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Does the Hyper IgM Phenotype Affect Prognosis in Ataxia Telangiectasia?

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ABSTRACT

Objective: To evaluate the characteristics of the patients who were followed-up with the diagnosis of ataxia telangiectasia (AT) and to assess the relationship between the hyper IgM (HIGM) phenotype and their prognosis.

Materials and Methods: From 2007 to 2019, the study included 68 patients aged 3-35 years who were followed-up with the diagnosis of AT. We retrospectively evaluated the clinical and immunological characteristics and follow-up results.

Results: There were 36 girls and 32 boys with a median follow-up of 10 years (1-12 years). The most common complaints upon admission were unsteady walk in 87%, infection in 6%, presence of a family history in 6%, and intracranial mass in 1%. The marriage was consanguineous in 85% of the parents. Ataxia was seen in 100% of the patients, telangiectasia in 97%, and immune deficiency in 88%. Bronchiectasis was observed in 23.5% of the patients, chronic diarrhea in 19%, lymphoproliferation in 15%, malignancy in 10%, autoimmunity in 10%, liver failure in 6%, and granulomatous skin lesions in 6%. Thirteen patients (19%) died during follow-up. The HIGM phenotype was identified in 31% of the patients. Recurrent upper and lower respiratory tract infections (p=0.004 and p<0.0001, respectively), liver failure (p=0.005), and autoimmune diseases (p=0.023) were significantly higher in the HIGM (+) group than the HIGM (-) group. Life expectancy was shorter in the HIGM (+) group with 14 ± 0.73 years (CI 95% 12.55-15.44) compared to the HIGM (-) group with 18 ± 1.64 years (CI 95% 14.77-21.22) (p=0.054).

Conclusion: During the early childhood period and before the characteristic findings of AT develop, the patients might present at a hospital with infections, autoimmunity, lymphoproliferation, or malignancy. Physical examination, high alpha-fetoprotein (AFP) levels and immunological testing provide important data for the correct diagnosis. The HIGM phenotype aggravates the clinical course of the disease resulting in fatalities at an earlier age and at a higher rate.

Keywords: Ataxia telangiectasia, clinic, immunological findings, HIGM phenotype, prognosis

INTRODUCTION

Ataxia-Telangiectasia (AT) develops due to a mutation of the ATM gene and is characterized by neurodegeneration, immune deficiency, radiation hypersensitivity and a predisposition to malignancy (1). The ATM gene is a large gene with 66 exons and is located on the 1q22-23 section of chromosome 1 (2-4). It plays a critical role in establishment of genomic stability, initiation of the response to DNA damage, repair of DNA double helix breaks, and regulation of *Class Switched Recombination*-CSR and T cell receptors (TCR) (2-4). Cerebellar ataxia, oculocutaneous telangiectasia, dysarthritic speech, oculomotor apraxia, choreoathetosis, tremor, immune deficiency, predisposition to malignancy, and ionizing radiation sensitivity are its classical clinical manifestations (5-7).

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The immune deficiency in AT presents itself as hypogammaglobulinemia stemming from the disruption of V(D)J and *class switched* recombinations together with deterioration of thymus development resulting in T cell, specifically naive T cell, lymphopenia (5, 6, 8). Clinical and laboratory findings of the disease are heterogeneous (1, 8-10). Lymphopenia is encountered in 1/3 of the patients and 85% have low levels of IgA and IgE (9, 10). Some patients have low levels of IgG, specifically IgG2. CSR defects are seen at a rate of 21% and hyper-IgM phenotype (HIGM; IgG and IgA levels can be low while IgM levels are normal or increased) at a rate of 10% (11). When these patients are admitted to the hospital at an early age while ataxia or telangiectasia are not present, they are erroneously diagnosed as HIGM (11-15). In patients with the HIGM phenotype, the development of bronchiectasis, autoimmune disease, granulomatous skin lesions and malignancy is more common; the prognosis is more unfavorable and the life expectancy is shorter (11-16).

There is no curative treatment for AT. The success of bone marrow transplantation is around 25% and it cannot prevent the progression of neurodegenerative findings (17). Our aim was to evaluate the characteristics of the patients with a diagnosis of AT and to assess the relationship between the HIGM phenotype and the prognosis.

MATERIAL and METHOD

From 2007 to 2019, 68 patients who presented to the Ankara University School of Medicine, Department of Pediatric Immunology-Allergy and Dr. Sami Ulus Pediatric Health and Diseases Research and Training Hospital and who were diagnosed and followed-up as AT were included in this study. The diagnosis of AT was established according to the *European Society for Immunodeficiencies (ESID)* criteria. Demographic characteristics and clinical symptoms (symptom at admission, physical examination findings, the number and type of previous infections, bronchiectasis, liver failure, malignancy, autoimmunity and the presence of granulomatous skin lesions), laboratory findings [lymphocyte counts, IgG, A, M, E levels, peripheral blood lymphocyte subgroups (CD3+ T, CD3+CD4+ T, CD3+CD8+ T, CDl9+ B, CD3-CD16+CD56+ NK cells), lymphocyte activation responses to PHA and anti-CD3] and the administered treatments were evaluated retrospectively. The patients who had low levels of IgG and IgA, and normal or high levels of IgM with reference to age normals were evaluated as HIGM phenotype (+). The patients were divided into two groups as HIGM phenotype (+) and (-). The groups were compared with regards to above mentioned immunological characteristics and prognosis. In the patients who underwent genetic studies, ATM gene mutations were investigated by utilizing new generation sequencing techniques (Illumina-Miseq- San Diego USA). Approval of the Ankara University School of Medicine Human Research Ethics Board was obtained for this study (Decision no: İ2-122-20). The cases and/or families of the cases participating in the study signed informed consent forms.

Statistical Analysis

Descriptive statistics were given as mean ± standard deviation or median (minimum-maximum) for continuous variables and as frequency (percentage) for categorical variables depending on the normalcy of the data. Comparisons between the HIGM (+) and HIGM (-) groups were made using the Mann-Whitney U test for numerical and Chi-Square or Fisher's Exact test for categorical variables. The Kaplan-Meier method was used when obtaining survival curves for the HIGM positive and negative groups and the Mantel-Cox (log-rank) method was used for their comparisons. A p value of 0.05 was accepted as the level of statistical significance. All statistical analyses were carried out with the Statistical Package for Social Sciences (SPSS, Version 15.0, Chicago, IL). "ggplot2" package for R statistical software was used to visualize the immunological characteristics of the patients (RStudio, Version 1.1.463, RStudio, Inc.).

RESULTS

Demographical Features

A total of 68 patients were included in the study (36 girls/32 boys). A consanguineous marriage was found in 85% (n=58) of the parents while 44% (n=30) of the patients had a positive family history and 30% (n=9) had a positive sibling history. The median age at the onset of symptoms was 12 months (min-max: 3 months -72 months), median age at the time of diagnosis was 60 months (min-max: 3 months - 192 months), median time between the start of the symptoms and the establishment of the diagnosis was 36 months (min-max: 0-174 months), and the mean current age of the patients was 9 years (min-max: 3-35 years). The mean duration of follow-up was 10 years (min-max: 1-12 years).

Clinical Findings

The symptom on first presentation was unsteady walk in 87% (n=59) of the patients, infections (pneumonia, diarrhea) in 6% (n=4) and intracranial masses in 1% (n=1), while 6% (n=4) of the patients applied for family screening due to a relevant family history. Physical examination showed ataxia in all of the patients and telangiectasia in 97% except for two patients who were under the age of two years (Figure 1). Oculomotor apraxia was observed in 83% (n=57) of the patients, dysarthria in 83% (n=57), tremor in 75% (n=51), frequent upper respiratory infections in 72% (n=49), frequent lower respiratory tract infections in 54% (n=37), bronchiectasis in 23.5% (n=16), chronic diarrhea in 19% (n=13), malignancy (Hodgkin and Non-Hodgkin lymphoma) in 10% (n=7), splenomegaly in 10% (n=7), lymphadenopathy in 10% (n=7), autoimmune diseases in 10% (n=7) (thyroiditis: 2, autoimmune hemolytic anemia (OIHA)+immune thrombocytopenia (ITP): 2, ITP: 2, type I DM:1), various degrees of liver failure in 6% (n=4), and granulomatous skin lesions in 6% (n=4) (Figure 2) (4). AFP levels were above age-matched reference levels with a median level of 90 ng/ml (min-max: 15-592 ng/ml). Twenty-one patients had undergone cranial MRI; nine of these had variable degrees of cerebellar atrophy, two had cerebellar and cerebral atrophy, and 10 had normal findings. All the patients with normal cranial MRI findings were below the age of five.

The demographical findings of the patients and their disease-related classical characteristics are presented on Table I.

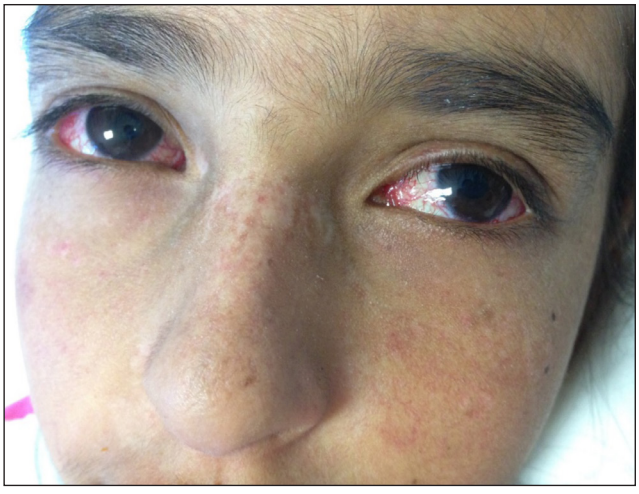

Figure 1. Telangiectasia in the eyes and on the cheeks.

Genetic analyses were performed on 10 patients. Three patients were identified as having new mutations in the AT gene, and were admitted to the hospital with findings other than the classical ones; two had the HIGM syndrome, one had been referred to our department with a preliminary diagnosis of common variable immunodeficiency (CVID).

The first case was diagnosed as Evans syndrome as the patient had ITP, OIHA and splenomegaly at one year of age. While he was being investigated for generalized lymphadenopathy, his IgG and IgA levels were found to be low and the IgM levels to be high, leading to a diagnosis of HIGM syndrome. The patient developed seizures when three years old; a mass was identified in the right frontotemporal region during MRI examination and he was then referred to our department. The physical examination showed that he could not walk and had telangiectasias on the eyes and the auricles in addition to hepatosplenomegaly. His AFP level was 105 ng/ml (0-9ng/ml) and EBV PCR revealed 1840 copies/ml. CD40 and CD40L expressions were normal. The supraclavicular lymph node biopsy result was compatible with B cell lymphoma. Following two courses of R-CHOP treatment, the patient died due to intracranial herniation.

The second case was a four-year old girl. As she was examined for recurrent sinopulmonary infections, her IgG and IgA levels were found to be low, her vaccine responses were insufficient, her IgM levels were normal, and the CD19+ B cell levels were measured as 2%.

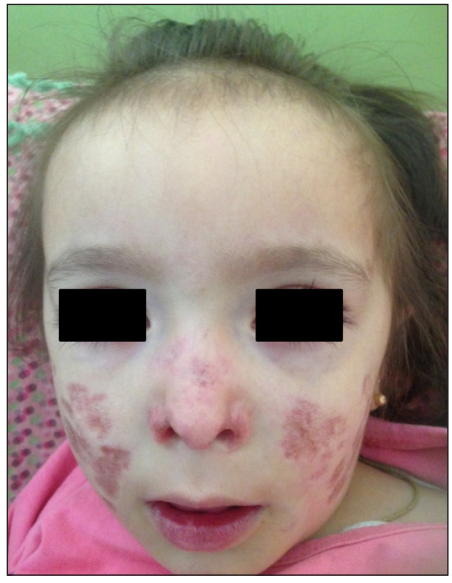

Figure 2. Granulomatous skin lesions.

With these findings, she was referred to our department with the suspicion of CVID. Physical examination revealed hypotonia of the trunk, mild ataxia, loss of strength, ocular telangiectasia and splenomegaly. Her AFP level was 87 ng/ml (0-9).

The third case was assessed for recurrent pneumonia, chronic diarrhea and growth retardation. He had lymphopenia, low levels of IgG and IgA, and high levels of IgM. CMV was measured as 35000 copy/ml. Therefore, a preliminary diagnosis of combined immunodeficiency, HIGM syndrome (CD40, CD40L deficiency) was made and the boy who was 1.5 years old was hospitalized in our department. On his physical examination, there was truncal hypotonia, loss of strength and splenomegaly. CD40-CD40L expressions were normal. The AFP level was 96 ng/ml (0-9).

Newly identified mutations are presented in Table II.

Immunological Characteristics

Defects in at least one of the components of the humoral and/or cellular immune system were present in 88% (n=60) of the patients. There was IgG deficiency in 38% (n=26) of the patients and IgA deficiency in 73.5% (n=50). Among the patients with low levels of IgA, 76% (n=38) had selective IgA deficiency and 24% (n=12) had partial IgA deficiency. IgM deficiency was seen at a rate of 7.4% (n=5). Total IgE levels were measured in 43 patients

Table I. Demographical and clinical features of patients, treatment and follow-up results.

	n	%
Sex (F/M)	36/ 32	52.9/47.1
Consanguineous marriages	58	85.3
Positive family history	30	44.1
Median age at the onset of symptoms (months) [mean (min-max)]	12 (3-72)	
Median time of diagnosis (months) (min-max)	60 (3-192)	
Median delay in diagnosis (min-max)	36 (0-174)	
Current age (year) [median(min-max)]	9 (3-35)	
Ataxia	68	100
Telengiectasia	66	97.0
Oculomotor apraxia	57	83.8
Dysarthria	57	83.8
Tremor	51	75.0
Immunodeficiency	60	88.2
Recurrent upper and/or lower respiratory tract infections	51	75.0
Bronchiectasis	16	23.5
Chronic diarrhea	13	19.1
Lymphoproliferation (LAP and/or splenomegaly)	10	14.7
Malignancy	7	10.3
Autoimmune diseases	7	10.3
Liver failure	4	5.9
Granulomatous skin lesions	4	5.9
Antibiotic prophylaxis	55	80.9
Ig replacement treatment	40	58.8
Follow-up duration (y) [median (min-max)]	10 (1-12)	
Died	13	19.1
Alive	55	80.9

and were low in 95% (n=41). The HIGM phenotype was seen in 31% (n=21) of the patients. Lymphopenia was present in peripheral blood lymphocyte subgroup analysis in 45% (n=31) while 65% (n=44) had low levels of CD3+T cells, 60% (n=41) had low levels of CD4+ T cells, 25% (n=17) had low levels of CD8+T cells, and 50% (n=34) had low levels of CD19+ B cells. The level of NK cells was high in 48.5% (n=33). Lymphocyte activation response for PHA was measured in 44 patients and was low in 50%. CD+CD45RA+CD31+ RTE *(recent thymic emigrant)* measurements were present in 13 patients and 92% had very low levels for their age (4-25%).

The most frequently encountered infections were upper and lower respiratory tract infections. A total of 55 patients had recurrent upper and/or lower RTI; 47% (n 26) of these had low levels of IgG and 52.7% (n=29) had low levels of IgA. Two patients with partial and four patients with selective IgA deficiency did not have frequent infections.

Clinical and Laboratory Findings of the HIGM (+) and HIGM (-) Groups

Liver failure, autoimmunity, upper and lower respiratory tract infections, and lymphadenopathy were significantly more common in the HIGM (+) group. Although bronchiectasis, chronic diarrhea, malignancy, splenomegaly and granulomatous skin lesions rates were higher in the HIGM (+) group, there was no statistically significant difference.

The mortality rate throughout the follow-up period was 33% (n=7) in the HIGM (+) group and 12.8% (n=6) in the HIGM (-) group (p=0.091). Median survival time was 14y (95% CI: 12.56-15.44) for the HIGM (+) group while it was 18y (95% CI: 14.78-21.22) for the HIGM (-) group. There was an insignificant difference between the survival curves of the two groups (p=0.054) (Figure 3). Clinical and laboratory data of the two groups are presented on Table III.

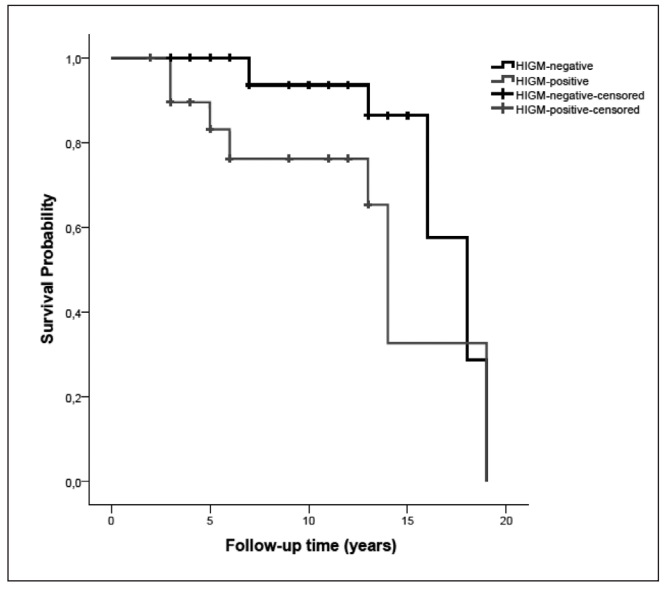

Figure 3. Survival curves of the AT patients with HIGM (-) and HIGM (+).

Table II. Clinical findings and mutation results of patients identified to have new mutations of the ATM gene.

Patient no	Clinical course	Mutation result
P1	1y, pneumonia, OIHA+ITP, SM (Evans Syndrome?) 3y, generalized lymphadenopathy, intracranial abscess? Does not walk, telangiectasia (+) IgG:135mg/dl(304-1231), IgA<6mg/dl(30-107), IgM:4900mg/dl (32-203) HIGM phenotype (+) Lymph node biopsy EBV associated B cell lymphoma Exitus after 2 courses of R-CHOP regimen	P.L1647R(c.4940T>G)
P2	Recurrent pneumonia, hypogammaglobulinemia Common variable immunodeficiency? Loss of strength, unsteadiness and mild telangiectasia and splenomegaly (+) AFP:87ng/ml(0-9ng/ml) IgG: <35mg/dl(640-2010), IgA:<6 mg/dl(26-296), IgM:196mg/dl (52-297) HIGM phenotype (+)	c.8585-15_8596 deletion TTCTTTTTTCTCCAGGTTACATAC Large deletion at exon 58 and intron 59 region
P3	Recurrent pneumonia, chronic diarrhea, growth retardation IgG:242 mg/dl(605-1430) IgA:<6 mg/dl(30-107) IgM:890 mg/dl(66-228) HIGM phenotype (+)	c.312delC(p. F104Lfs*12) (p.Phe104Leufs*12) frame shift and early stop codon

Table III. Clinical findings and results of HIGM (-) and HIGM (+) groups.

	HIGM (-) N= 47 n (%)	HIGM (+) N=21 (n) %	p value	OR (95 % CI)
Frequent URTI (≥8/year)	29 (61.7)	20 (95.2)	0.004	12.41 (1.53-100.64)
Frequent LRTI (≥2/year)	19 (40.4)	18 (85.7)	0.001	8.84 (2.28-34.24)
Bronchiectasis	8 (17.4)	8 (42.1)	0.056	3.45 (1.05-11.33)
Malignancy	4 (8.5)	3 (15.8)	0.401	2.02 (0.41-10.02)
Autoimmune disease	2 (4.3)	5 (25.0)	0.023	7.33 (1.28-41.84)
Liver failure	0 (0.0)	4 (21.1)	0.005	-
Granulomatous skin lesions	2 (4.3)	2 (9.5)	0.582	2.37 (0.31-18.07)
Mortality rate	6 (12.8)	7 (33.3)	0.091	3.42 (0.98-11.90)
Median survival time	18y (95% CI: 14.78-21.22)	14y (95% CI: 12.56-15.44)	(p=0.054)	

URTI: Upper respiratory tract infections, **LRTI:** Lower respiratory tract infections, **OR:** Odds ratio, **CI:** Confidence interval.

CD4+ T cell lymphopenia was seen more frequently In HIGM (+) cases (p=0.030). There were no differences between the two groups with respect to CD3+ T, CD8+ T, CD19+ B cell lymphopenia, NK elevation and insufficient activation response for PHA.

Treatment and Follow-up

Prophylactic antibiotics (trimethoprim-sulfamethoxazole) were administered to 80% (n=55) of the patients while 59% (n=40) had Ig replacement therapy.

Thirteen patients (19%) died during the median follow-up of 10 years (2-12 years). The most common causes of death were respiratory failure accompanied by bronchiectasis in 38%, malignancy in 38%, malignancy + bronchiectasis in 15%, and liver failure in 8%. Of the 2 HIGM cases, one had respiratory failure and the other one had liver failure; both of these patients also had findings of monoclonal gammopathy (IgM levels of both patients were >5000 mg/dl). In this series, bronchiectasis, malignancy, autoimmunity and liver failure, which aggravate the course of the disease, were more common in patients having the HIGM phenotype, together with higher mortality rates and shorter survival.

DISCUSSION

AT is a neurodegenerative disease with an adverse course. The disease usually starts at 1-2 years of age with ataxic walking and unsteadiness in bodily movements; it progresses over time affecting the extremities and speech. Telangiectasia is the second most important finding. It generally appears between 2-8 years of age. It can be mainly seen on the conjunctiva and the auricle followed by the face, neck, and the antecubital and popliteal regions (1, 5, 10). Most of the patients are in a state that would not allow them to perform daily activities during the first decade of life. Many patients die around the third decade due to lung problems or malignancy. The worldwide prevalence is 1/40.000-1/100.000 (18). The incidence in our country is not known. However, Hacettepe, Istanbul and Ege Medical Schools in Turkey have large patient series (19-21). Given the rate of consanguineous marriages is 23% in our country, we can predict that the disease is seen more often than in Western countries. In our study, the consanguineous marriage rate was 88% and the presence of another affected individual in the family was seen in 44%. In AT series of countries like Iran that have high consanguineous marriage rates, the reported consanguinity rates were similar (13).

In AT, the diagnosis is usually established after 1-10 years following the onset of symptoms. In two different studies conducted in Iran in 2007 and 2019, the delays in diagnosis were 58 months and 46 months respectively; in a study from our country it was reported as 56 months (0-156 months) (6,13, 20). In our study, the mean delay in diagnosis was 36 months (0-174 months). When the patients diagnosed between 2015 and 2019 were evaluated, this delay has relatively been shortened to 20 months. Delays in diagnosis and erroneous diagnosis mostly occur in babies with long hospitalizations due to recurrent infections, chronic diarrhea, growth retardation and hypotonicity, as well as in patients who are admitted with autoimmune cytopenias, lymphoproliferation or HIGM phenotype (12, 13, 20).

Cerebellar atrophy on MRI is one of the diagnostic laboratory findings; it develops with age and progresses over time (5). In our study, cerebellar atrophy was detected in 9/21 patients, and cerebellar and cerebral atrophy in 2/21 patients. Normal MRI findings were detected in 10/21 patients who were below the age of five. There were reciprocal translocations between chromosomes 7 and 14 on lymphocytes, low levels of ATM protein, and low ATM kinase activity. The definitive diagnosis is made by demonstrating the presence of a mutation in the ATM gene. Low IgA levels and high AFP levels are not specific to the disease but they support the diagnosis (5). In AT, TREC *(T-cell receptor excision circles)* levels are low; during the newborn period when there are no clinical findings, the disease can be recognized by measuring TREC from a Guthrie card (22). In this study, the diagnosis was made according to the ESID diagnostic criteria on telangiectasia and a high AFP level in a patient with ataxia. Unfortunately, the diagnosis was confirmed by genetic analysis in only 10 patients. Three novel mutations were identified. IgA deficiency is the most common (73.5%) immunological feature of the current study. The RTE level was significantly lower than the age reference level, consistent with the literature.

The frequency of clinical findings in our study (ataxia, telangiectasias, immunodeficiency, oculomotor apraxia, dysarthria, tremor, recurrent upper and/or lower respiratory tract infections) was similar to those of previously reported studies (1, 5, 6, 13, 20).

Malignancies are seen in 25% of the patients. Leukemia and lymphomas are the most common ones. (5-9). Malignancy was seen in 10% of our patients. We may have experienced less malignancy because the patients' referral average age was young (9y, min-max: 3-35y), and median follow-up time (10y, min-max:1-12y) was short. The risk of malignancy increases with age (5, 7, 23, 24). Growth retardation, gonadal atrophy, delayed puberty and autoimmune diseases (especially type I diabetes mellitus) are other frequent findings (25). Granulomatous skin lesions are seen in 10% of the cases (26). In our series, autoimmunity and granulomatous skin lesions were more common in the HIGM (+) group at similar rates as in the literature.

Immunodeficiency findings in AT are variable (10). There are patients who can be admitted with findings of immunodeficiency and severe infections even before the development of ataxia (9-12). On the other hand, there are certain patients who have various defects during the examination of the immune system, but they do not have severe infections. In our series, the rate of immunodeficiency (88%) and the characteristics of immunological parameters (lymphopenia, low levels of IgG, IgA and Ig, low CD3+T, CD4+T cell counts, NK and IgM increase rates) were similar to the rates in the literature (6, 8, 20).

Bronchiectasis was seen at a rate of 20%, yet the rates were higher in AT patients with antibody deficiencies. In the current series, 13 of the 16 patients with bronchiectasis had decreased levels of at least one isotype. Respiratory tract infections, reduced muscle strength, recurrent aspirations, inadequate cleaning of the airways and insufficient immune response lead to chronic lung problems and bronchiectasis. Respiratory failure was reported as being the most important cause of death (7). In our series, respiratory failure and malignancy were identified as the most important causes of death.

In a multicenter study investigating the effects of immunodeficiency on survival in AT patients, IgA levels were not associated with the development of malignancy; however, patients with low levels of IgG2 had higher rates of malignancy and this was reported as the most important cause of death in these patients (7). In the same study, the presence of the HIGM phenotype was reported to decrease life expectancy significantly. In the HIGM phenotype, lung infections started even earlier than ataxia and telangiectasia, which are reported to result in deaths at an early age by progressing into respiratory failure. Seven patients who were HIGM (+) died due to respiratory failure. When the patients previously reported by centers participating in the study are included, 15 (68%) of the 22 HIGM (+) patients died before adolescence.

In our study, the HIGM phenotype was seen at a rate of 31%. This rate is similar to those of other series reported from Iran and Turkey (11, 20, 21). The deficiency in *class switched* immunoglobulins observed in patients with the HIGM phenotype leads to defects in Ig neutralization, complement activation, antibody dependent cellular toxicity, opsonization and immunomodulation. This situation results in increased infection risk as well as findings such as autoimmunity and lymphoproliferation in the patients. Respiratory tract infections, lymphadenopathy, splenomegaly and autoimmunity were more common in the HIGM (+) group compared to the HIGM (-) group in our study.

The HIGM phenotype can mask the diagnosis of AT. Three of the patients with the HIGM phenotype have been admitted to hospitals with complaints such as early onset infections, autoimmune cytopenia, chronic diarrhea, and growth retardation, and have been diagnosed with the HIGM syndrome or CVID. Bronchiectasis, malignancy, liver failure, autoimmune disease and granulomatous skin lesions were more common in patients with the HIGM phenotype. Median survival time was shorter in the HIGM (+) group with 14y ±0.73 (CI 95% 12.55-15.44), compared to the HIGM (-) group with 18y±1.64 (CI 95% 14.77-21.22) (p=0.054). HIGM develops due to CSR defects. CSR defects develop as a result of genetic instability, which is the cause of early aging, radiation sensitivity and DNA double helix breaks. When all these aspects are taken into consideration, we think we can talk about an additional risk for the development of malignancy and an adverse prognosis in patients with HIGM.

Nearly more than 400 mutations of the ATM gene have been identified so far. The diversity and severity of these findings might vary from patient to patient depending on the severity of the mutation. There are atypical forms without oculocutaneous telangiectasia as well as forms with adult onset (5, 7). Patients who have a mild course and who live longer have some residual ATM kinase activity and they are defined as "AT variant" (5, 7). The phenotype-genotype relationship has not been clarified in AT. However, a missense mutation (V2424G) caused by a change in 7271T>G was demonstrated to lead to a predisposition to breast cancer and slower neurological progression (5). A relationship between the HIGM phenotype and genotype has not yet been reported.

Although AT is one of the first described primary immunodeficiencies, there is still no curative treatment. Gradual worsening of the findings, the increasing need for parental care, and the absence of a curative treatment make it difficult to comply with treatment and follow-up. Gene therapies with lentiviral vectors are promising despite having a limited number of successful results (27, 28). Early and correct diagnosis, multidisciplinary treatment practices, and follow-up to prevent the development of complications and organ damage are relevant approaches for increasing the quality of life in these patients.

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