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TWENTY-YEAR FOLLOW-UP OF 160 PATIENTS WITH ATAXIA-TELANGIECTASIA*

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SUMMARY: Ersoy F, Berkel AI, Sanal Ö, Oktay H. (Immunology Unit, Hacettepe University Institute of Child Health, Ankara, Turkey). Twenty-year follow-up of 160 patients with ataxia-telangiectasia. Turk J Pediatr 33: 205-215, 1991.

The clinical and immunological findings of 160 patients diagnosed over a period of twenty years as having ataxia-telangiectasia (AT) are presented. The study group composed of 68 females and 92 males were members of 117 families. The rate of parental consanguinity was 65 percent. The incidence of AT in 117 families was 36.6 percent. All patients had the characteristic facial and postural features of AT. The mean duration of follow-up of 160 patients was 6.35 years. Fifty patients had died during the follow-up (36 of pulmonary infections, 14 of malignancies). Somatic growth retardation was a prominent feature. Recurrent sinopulmonary infections were detected in 66 percent of patients. Two patients had hypothyroidism, one had diabetes mellitus, and one had both conditions. The incidence of malignancies was found to be 2.3 percent in the immediate relatives of the patients.

The total lymphocyte count was low in 57 percent, and skin tests to PHA, candida, PPD and SK-SD were negative in 17.7%, 72.6%, 43.6%, and 78.2% of patients, respectively. In vitro blastogenic response to PHA was low in 61 percent of patients. The mean value of E-rosette formation was significantly lower than control values. Six patients had low serum IgG levels. The serum IgM level was high in 26.6 percent of patients and the IgA level was low or absent in 51.3 percent. There was no correlation between immune disturbance and duration of illness. *Key words: ataxia-telangiectasia, cellular immunity, humoral immunity, clinical features, malignancy.*

Ataxia-telangiectasia (AT) is an autosomal recessive disorder of childhood characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia, recurrent sinopulmonary infections, reduced cell-mediated immunity, absent or reduced serum IgA, reduced serum IgE, low or undetectable IgG2, premature aging and various endocrine disorders[1-12]. An increased incidence of cancer in patients and their relatives, elevated serum alpha fetoprotein levels, chromosomal abnormalities, and hypersensitivity of fibroblasts and lymphocytes to ionizing radiation are among the other findings in patients with AT[11,13-16]. Over a period of twenty years, we have evaluated and followed-up 160 patients with AT in 117 families. This communication describes the clinical and immunological findings and the outcome of these patients.

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Material and Methods

One hundred and sixty patients with AT, ranging in age from three to 32 years seen at the Immunology Unit of Hacettepe University Children's Hospital over a twenty-year period were reevaluated in 1988 in respect to clinical and immunological findings. They were diagnosed as having AT by the presence of progressive cerebellar ataxia and eye movements simulating ophthalmoplegia and oculocutaneous telangiectasia.

In addition to the history and physical examination, chest and sinus X-rays were obtained and routine blood counts (hemoglobin, WBC, peripheral blood smear, total lymphocyte counts) were taken. Intradermal skin tests were performed with *Candida albicans* extract, PPD, phytohemagglutinin (PHA) and streptokinase-streptodornase (SK-SD) with doses previously reported[8]. Induration of five mm or more after 48 hours was considered a positive skin test. In vitro blastogenic response was measured using a previously described method[17]. E-rosette forming cells were determined by the method of Jondal et al[18]. Serum immunoglobulins (IgG, IgM, IgA) were measured by radial immunodiffusion (Behring-Werke immunodiffusion plates). For statistical analysis the chi-square and the paired chi-square test were used[19].

Results

Of a total 160 patients with AT, 68 (42.5%) were females and 92 (57.5%) were males. The male/female ratio was 1.3/1. Ninety-two patients were alive (mean age 12.7 ± 5.8 years) and fifty patients had died. The remaining 18 patients were lost-to-follow-up (Table I). The mean death age of 50 patients was 14.8 ± 6.4 years. Of 50 patients, thirty-six had died of pulmonary infections and 14 of malignancies. The mean duration of follow-up of all patients was 6.35 years. Parental consanguinity was noted in 76 out of 117 AT families (65%). There were 440 children in 117 AT families and 160 (36.3%) children had ataxia-telangiectasia. Of 117 families, 80 families had one, 28 families had two, and nine families had three affected children. There was no relationship between consanguinity and the number of affected children in the families.

TABLE I: The Outcome of Ataxia-Telangiectasia Patients (n = 160)

Sex	Male : 92 (57.5%)	Female : 68 (42.5%)
Outcome of patients	Living : 92	(mean age: 12.7 ± 5.8 years)
	Deceased : 50	(mean age: 14.8 ± 6.4 years)
	Unknown : 18	
Mean duration of follow-up	: 6.35 years	

The clinical findings of our patients and the comparison with Boder's 101 cases[11] are shown in Table II. Ataxia, which was the first symptom noticed by the parents, was recognized between the ages of six months and six years in 140 patients (mean age 2.5 years). In 20 patients, the parents could not remember the age of onset of ataxia. Conjunctival telangiectasia was the second major clinical manifestation of the disease. Telangiectasia was noticed by parents in 57 children whose ages ranged from one year to eight years (mean age 3.7 years).

TABLE II: Clinical Features of Patients With Ataxia-Telangiectasia

Feature	Cases with Data Available (No.)	Cases with Clinical Feature No. (%)	Boder's[11] Findings (%)
Cerebellar ataxia	160	160 (100%)	100
Oculocutaneous telangiectasia	160	160 (100%)	100
Characteristic facies and postural attitudes	160	160 (100%)	100
Dysarthric speech	160	160 (100%)	100
Progeric changes of hair and skin	160	150 (93.8%)	88
Diminished deep tendon reflexes	160	114 (71%)	78
Choreoathetosis	160	114 (71%)	91
Negative Romberg sign	160	114 (71%)	78
Oculomotor signs			
Apraxia of eye movements	84	68 (81%)	84
Nystagmus	84	66 (79%)	83
Strabismus	84	43 (51%)	47
Frequent sinopulmonary infections	160	106 (66%)	83
Retardation of somatic growth	160	100 (63%)	72
Parental consanguinity	117 (families)	76 (65%)	–

All patients had the characteristic facies and postural features due to cerebellar hypotonia and ataxia. Progeric changes of hair and skin with some gray hair, atrophic facial skin resembling scleroderma, inelastic ears, pigmentary changes and chronic seborrheic blepharitis were detected in 93.8 percent of patients (150/160). Deep tendon reflexes (DTR) were diminished in 71 percent (114/160) of patients. Choreoathetosis was a prominent extrapyramidal feature and the Romberg sign was negative in 71 percent (114/160) of patients.

Of 84 AT patients, 68 patients (81%) had oculomotor apraxia, 66 patients (79%) had nystagmus and 43 patients (51%) had strabismus.

Retardation of somatic growth was a prominent feature and the respective heights and weights of 100 patients (63%) were below the tenth percentile, with 75 of these patients being below the third percentile.

Recurrent sinopulmonary infections were detected in 106 patients (66%) with 43 patients having atelectasis and/or bronchiectasis. The growth of 66 of 106 patients with recurrent infections (62.2%) and 20 of 48 patients without infections (41.6%) were below the third percentile. The difference between these two groups was significant with respect to the presence of growth retardation ($P < 0.05$).

Three patients had hypothyroidism and one of them developed diabetes mellitus at 15 years of age. Another patient was also diagnosed as having diabetes at the age of 22 years.

Fifteen patients (9.4%) developed malignant neoplasms (Table III). Of these 15 patients, seven had acute lymphoblastic leukemia (ALL), two had Hodgkin's

TABLE III: Type and Outcome of Malignancy in Ataxia-Telangiectasia Patients

Patient	Sex	Age at Onset of Malignancy (yrs)	Type of Malignancy	Outcome
1. ZT	F	15	Non-Hodgkin's lymphoma	Living
2. YA	M	31	Chronic myeloid leukemia	Ex (35 yrs)
3. ŞB	F	7	Pons glioma	Ex (7 yrs)
4. ÖK	M	17	Acute lymphoblastic leukemia	Ex (18 yrs)
5. ÖD	M	5	Acute lymphoblastic leukemia	Ex (?)
6. ÖA	M	11	Acute lymphoblastic leukemia	Ex (11 yrs)
7. OA	M	10	Non-Hodgkin's lymphoma	Ex (10 yrs)
8. ŞA	M	7	Acute lymphoblastic leukemia	Ex (9 yrs)
9. SA	M	7	Hodgkin's lymphoma	?
10. AA	M	8	Acute lymphoblastic leukemia	Ex (8 yrs)
11. SA	M	10	Burkitt's lymphoma	Ex (?)
12. İS	F	12	Hodgkin's lymphoma	Ex (12 yrs)
13. MY	F	17	Lung Ca (?)	Ex (17 yrs)
14. AA	F	11	Acute lymphoblastic leukemia	Ex (11 yrs)
15. AY	M	15	Acute lymphoblastic leukemia	Ex (15 yrs)

* Exitus

lymphoma and two had non-Hodgkin's lymphoma. The incidence of malignancies was found to be 2.3 percent (14/600) in the immediate relatives of AT patients (Table IV).

Immunological findings of AT patients are shown in Table V. The total lymphocyte count was less than 2000/mm^3 in 57 percent (78/136) of patients when first seen. Decreased lymphocyte counts were detected in another eight patients during

TABLE IV: Type of Malignancy in Relatives of Ataxia-Telangiectasia Patients

Families	Relative with Malignancy	Type of Malignancy
1	Brother	Acute lymphoblastic leukemia
2	Brother	Acute lymphoblastic leukemia
3	Grandfather	Larynx carcinoma
4	Mother	Breast carcinoma
	Grandmother	Breast carcinoma
5	Grandmother	Lung carcinoma
6	Grandfather	?
7	Grandmother	Lung carcinoma
8	Great grandfather	Rectum carcinoma
9	Great grandfather	?
10	Grandfather	Stomach carcinoma
11	Uncle	Larynx carcinoma
	Grandfather	Larynx carcinoma
12	Uncle	Larynx carcinoma

TABLE V: Immunological Findings in Ataxia-Telangiectasia Patients

Lymphopenia		78/136 patients	57 %
Negative skin tests	PHA	22/124 patients	17.7%
	Candida	90/124 patients	72.6%
	SK-SD	54/123 patients	43.6%
	PPD	93/119 patients	78.2%
Decreased E-rosettes		35/110 patients*	31.8%
Reduced in vitro PHA response		47/77 patients	61 %
IgA deficiency		79/154 patients	51.3%
High serum IgM level		41/154 patients	26.6%

* Two SD below normal values. Mean value of E-rosettes of AT patients was significantly lower than control values ($P < 0.001$).

follow-up and increases were observed in ten patients whose initial counts were low.

The phytohemagglutinin skin test was negative in 17.7 percent (22/124), the candida skin test in 72.6 percent (90/124), SK-SD in 43.6 percent (54/124) and PPD in 78.2 percent (93/119) of patients.

Of 110 patients tested, E-rosette formation was low in 35. The mean value (54.8 ± 11.6) of E-rosette formation was significantly lower than control values (69.2 ± 8) ($P < 0.05$). No significant change was observed in the percentage of E-rosette formation during the follow-up period.

In six patients, serum IgG levels were two standard deviations below normal, one (61%). No significant change was detected in PHA response in AT patients during their follow-up except for three patients who had showed transient increases (one patient was treated with transfer factor and two with levamisole).

In six patients serum IgG levels were two standard deviations below normal, one of them had very low IgG (120 mg/dl). Although the patient was given standard gammaglobulin monthly, he died of pulmonary infection. Of 154 patients, serum IgM levels were found to be increased in 41 (26.6%). IgA levels were low in 57.5 percent (61/106) of patients with recurrent sinopulmonary infections and in 37.5 percent (18/46) of patients without infection. The difference between these two groups was significant with respect to presence of recurrent sinopulmonary infections ($P < 0.001$). Serum IgA levels were low in all 41 patients with high IgM. Immunoglobulin determinations were repeated in 47 patients and no significant change was observed.

Discussion

Ataxia-telangiectasia is a complex multisystemic disorder. It can be easily diagnosed on purely phenotypic characteristics of progressive cerebellar ataxia, oculocutaneous telangiectasia and proneness to progressive sinopulmonary disease. The first cases from Turkey were published by Kıran et al[20]. Another study on clinical and immunological aspects of 31 patients was reported by our group in the same year[8]. Including these 31 patients, we were able to evaluate and follow-up 160 patients in 117 families (68 females and 92 males) between the ages of three and 32 years. The incidence of AT was found to be 36.6 percent in these families, supporting an autosomal recessive inheritance. This figure was reported to vary between 25-36 percent in previously reported series[8,21,22].

In our series, the parental consanguinity rate was recorded as 65 percent. This high rate is attributed to the common practice in Turkey of marrying relatives. In fact, the incidence of such marriages has been reported to be 20.9 percent[23].

Typical AT can be easily diagnosed on the basis of clinical characteristics. In the series presented, ataxia was noticed by parents in children ranging in age from six months to six years while telangiectasia was recognized by parents when the children ranged in age between one year to eight years. All patients had the characteristic facies of AT, dysarthric speech and diminished DTR, compatible with previous reports[3,4,7,8,11]. Oculomotor signs are almost uniformly present in AT and are diagnostically important, particularly since they may be present before

the appearance of the ocular telangiectasis. Since the oculomotor signs are subtle, they can easily be overlooked in the early stage while in the advanced stage they are severe and can simulate ophthalmoplegia[1,11,24-27]. In our series the rates of oculomotor apraxia, nystagmus and strabismus were compatible with those reported in previous studies[11,26].

Progeric changes involving the hair and skin are cardinal features of AT[4,11]. Some gray hair is usually found even in young children. Diffuse graying of the hair may continue throughout adolescence but it progresses normally thereafter[11]. Subcutaneous baby fat is lost early. In the early stages of the disease, facial skin tends to become atrophic and the ears inelastic. Such progeric findings and pigmentary changes of the skin were detected in 93 percent of our patients.

Somatic growth retardation is a prominent feature of AT and is found in most patients[4,11]. The respective heights and weights of children between four and seven years of age are typically at the tenth percentile and fall below the third percentile in adolescence. The cause of growth retardation is not clearly understood. It has been suggested that it is influenced by chronic sinopulmonary disease but it also occurs in its absence[11]. In our series, 62.5 percent of AT patients were below the tenth percentile and 47 percent of patients were below the third percentile. Growth retardation was observed more frequently in patients with recurrent sinopulmonary infections.

In our series, severe recurrent sinopulmonary infection was the main cause of death. In previous studies, the presence of sinopulmonary infections was found to be between 50-85 percent of AT patients, and it was noted as being the third major component of the syndrome and also the most frequent cause of death[3,8,11].

AT patients are prone to develop malignant neoplasms similar to patients with other immunodeficiency diseases. The incidence of malignant neoplasms among AT patients has been estimated to be 10-15 percent[28]. Although lymphoreticular malignacies occur most commonly, other neoplasms such as basal cell carcinoma, adenocarcinoma of stomach, ovarian dysgerminoma, medulloblastoma and glial tumor of brain may develop in these patients[11,13-15,28]. In our series, 15 patients developed malignancies, and of these, 12 had lymphoid neoplasms. The incidence of malignancies was found to be 9.4 percent which is compatible with previous reports[11,13,28]. Two explanations have been suggested for the high incidence of lymphoid cancer in AT patients[29]. T-cell immunodeficiency may be caused by inefficient joining of T-cell receptor genes which results in inversions and translocations and this type of immunodeficiency then fosters oncogenesis. A second possibility is that the translocations and inversions involve nearby oncogenes.

The incidence of malignancies has also been found to be increased in the immediate relatives of AT patients. Swift and co-workers[13] have estimated the risk of death from a malignant neoplasm as being five-fold greater in close relatives of AT patients than in the general population. The incidence of leukemia, lymphoma, ovarian, and gastric and biliary system carcinomas is increased in AT families. Furthermore, heterozygous females are at risk of breast cancer[30]. In our series, malignant neoplasms were detected in 14 immediate relatives (2.3%) of our patients. Of the 14 relatives, two had breast cancer, two had ALL, four had cancer of the larynx and two had lung cancer. While it has been reported that breast cancer and gastric cancer are the more common malignancies in AT heterozygotes[13,30], in our series, respiratory tract malignancies (larynx and lung Ca) were seen mainly in close relatives.

Various endocrine abnormalities including ovarian dysgenesis and insulin-resistant diabetes have been reported in AT patients[31,32]. In our series, three patients had hypothyroidism with clinical symptoms and one of them had developed type-I diabetes mellitus at 15 years of age. Another patient had also been diagnosed as having diabetes at the age of 22 years. To our knowledge, no reports of hypothyroidism associated with ataxia-telangiectasia have been published in the literature. In a previous study, normal thyroid functions and increased growth hormone levels following L-dopa stimulation were detected in 12 of our AT patients studied[33]. Of 12 patients, four showed an abnormal glucose tolerance test and increased production of insulin during the test.

Immunological evaluation of 160 AT patients showed variable degrees of humoral and/or cellular immune dysfunction. The absolute lymphocyte count was low in 57 percent of patients, a result compatible with previous studies[6-9]. No significant change in lymphocyte counts was observed during the follow-up period.

Delayed hypersensitivity responses to common skin test antigens have been found to be negative in the majority of AT patients[6-9,20]. McFarlin et al[7] have found a higher percentage of positive reactions to dinitrochlorobenzene (DNCB) than that reported by other investigators[34,35]. In our series, delayed hypersensitivity reaction to PHA, *Candida*, SK-SD and PPD were negative in 17.7-78.2 percent of patients and there was no change in responses to repeated tests.

The percentage of E-rosette forming cells was low in 31 percent of our patients and the mean value was significantly lower than control values ($P < 0.05$). Although in some studies a normal percentage of E-rosettes has been reported, it has been found to be low in most reports[8,36,37]. No change was observed in the percentages of E-rosettes in the repeated tests. In vitro blastogenic responses to mitogens and common antigens have been found to be low in 50-60 percent of patients[7,8,21]. McFarlin and Oppenheim[38] have reported that the blastogenic response of lymphocytes may vary during the course of a patient's illness.

Furthermore, in some patients, reduced responses to PHA and Pokeweed mitogen (PWM) can be improved by increasing the concentration of stimulant. An inhibitory serum factor has been shown to decrease the response of normal lymphocytes to PHA. In our series, 61 percent of patients had a low blastogenic response to PHA, and only three patients showed a transient increase following transfer factor or levamisole therapy. In one of our previous studies, 11 out of 15 patients showed a normal response in mixed lymphocyte culture, even though their responses to PHA and antigens (*Candida*, SK-SD) had been low[8]. This finding was attributed to different T lymphocyte subpopulations responding to different antigens and allogeneic lymphocytes.

Some abnormalities in humoral immunity have been reported in AT patients, the most striking of which is IgA deficiency. It is found in about 70% of cases[5-8,31,34,35]. In this study, 51.3 percent of AT patients had IgA deficiency and the occurrence of frequent pulmonary infections was more common in patients with low serum IgA than in patients with normal IgA, a finding contrary to previous reports[8,11]. Serum IgG levels were low in six patients, and in one patient, it was especially low (120 mg/dl). This patient was given standard gammaglobulin but he died of pulmonary disease. Serum IgM levels were high in 26.6 percent of patients, all of whom had decreased IgA levels. The increase of the IgM level was attributed to frequent infections or compensation of the low IgA level in these patients.

We found no correlation between the disturbance of immune functions and the duration of illness. Our study showed that IgA deficiency is a factor responsible, at least in part, for sinopulmonary infections and that recurrent infections may be an additional factor influencing somatic growth in AT patients.

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