. One of twelve

patients with AT (8%) became wheelchair dependent when he was eight years old (Table I). Our patients had a history of frequent recurrent upper respiratory tract infections. We detected respiratory syncytial virus infection in 8% (n=1) of the patients and influenza infection in 8% (n=1). We detected sinopulmonary infection in 25% of our patients. There was bronchiectasis in 8% (n=1) of our patients. We started intravenous immunoglobulin treatment in 83.3% (n=10) of our patients, and the mean age for starting IVIG therapy was 5.5 (1.5–16) years (Table II).

When the complete blood counts of the cases were evaluated, we found neutropenia in 8.3%, lymphopenia in 58.3%, and eosinophilia in 8.3% of the patients. We did not detect inhalant and/or food allergy according to the results of the skin prick test and/or allergen-specific IgE measurements. The *ATM* gene mutation was detected in 58.3% (n=7) of the patients. We detected the homozygous c.4940T>G (p.L1647R) mutation in 25% (n=3), homozygous c.6047A>G (p.D2016G) mutation in 25% (n=3), and compound heterozygous c.2251-4A>G (IVS14-4A>G) / c.3576G>A (p.K1192K) (p.Lys1192Lys) mutations in 8.3% (n=1). The homozygous c.4940T>G (p.L1647R) mutation has not been previously identified in ataxia-telangiectasia patients. Those with the homozygous c.4940T>G (p.L1647R) mutation belonged to the same family. We did not detect any *ATM* gene mutations in five patients. Four patients without *ATM* gene mutations belonged to the same family.

Patients with the homozygous c.6047A>G (p.D2016G) mutation were unrelated. We determined below -2 SD for age IgE levels in 25%, IgA levels in 58.3%, and IgG levels in 8.3% of patients. Also, the IgM levels were above +2 SD for age in 16.7% of the patients. When the IgG subgroups were evaluated, we found below -2 SD for age IgG2 levels in 50% (n=6), IgG levels in 8.3% (n=1), and IgG4 levels in 66.7% (n=8) (Table II). When the lymphocyte subgroups of the patients were evaluated, we showed below -2SD for age CD3 levels in 58.3% (n=7), CD4 levels in 41.7% (n=5), CD8 levels in 25% (n=3), CD19 levels in 58.3% (n=7), CD20 levels in 50% (n=6), CD45RA levels in 16.7% (n=2), and HLA-DR levels in 25% (n=3). When we evaluated IgG antibody levels that developed against previous infections and/or vaccinations, they were negative in terms of anti-

Table I: Sociodemographic features of patients with ataxia- telangiectasia.

Features	
Male patients, n (%)	6 (50)
Age (year)*	10.5 (3.5-20)
Family history of ataxia-telangiectasia, n (%)	7 (58.3)
Consanguineous marriage between parents, n (%)	11 (91.7)
Age at onset of the complaints (years)*	5.5 (0.5-9)
First manifestation detected by the family, n (%)	
Ataxic gait	9 (75)
Telangiectasia	0 (0)
Frequently recurring infections	3 (25)
Age at diagnosis (years)*	5.5 (1.5-10)
Cutaneous findings, n (%)	
Conjunctival telangiectasia	8 (66.6)
Cutaneous telangiectasia	3 (25)
Café-au-lait spots	5 (41.6)
Hypopigmentation	4 (33.3)
Nevus	5 (41.6)
Granulomatous skin lesion	5 (41.6)
Wheelchair-dependent patients, n (%)	1 (8.3)
Age of becoming wheelchair-dependent (years)*	8
Malignancy development n (%)	0 (0)
Malignancy development in the family n (%)	1 (8.3)
Microcephaly, n (%)	4 (33.3)

*Median (Minimum-Maximum)

Table II: Clinical findings of patients with ataxia- telangiectasia.

Clinical characteristics	
History of recurrent sinopulmonary infection (number per patient/year)*	3 (1-7)
Age of onset of sinopulmonary infection*	3.35 (3-12.4)
Otitis media (number per patient/year)*	2 (0-5)
Diarrhea (number per patient/year)*	3 (1-6)
Cold episodes (number per patient/year)*	3 (2 -7)
Microorganisms detected during infections (culture/PCR) n (%)	
Bacteria	0 (0)
Viruses	2 (16.6)
RSV	1 (8.3)
Influenza	1 (8.3)
Fungus	0 (0)
Other	0 (0)
Bronchiectasis, n (%)	1 (8.3)
Intravenous immunoglobulin therapy, n (%)	10 (83.3)
Age of onset of intravenous immunoglobulin therapy (years)*	5.5 (1.5-16)

*Median (Minimum- Maximum)

Hepatitis B surface (HBs) IgG (n=5) in 41.7%, anti-measles IgG (n=7) in 58.3%, anti-mumps IgG (n=6) in 50%, anti-VZV IgG (n=6) in 50%, anti-tetanus IgG (n=6) in 50%, and anti-hepatitis A virus IgG (n=3) in 25% of the patients (Table III).

We performed brain magnetic resonance imaging (MRI) in 50% (n=6) of our patients and found Joubert syndrome in 16.6% (n=1) and a developmental venous anomaly in 16.6% (n=1) of the cases. The brain MRI results of the other patients were normal.

Table III: Laboratory parameters of the patients with ataxia-telangiectasia

Parameters	n (%)
Lymphopenia	7 (58.3)
Neutropenia	1 (8.3)
Eosinophilia	1 (8.3)
Alpha-fetoprotein elevation	12 (100)
Reduced serum IgG levels	1 (8.3)
Reduced serum IgA levels	7 (58.3)
Increased serum IgM levels	2 (16.7)
Reduced serum IgE levels	3(25)
Reduced serum IgG2 levels	6 (50)
Reduced serum IgG3 levels	1 (8.3)
Reduced serum IgG4 levels	8 (66.7)
Reduced CD3+ T lymphocyte levels	7 (58.3)
Reduced CD4+ T lymphocyte levels	5 (41.7)
Reduced CD8+ T lymphocyte levels	3 (25)
Reduced CD19+ B lymphocyte levels	7 (58.3)
Reduced CD20+ B lymphocyte levels	6 (50)
Reduced CD45RA+ levels	2 (16.7)
Reduced HLADR+ levels	3 (25)
Anti -HBs IgG-negativity	5 (41.7)
Anti -measles IgG-negativity	7 (58.3)
Anti -mumps IgG-negativity	6 (50)
Anti- VZV IgG-negativity	6 (50)
Anti- tetanus IgG-negativity	6 (50)
Anti -HAV IgG-negativity	3 (25)
Mutations in ATM gene:	7 (58.3)
Homozygous c.4940T>G (p.L1647R) mutation	3(25)
Homozygous c.6047A>G (p.D2016G) mutation	3(25)
Compound heterozygous mutation	1(8.3)

Ig: Immunoglobulin, **CD:** Cluster of differentiation.

DISCUSSION

Ataxia-telangiectasia is seen equally in girls and boys. The female/male ratio in studies has ranged between 0.83 and 1.02 (8–10). The age at diagnosis in patients with AT is around 6–7 years. In studies, the AT history rate in AT patients' families has been reported to range between 29% and 45%. The rate of consanguineous marriage between the parents of AT cases has been reported to range between 58.2% and 100% (8–10). Similar to the literature, our patient population consisted of an equal number of boys and girls, and the rate of consanguineous marriage between the parents was 91.7 percent. We found a family history of AT in 58.3% of our patients, which is higher than the studies reported in the literature. This higher rate of family history for AT has urged us to make diagnostic tests earlier. The age at diagnosis of our patients with AT was 5.5 (1.5-10) years.

Different degrees of cellular and humoral immune deficiencies can be seen in patients with AT. About two-thirds of patients with AT have immune system abnormalities (11,12). The most common abnormalities are low levels of one or more immunoglobulin classes (IgG, IgA, IgM or IgG subclasses), inability to produce antibodies in response to vaccines or infections, and lymphopenia, particularly affecting T lymphocytes. A small percentage of cases with AT may have elevated IgM levels with IgG and IgA deficiencies. In this case, the diagnosis of AT can be confused with hyper-IgM syndrome (13). The most common humoral disorder is IgA deficiency, with a rate of 80-90 percent. IgG deficiency is seen at a lower rate (12-27%). IgG2 and IgG4 subgroup deficiencies accompany approximately 50% of cases of IgA deficiency. (3,5,8-10). Moin et al. reported low serum IgM levels in 67.7% of their patients (8). Sanal et al. determined that IgE deficiency might be seen in patients with AT (6). In contrast, Akturk et al. detected IgE elevation in 6.6% of patients with AT. T-cell lymphopenia can also be seen in AT patients (10). Typically, CD4CD45RA+ (naive) T cells are reduced (14). In the studies performed, the frequency of lymphopenia in AT patients ranged between 33 and 63 percent (8-10). In these studies, low CD8 levels were reported in 34.1%, low CD19 levels in 41.8%, low CD4 levels in 35.2-54.5%, and low CD3 levels in 26.4% of the patients (8-10). Some studies have also reported an inadequate response to vaccine protein and polysaccharide antigens in 50% of AT patients (9,13). We found lymphopenia and a decrease in

serum IgA levels – both in 58.3% of our patients. Also, our patients had a low serum IgG level rate of 8.3%, and this information was less than reported in the literature. We also determined low IgG4 levels in 66.7%, low IgG3 levels in 8.3%, low IgG2 levels in 50%, and low IgE levels in 25% of the patients. In light of the literature, a decrease in the IgG subgroup of our patients was comparatively more prominent. This difference may be due to the number of cases studied and genetic and racial factors. We also found that 50% of our cases did not have IgG responses to vaccinations or previous infections.

The diagnosis of AT is primarily based on clinical findings. High levels of serum AFP are detected in 95-98% of patients after age two, and AFP levels increase with age (9,10,13). It is unknown why individuals with AT have higher AFP levels (13). An increase in AFP levels is a reliable diagnostic marker in most cases after two years of age. However, it should not be forgotten that there may be an increase in AFP levels in some tumors (3,6,10). The diagnosis of AT can also be confirmed by demonstrating mutations in the *ATM* gene (15). Sfaihi et al. reported a 54% frequency of *ATM* gene mutations in AT patients (9). Also, differential diagnoses should be made with diseases with DNA repair defects during the AT diagnosis. Ataxia-telangiectasia-like disorder (ATLD) is a rare genomic instability syndrome caused by biallelic variants of MRE11 (meiotic recombination 11) characterized by progressive cerebellar ataxia and typical karyotype abnormalities (16). The main symptoms of ATLD are neurologic and begin during childhood. Patients develop progressive cerebellar ataxia with progressive cerebellar atrophy. They typically present with dysarthria, oculomotor apraxia, writing dystonia, choreiform movements, and walking difficulties. These symptoms are common to those of AT. These symptoms are common to those of AT, but the age of onset is usually later, and the progression is slower and less severe in ATLD (16). Unlike AT patients, ATLD patients do not have ocular telangiectasia. Additionally, clinical and cellular features and the degree of radiosensitivity at the cellular level in ATLD patients are slightly milder than in AT patients (16-18). However, other typical features of AT never reported in ATLD are telangiectasia, high serum alpha-fetoprotein (AFP) levels, immunodeficiency, and proneness to lymphoid tumors. Nijmegen breakage syndrome is another rare paediatric disease caused by NBN biallelic variants that also share some AT features. The main symptoms are severe microcephaly with inconstant mental retardation, growth defects, characteristic dysmorphic features (bird face), and immunodeficiency and proneness to malignancies, as in AT (16-18). *ATM* gene mutations were detected in 58.3% of our cases. In these patients, the following mutations were detected: homozygous c.4940T>G (p.L1647R) in 25%, homozygous c.6047A>G (p.D2016G) in 25%, and combined heterozygous c.2251-4A>G (IVS14-4A>G) / c.3576G>A (p.K1192K) (p.Lys1192Lys) in 8.3%. We did not detect any *ATM* gene mutations in five patients. Four patients without *ATM* gene mutations belonged to the same family.

Various forms of AT have been described in the literature. The severe forms were classified as 'classic', 'typical', 'early onset' or 'childhood-onset' AT, while the milder forms were designated as 'variant', 'atypical', 'late-onset' or 'adult-onset' AT. The terms 'classic' and 'mild' distinguish these two different clinical manifestations of AT. In patients with AT, the first finding is usually ataxia. In the classical form of the disease, ataxia first appears when children begin to sit and walk (13). On average, ataxia was noticed around the age of two. Ataxia can be discerned around 9–12 months post-birth by careful families; however, it may not appear until 8–9 years of age in some patients. Pathological findings, such as intentional tremor, segmental myoclonus, oculomotor apraxia, progressive dystonia of the fingers, and nystagmus may occur in patients over time. Also, cerebellar atrophy is seen in the cranial MRI of the patients (19). Patients with AT usually have unremarkable neuroimaging studies in early childhood. Progressive and diffuse cerebellar atrophy occurs as the disease progresses (9,10,20,21). Children with classic AT tend to start using a wheelchair at the beginning of the second decade of life (1). We found Joubert syndrome in 16.6% of our patients and a developmental venous anomaly in 16.6% of our patients who underwent MRI. MRI scans of other patients were reported as normal. We speculate that cerebellar atrophy was not observed in our patients because we performed cranial imaging in our patients in the very early period. The first finding in our patients was ataxic gait in 75% of the cases. One of our patients became wheelchair dependent at the age of eight.

In patients with ataxia-telangiectasia, the most common finding is telangiectasia. However, the absence of telangiectasia does not exclude the diagnosis of AT. It is usually noticed before two years but the appearance of telangiectasia may be delayed until 5–9 years. Although

it first appears on the bulbar conjunctiva, it can also be seen on the earlobe and nose. It is seen less frequently on the eyelids, neck, elbows and extremities' extensor regions (4,5). Strabismus, oculomotor apraxia, and nystagmus are also seen in AT patients. On the other hand, visual acuity is normal in AT patients (13). Other telangiectasias and cutaneous findings include pigmentation anomalies (e.g. hyperpigmentation, hypopigmentation, café-au-lait spots, macules, albinism), papulosquamous facial eruptions, and hypertrichosis, which can also be seen in AT patients (5). Consistent with the literature, we found conjunctival telangiectasia in 66.6%, nevus in 41.6%, café-au-lait spots in 41.6%, hypopigmentation in 33.3%, and skin telangiectasia in 25% of our cases.

Sinopulmonary infections are common in patients with AT. As a result of these infections, bronchiectasis (more than 25%) may develop in patients of advancing age (8-11,22). Therefore, patients with recurring infections and immunodeficiency should be given IVIG treatment, and prophylaxis should be started with trimethoprim-sulfamethoxazole. Studies have reported that 15.4%–56% of AT patients require IVIG therapy (9,10,23). Also, patients with AT have an increased risk of developing autoimmune diseases. The most common examples of such disorders in AT include immune thrombocytopenia, various forms of arthritis, and vitiligo (13). Growth retardation is also observed in most patients, while endocrine disorders, such as diabetes mellitus, hypothyroidism and hypogonadism, can be observed in some patients (4). There were no accompanying autoimmune diseases in our cases. There was bronchiectasis in 8% of our patients. Also, we started IVIG treatment in 83.3% of patients included in the study. We think that the higher rate of starting IVIG therapy in our patients than in other studies is due to the higher incidence of IgG deficiency subgroups. Cancer incidence (approximately 25%) greatly increases in patients with AT (24,25). Individuals with heterozygous *ATM* gene mutations have been reported to have a shorter lifespan due to ischemic heart disease and development of malignancy involving the breast and gastrointestinal system (26). In a study of 20 patients with ataxia-telangiectasia and their 31 parents, two parents developed malignancies (breast cancer and gastric adenocarcinoma). Immune abnormalities observed in the heterozygous parents of AT patients also revealed the importance of *ATM* protein in normal cellular development (27). No malignancy developed in our cases. One patient's aunt had colon cancer. Head circumference below -1 SD (3–10p) has been observed in approximately 50% of AT patients (28). Microcephaly was present in 33.3% of our cases.

Treatment for AT is geared towards preventing and managing symptoms. These treatment methods include physical therapy, postural drainage, regular injection of immunoglobulins, antibiotic prophylaxis, and avoidance of undue exposure to sunlight. Promising treatments in the investigational therapies include vitamin E therapy as an antioxidant, diazepam and beta-adrenergic blockers for improving motor coordination, deferoxamine to increase genomic stability, levamisole to heighten the immune response, histone deacetylase inhibitors, glucocorticoids for inducing alternate splicing sites in the mutated gene, gene therapy and hematopoietic bone marrow transplant (29). Gene therapy for AT seems to be a promising treatment in the future. However, it has been reported that there are some problems faced by gene therapy for AT. It should be decided which cells to target for gene therapy (e.g. cerebellum, bone marrow). Other challenges include ATM being a very huge gene and producing a very large protein. The production of this large protein means that there is too much DNA to be transported, and many potential vectors cannot carry this payload. Also, the gene's large size may make it technically difficult to cross the blood-brain barrier. Patients should be carefully monitored for increased susceptibility to cancer, one of the potentially harmful consequences of gene therapy (29-32). As another treatment method, bone marrow transplantation from a suitable donor may be a treatment option for selected ataxia-telangiectasia patients to improve immunodeficiency and prevent leukemia and lymphoma. Unfortunately, a successful bone marrow transplant is not expected to improve these patients' neurologic findings, representing the main disability (32). Because AT patients are radiosensitive to ionizing radiation, they require non-myeloablative regimens before bone marrow transplantation. The protocol guidelines for bone marrow transplantation to be applied to patients with AT have yet to be determined (29,33).

In conclusion, AT is an autosomal recessive and progressive neurodegenerative disease that is more common in regions where consanguineous marriages are common. Patients with AT disease should be provided with genetic counseling. It is important to recognize potential malignancies early and prevent the development of chronic lung pathologies.

Conflict of Interest

The authors report no conflicts of interest.

Authorship Contributions

Concept: **Mehmet Kılıç,** Design: **Mehmet Kılıç, Erdal Taşkın,** Data collection or processing: **Bünyamin Dağ, Elif Küçük, Ömer Günbey, Fatma Betül Günbey,** Analysis or Interpretation: **Mehmet Kılıç, Erdal Taşkın, Aşkın Şen, Ömer Günbey,** Literature search: **Bünyamin Dağ, Elif Küçük, Ömer Günbey, Fatma Betül Günbey,** Writing: **Mehmet Kılıç, Erdal Taşkın, Ömer Günbey, Aşkın Şen,** Approval: **Mehmet Kılıç, Erdal Taşkın, Aşkın Şen.**

REFERENCES

1. Bezerra MC GM, Carvalho BTC. Ataxia-telangiectasia: Caracteristicas clinico-laboratoriais. Ataxia-telangiectasia: A review. Rev Bras Alerg Imunopat 2001;24:98-105.
2. Kastan MB, Lim DS. The many substrates and functions of ATM. Nat Rev Mol Cell Biol 2000;1:179-86.
3. Sasihuseyinoglu AS, Yılmaz M, Bisgin A, Dogruel D, Altintas DU, Duyuler G, Serbes M. Ataxia-telangiectasia clinical and laboratory features: Single center results. Pediatr Allergy Immunol Pulmonol 2018;31:9-14.
4. Ersoy F, Berkel AI, Sanal O, Oktay H. Twenty-year follow up of 160 patients with ataxia-telangiectasia. Turk J Pediatr 1991;33:205-15.
5. Greenberger S, Berkun Y, Ben-Zeev B, Levi YB, Barziliai A, Nissenkorn A. Dermatologic manifestations of ataxia-telangiectasia syndrome. J Am Acad Dermatol 2013;68:932-6.
6. Sanal O, Ozbaş-Gerçeker F, Yel L, Ersoy F, Tezcan I, Berkel AI, et al. Defective anti-polysaccharide antibody response in patients with ataxia-telangiectasia. Turk J Pediatr 2004;46:208-13.
7. Ataxia Telangiectasia Diagnostic Guidelines. ESID-European Society for Immunodeficiencies. Available online: https://esid.org/Education/Diagnostic-Criteria-PID (accessed on 6 December 2021).
8. Moin M, Aghamohammadi A, Kouhi A, Tavassoli S, Rezaei N, Ghaffari SR, et al. Ataxia-telangiectasia in Iran: Clinical and laboratory features of 104 patients. Pediatr Neurol 2007;37:21-8.
9. Sfaihi L, Lyonnet DS, Ameur SB, D'enghien CD, Kamoun T, Barbouch MR, et al. Ataxia-telangiectasia in the south of Tunisia: A study of 11 case. Tunis Med 2015;93:511-5.
10. Akturk H, Sutcu M, Somer A, Piskin S, Acar M, Ozmen M, et al. Ataxia telangiectasia in Turkey: Multisystem involvement of 91 patients. World J Pediatr 2017;13:465-71.
11. Nowak-Wegrzyn A, Crawford TO, Winkelstein JA, Carson KA, Lederman HM. Immunodeficiency and infections in ataxia telangiectasia. J Pediatr 2004;144:505-11.
12. Driessen GJ, Ijspeert H, Weemaes CMR, Haraldsson A, Trip M, Warris A, et al. Antibody deficiency in patients with ataxia telangiectasia is caused by disturbed B- and T-cell homeostasis and reduced immune repertoire diversity. J Allergy Clin Immunol 2013;131:1367-75.
13. Rothblum-Oviatt C, Wright J, Lefton-Greif MA, McGrath-Morrow SA, Crawford TO, Lederman HM. Ataxia telangiectasia: A review. Orphanet J Rare Dis 2016;11:159.
14. Meyts I, Weemaes C, Wolf-Peeters CD, Proesmans M, Renard M, Uyttebroack A, et al. Unusual and severe disease course in a child with ataxia-telangiactasia. Pediatr Allergy Immunol 2003;14:330-3.
15. Taylor AM, Byrd PJ. Molecular pathology of ataxia telangiectasia. J Clin Pathol 2005;58:1009-15.
16. Fiévet A, Bellanger D, Valence S, Mobuchon L, Afenjar A, Giuliano F, et al. Three new cases of ataxia-telangiectasia-like disorder: No impairment of the *ATM* pathway, but S-phase checkpoint defect. Hum Mutat 2019;40:1690-9.
17. Taylor AMR, Groom A, Byrd PJ. Ataxia-telangiectasia-like disorder (ATLD)-its clinical presentation and molecular basis. DNA Repair 2004;3:1219-25.
18. Delia D, Piane M, Buscemi G, Savio C, Palmeri S, Lulli P, et al. MRE11 mutations and impaired ATM-dependent responses in an Italian family with ataxia-telangiectasia-like disorder. Hum Mol Genet 2004;13:2155-63.
19. Nissenkorn A, Levi YB, Vilozni D, Berkun Y, Efrati O, Frydman M, et al. Neurologic presentation in children with ataxia-telangiectasia: Is small head circumference a hallmark of the disease? J Pediatr 2011;159:466-71.
20. Sahama I, Sinclair K, Pannek K, Lavin M, Stephen R. Radiological imaging in ataxia telangiectasia: a review. Cerebellum 2014;13:521-30.
21. Hoche F, Seidel K, Theis M, Vlaho S, Schubert R, Zielen S, et al. Neurodegeneration in ataxia telangiectasia: What is new? What is evident? Neuropediatrics 2012;43:119-29.
22. Schroeder SA, Zielen S. Infections of the respiratory system in patients with ataxia-telangiectasia. Pediatr Pulmonol 2014;49:389-99.
23. Çatal F, Topal E, Çeliksoy MH, Ermiştekin H, Kutlutürk K, Yıldırım N, et al. Demographic and systemic manifestations of patients diagnosed with ataxia-telangiectasia. Asthma Allergy Immunol 2014;12:83-9.
24. Reiman A, Srinivasan V, Barone G, Last JI, Wootton LL, Davies EG, et al. Lymphoid tumours and breast cancer in ataxia telangiectasia; Substantial protective effect of residual *ATM* kinase activity against childhood tumours. Br J Cancer 2011;105:586-91.
25. Suarez F, Mahlaoui N, Canioni D, Andriamanga C, d'Enghien CD, Brousse N, et al. Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: A report from the French national registry of primary immune deficiencies. J Clin Oncol 2015;33:202-8.
26. van Os NJH, Roeleveld N, Weemaes CMR, Jongmans MCJ, Janssens GO, Taylor AMR, et al. Health risks for ataxia-telangiectasia mutated heterozygotes: a systematic review, meta-analysis and evidence-based guideline. Clin Genet 2016;90:105-17.

27. Ogulur I, Ertuzun T, Kocamış B, Demirkol Y, Uyar E, Kıykım A, et al. Parents of ataxia-telangiectasia patients display a distinct cellular immune phenotype mimicking *ATM* mutated patients. Pediatr Allergy Immunol 2021;32:349-57.
28. Voss S, Pietzner J, Hoche F, Taylor AMR, Last JI, Schubert R, et al. Growth retardation and growth hormone deficiency in patients with ataxia telangiectasia. Growth Factors 2014;32:123-29.
29. Chaudhary MW, Al-Baradie RS. Ataxia-telangiectasia: Future prospects. Appl Clin Genet 2014;7:159-67.
30. Cortés ML, Oehmig A, Saydam O, Sanford JD, Perry KF, Fraefel C, et al. Targeted integration of functional human ATM cDNA into genome mediated by HSV/AAV hybrid amplicon vector. Mol Ther 2008;16:81-8.
31. Carranza D, Torres-Rusillo S, Ceballos-Pérez G, Blanco-Jimenez E, Muñoz-López M , García-Pérez JL, et al. Reconstitution of the ataxia-telangiectasia cellular phenotype with lentiviral vectors. Front Immunol 2018;9:2703.
32. Du L, Pollard JM, Gatti RA. Correction of prototypic ATM splicing mutations and aberrant ATM function with antisense morpholino oligonucleotides. Proc Natl Acad Sci USA 2007;104:6007-12.
33. Pinho de Oliveira BS, Putti S, Naro F, Pellegrini M. Bone marrow transplantation as therapy for ataxia-telangiectasia: A systematic review. Cancers (Basel) 2020;12:3207.