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Ataxia telangiectasia and secondary diseases

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Summary

Aim: Ataxia telangiectasia is a rare autosomal recessive neurodegenerative disorder. In this retrospective study, it was aimed to evaluate

Material and Method: Twenty patients diagnosed as ataxia telangiectasia were retrospectively evaluated in this study. The initial complaints, age at diagnosis, consanguinity of the parents, similar disease history or death of the siblings, the distribution of lymphocyte subset, level of immunoglobulin and the results of thorax tomography, pathological examination, thyroid hormone and auto-antibody related to the secondary disease, clinical courses were analyzed.

Results: The most frequent complaint at admission was unstable gait and repeated sinopulmonary infections. The most common findings were low immunoglobulin A levels and low number of T helper lymphocytes. Three of the patients developed bronchiectasis and two of the patients developed Hashimoto's thyroiditis, whereas two patients who suffered from Hodgkin's lymphoma died due to infections subsequently.

Conclusions: Several secondary clinical situations may be associated with ataxia telangiectasia. Clinical suspicion of this entity allows an early diagnosis and treatment of complications. Genetic counseling is crucial in the prevention of this disease which has no definitive treatment. *(Turk Arch Ped 2012; 47: 40-4)*

Key words: Ataxia telangiectasia, cancer, Hashimoto's thyroiditis, immunological disorder, secondary diseases

Introduction

Ataxia telangiectasia (AT) is a rare disease characterized by progressive cerebellar ataxia, telengiectasies in the eyes and skin, recurrent sinopulmonary infections and humoral and cellular immune deficiency of variable degree, sensitivity to ionizing radiation and increase in the frequency of cancer (1,2). Telengiectasies are typically observed on the conjunctivae, auricle and nose. It is estimated that the incidence of the disease is one per 40 000-100 000 live births. Boys and girls are affected equally with this disease which is inherited in an autosomal recessive pattern (3). As a result of a mutation in ATM gene localized on the chromosome 11q22-23 which codes a protein in charge of control of cellular cycle chromosomal breaks occur (4,5). Because of disruption of arrangement of chromosomes in lymphocytes the risk of lymphoreticular system cancers including leukemia and lymphoma is increased.

The disease starts between the ages of 1-4 years with imbalanced gait. Oculo-motor apraxia and disarthria are common, but it is difficult to determine these in young children (1). In most patients, telengiectasies occur years after neurological findings (6). Increase in serum alpha feto-protein (AFP) level and immunologic abnormalities are observed in 95% of the patients (7,8).

The neuropathological finding in ataxia telengiectasia is atrophy in the brain cortex related to degeneration in granular and Purkinje cells. Some investigators suggest that neurological abnormalities are related to the degree of atrophy (9).

In this retrospective study, it was aimed to define the immunological abnormalities and secondary diseases observed during the follow-up in patients with AT.

Material and Method

Complaints at presentation, ages at the time of diagnosis, consanguinity between the mother and the father, history of a similar disease or death in siblings, immunological evaluation, serum AFP levels, problems confronted during the follow-up and

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prognoses of 20 patients who were followed up in the division of Pediatric Immunology were evaluated retrospectively.

Results

The diagnosis of ataxia telengiectasia was made in the presence of progressive cerebellar ataxia and progressive ocular and cutaneous telengiectasia. AT mutation was not tested in any patient. 20 patients (10 girls and 10 boys) were being followed up because of AT. The mean age at the time of diagnosis was 9 years. It was learned that a similar disease was found in one sibling of 9 patients (45%) and in three siblings of one patient. The complaint at presentation in all patients was gait imbalance and this was present from the time when the patients first started to walk. In 13 patients, a history of recurrent sinopulmonary infection was present. Physical examination revealed ataxia, inadequacy in cerebellar tests, telengiectasias in bulbar conjunctivae in all patients and growth retardation was present in 8 patients (40%). Hodgkin lymphoma was found in two patients during follow-up and both were lost because of infection. Hashimoto thyroiditis was found in two patients who presented with a complaint of swelling in the neck. In three patients, bronchiectasia was observed to have developed as a result of recurrent sinopulmonary infection. Cranial magnetic resonance imaging (MRI) in three patients revealed cerebellar atrophy.

Immunglobulin (Ig) measurements of all patients were done before administration of intravenous immunoglobulin (IVIG). 10 patients had IgA deficiency and 8 patients had IgG2 deficiency. Three patients had IgA deficiency alone, 6 patients had IgG2 deficiency and one patient had hypogammaglobulinemia (IgM, IgG and IgG2 deficiency). In 6 patients, the count of helper T lympocytes was found to be decreased. Serum AFP levels were found to be increased in all patients. Kariotype test revealed chromosome instabilities in three patients. IVIG (400mg/kg) every 3 weeks was administered because of recurrent sinopulmonary infections to 8 patients with immunoglobulin G2 deficiency and to one patient with a lower then normal IgG value (Table 1,2).

Discussion

Neurological symptoms and especially cerebellar ataxia is the first clinical feature to occur in AT and is observed in all patients. Ataxia typically occurs a short time after the children start to walk (at the 12-18th months averagely) (10). The first complaint in all of our patients was gait imbalance and this symptom was present from the day when they first started to walk. Telengiectasias is one of the most characteristic findings of the disease and usually occur at the age of 6-8 years (10). In the literature, the age at the time of diagnosis was reported to be related to the occurence of ocular telengiectasias (2). The mean age in our patient group was 9 years and ocular telengiectasias were present in all of our patients at the time of diagnosis.

Table 1. Characteristics of the patients with ataxia telengiectasia

Gender	Female	10 (50%)
	Male	10 (50%)
Age of onset of the complaint		4 (1.5-7)
Age at the time of diagnosis		9 (2-14)
Finding at baseline	Ataxia	20 (100%)
	Telangiectasia	17 (85%)
Accompanying findings	Recurrent sinopulmonary infection	13 (65%)
	Mental retardation	4 (20%)
	Alopesia areata	1 (5%)
	Growth retardation	8 (40%)
Consanguinity	2nd degree	4 (20%)
	3rd degree	5 (25%)
History of death of sibling		3 (15%)
Familial history of AT		5 (25%)
		mean±SD (the lowest-the highest)
Years of follow-up		8±7 (1-15)
Laboratory	Anemia	5 (25%)
	Lymphopenia	5 (25%)
Cranial MRI	Atrophy in the brain	3 (15%)
Laboratory values		mean±SD (the lowest-the highest)
	IgG (mg/dl)	985±398 (36.8-1700)
	IgA (mg/dl)	77.9±74 (5.85-228)
	IgM (mg/dl)	146±70 (65-309)
	IgE (IU/ml)	25±67 (0.02-305)
	IgG1 (mg/dl)	961±248 (504-1330)
	IgG2 (mg/dl)	112±102 (29-356)
	IgG3 (mg/dl)	50±39 (9-136)
	IgG4 (mg/dl)	21±27 (0.71-90.8)
	CD3 (%)	60±10 (39.1-73.9)
	CD3 CD4+ (%)	32±9 (13.3-52)
	CD3 CD8+ (%)	29±9 (17.7-50)
	CD16 (%)	26±16 (2.2-62.8)
	CD19 (%)	11±6 (1.5-22.4)
	AFP (ng/ml)	203±166 (12.3-579)

AFP: alfa feto-protein, AT: Ataxia-Telangiectasia, CD: cluster of differentiation, Ig: immunglobulin, MRG: magnetic resonance imaging

Table 2. Clinical and laboratory features of the patients with AT who have secondary disease

Patient	A	B	C	D	F	G
Gender	Female	Female	Female	Male	Male	Female
Age at onset of the complaint	7	4	1.5	5	2	5
Age at the time of the diagnosis of AT	9.5	9	12	14	6	8
Accopanying findings	-	Mental retardation	-	-	-	Alopesia areata
Consanguinity	3rd degree	2nd degree	2nd degree	-	3rd degree	-
Familial history of AT	+	-	-	+	-	-
Laboratory values						
IgG (mg/dl)	1200	729	552	872	368	1360
IgA (mg/dl)	228	5.85	19.8	60	6.2	6.67
IgM (mg/dl)	244	83	88.7	174	107	80.6
IgE (ıu/ml)	1	4.5	5	61	5.2	5
IgG1 (mg/dl)	942	114	536	715	1190	1060
IgG2 (mg/dl)	279	40.9	105	47	39.3	16.5
IgG3 (mg/dl)	88	18.4	94.5	10	11.4	14
IgG4 (mg/dl)	51	6.7	6.95	11	9.08	6.95
Absolute lymphocyte count (/mm3)	3040	2260	1872	1970	1686	1930
CD3 (% - absolute count)	58.3-1772	85.2-1925	62.5-1170	54.1-1065	64.7-1090	54.7-1055
CD3 CD4+ (% - absolute count)	34.8-1057	29.6-669	25.1-471	21.8-429	13.3-224	27.4-529
CD3 CD8+ (% - absolute count)	35.6-1082	49.8-1125	32.6-610	33.2-654	29.3-494	32.7-633
CD16 (% - absolute count)	28-851	8.1-183	25.6-479	31.3-616	18.9-318	23.2-448
CD19 (% - absolute count)	12.5-380	3.0-68	2.8-52	3.2-63	22.4-377	6.4-123
AFP (ng/ml)	127.5	5540-3280	145	106	77	53
Secondary disease						
	Hashimoto thyroiditis	Hashimoto thyroiditis	Hodgkin lymphoma and bronchiectasia	Hodgkin lymphoma	Bronchiectasia	Bronchiectasia

AFP: alfa feto-protein, AT: Ataxia-Telengiectasia, CD: cluster of differentiation, Ig: immunglobulin

Although brain MRI is normal in the initial period of the disease, cerebellar atrophy develops a few years after the symptoms start (approximately at the age of 10) (9). Atrophy was found in the cerebellar hemisphere and vermis in our three patients in whom cranial imaging was performed. After increase in serum AFP is defined, AFP level is used in the differential diagnosis. In all of our patients, AFP level was found to be increased at the time of diagnosis. According to the literature the most common humoral immune deficiencies are IgA and IgG2 deficiency and the most common cellular immune deficiency is decreased number of T lymphocytes (10). Similarly, the most common humoral immune deficiencies in our patients were IgA deficiency (76.9%) and IgG2 deficiency (61.5%). In 46.1% of the patients, T lymphocyte count was decreased.

The diagnosis was made clinically in patients with early onset cerebellar ataxia and ocular and cutaneous telengiectasias which are two specific findings of ataxia telengiectasia. In cases where the diagnosis is suspicious, increase in serum AFP level and demonstration of ATM gene mutation are diagnostic. The presence of recurrent sinopulmonary infections and familial history may provide early diagnosis. Since it is an autosomal recessive disease, it is more prevalent in communities in which consanguineous marriages are common like our country (21% in Turkey) (11). In 75% of our patients, consanguineous marriage was present and a history of a similar disease was present in 25%.

Another main finding of the disease is immune deficiency and increased tendency to infections. Different disorders have been described in humoral and cellular immunity. The most common humoral immune deficiencies include IgA deficiency, IgE deficiency and IgG deficiency with a lower rate. IgG2 deficiency may accompany especially in half of the subjects

with IgA deficiency. Immunglobulin M may be mildly high. Immunglobulin changes observed in ataxia telengiectasia are not related to decrease in B cell count, but they arise from disruption of cellular differentiation. Decrease in maturation of B cells to plasma cells which synthetize IgA and IgE or decrease in helper T lymphocte function are blamed. In addition, severe combined immune deficiency may be observed (12-15). Ersoy et al. (12) reported IgA deficiency in 51.3% of the subjects and increase in IgM levels in 26.2% of the subjects in their study in which they evaluated clinical and immunological features of 160 subjects with AT. Mild lymphocytopenia may be present in 1/3 of the patients with ataxia telengiectasia. Cytotoxic T cells are decreased. Decrease in antibiotic responses against viral and bacterial antigens may be observed. In addition, no reaction may be obtained in cutaneous delayed type hypersensitivity tests, decrease in lymphoproliferative response against various antigens and mitogens may be found and antibody irresponsiveness may be observed against specific antigens (12-15). Among our patients, IgA deficiceny was found in 10 patients and IgG2 deficiency was found in 8 patients. Three patients had IgA deficiency alone, 6 patients had IgG2 deficiency and one patient had hypogammaglobulinemia (IgM, IgG and IgG2 deficiency). In 6 patients, decrease in helper T lymphocyte count was found.

As a result of humoral and cellular immune deficiency frequently recurring sinopulmonary infections and ultimately bronchiectasia may develop (12). In 13 of our patients, sinopulmonary infection was found. The reasons for lung involvement which is observed frequently in ataxia telengiectasia patients include recurrent sinopulmonary diseases and bronchiectasia, interstitial lung disease/pulmonary fibrosis, aspiration pneumoniae found as a result of neuromuscular abormalities, swallowing difficulty and weakness in respiratory muscles (16). Brochiectasia was found to have developed in three of our patients. Pediatricians should pay attention to lung involvement in AT patients, but it should be kept in mind that imaging tests involving ionizing radiation should be avoided as much as possible. In addition, AT patients should be immunized with pneumococcal vaccine and influenza vaccine should be administered yearly.

Ataxia telengiectasia is one of the main diseases involving disruption of DNA repair. Among this group of diseases, AT like disorder, Nijmegen-Breakage syndrome, Bloom syndrome and centromeric region instability and face anormalies syndrome (ICF syndrome) should be remembered. In the differentiation of these diseases which are all similar to each other and which have autosomal reccesive inheritance, immunological findings and genetic disorders should be considered in addition to specific clinical features of the disease. The fact that AFP level is not high in any of of these diseases except for ataxia telengiectasia is significant in terms of differential diagnosis. High AFP in all of our patients was the most important finding supporting the diagnosis of AT. Disorder in DNA repair may result in loss of tumor inhibiting genes, genomic losses, cell death and formation of new oncogenes. Cancer develops in 1/3 of these patients. The most commonly observed cancer is leukemia and lympomas (13). In this study, Hodgkin lymphoma was found to have developed in 2 patients (10%).

In patients with primary immune deficiency (PID), autoimmune diseases may be observed paradoxically. It has been reported that disruption of the control mechanism of self reactive B and T lymphocytes may lead to this. Autoimmunity is observed more frequently in three PID syndromes including APECED (autoimmune polyendocrinopathy), ALPS (candidiasis, ectrodermal dysplasia, autoimmune lymphoproliferative syndrome) and IPEX (immundisregulation, polyendocrinopathy, enteropathy, X-linked genetic inheritance). However, problems related to autoimmunity may also be observed in other PID diseases including CVID (common variable immune deficiency), Good syndrome and hyperimmunoglubulin M syndrome. Type 1 diabetes and Hashimoto thyroiditis are the most common diseases among autoimmune diseases (17). We could not find any data related to association of Hashimoto thyroditis and AT. In 2 patients with Hashimoto thyroiditis, IgA deficiency was present in addition to IgE deficiency and CD4/CD8 ratio was <1 in both patients. The most common reasons of death in patients with ataxia telengiectasia include cancer and lung infections (8,9). In our group, 2 patients were found to have died with lymphoma and one patient was found to have died with lung infection.

Early diagnosis in the follow-up of patients with AT which has no definite treatment is important in terms of earlier and more successful management of other accompanying problems. To prevent this disease which has no definite treatment avoidance of consanguineous marriages and genetic consultancy are important.

Conflict of interest: None declared.

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