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Clinical and Immunological Studies in Twenty Families with Ataxia-Telangiectasia*

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Ataxia-Telangiectasia (A-T), was first published by Syllaba and Henner[1] and later Mme Louis Bar described this syndrome to which her name is given.[2] Boder and Sedgwick called attention to the frequency of sinopulmonary infections in patients with A-T.[3] Later, deficiency in serum IgA[4,5] and in the thymic system[6] and impaired lymphocyte transformation were noticed.[7-9] Endocrine disorders such as insulin resistant diabetes[10] and ovarian changes[11] are not rare in patients with A-T. The incidence of lymphoreticular malignancies in these patients is estimated to be around 10 %.[12]

In this communication we will report clinical and immunological findings in 31 patients with A-T from 20 families.

Material and Methods

Fourteen females and 17 males (between ages of 2.5 and 24 years) with A-T, their 23 parents, 4 healthy siblings and 22 healthy children of the same age were studied.

In addition to the history and physical examination, chest and sinus films were obtained and routine blood counts (hemoglobin, hematocrite, WBC, smear) were done. Skin tests were applied to the volar surface of the forearms in appropriate dilutions (P.P.D, Refik Saydam Hıfzısıhha Enst., 3 U/0.1 ml; Candida, Hollister Stier Labs-50 PNU/0.1 ml; SKSD or Streptokinase-streptodornase, Lederle Labs-50 U SK,12.5 U SD/0.1 ml, PHA-P (Phytohemagglutinin), Burroughs-Wellcome Labs.

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10μg/0.1 ml) and were read 48 hours later. An induration greater than 5 mm was considered as positive. Lymphocyte transformation was done by using PHA, Candida, SKSD and allogeneic lymphocytes by previously published methods.[14,15] Incorporation of H_3Tdr into DNA was determined by a modification of the method of Mans and Novelli.[16] All cultures were performed in duplicates and were harvested on the 3rd day for PHA, and on the 7th day for candida, SKSD and allogeneic lymphocytes. Results were expressed as CPM x 10^3 per $1x10^6$ lymphocytes. A stimulation index (SI=CPM of stimulated/CPM of unstimulated) greater than 20 for PHA and greater than 2 for candida or SKSD was considered as a positive response. For mixed lymphocyte cultures a SI (CPM of responding lymphocytes x mitomycin C treated stimulating lymphocytes/CPM of unstimulated lymphocytes of responding) greater than 2.5 was taken as a positive response. For detecting the effect of plasma on in vitro response of the lymphocytes to PHA, 0.05 ml of plasma was added to each culture tube of controls set up with PHA. T cell rosette test was done by the method of Jondal et al.[17] For the detection of humoral immunity, total proteins and serum electrophoresis[18] immunoelectrophoresis,[19] quantitative immunoglobulins (IgG,IgM,IgA), salivary IgA and serum complement (B_1C) (by using Behring-Werke immunodiffusion plates) levels,[20] in some cases serum IgE*[21] and erythrocyte adenosine deaminase levels[22] were determined. For statistical analysis student's *t* and x^2 tests were applied.[23]

Findings

Seventeen out of 20 parents were relatives with a consanguinity rate of 85 %. Twelve were first cousins, the rest being distant relatives. Thirty-seven out of 101 or 36.5 % of the total children had A-T supporting an autosomal recessive inheritance. Five families had 3, seven families had 2 and 8 families had one, affected children. Six children died, therefore they were not included. The onset of ataxia was 6 months in the earliest and 4 years in the latest, mean and median being at two years. The duration of the illness varied between 1 and 22 years, the mean was 8 and the median was 7 years. Fourteen patients had a mild degree and seventeen patients had a severe degree of ataxia.

Infections were severe in 18 patients of which 9 had bronchiectasis and atelectasis. Associated physical findings included nystagmus in 8, strabismus in 4, and café au lait spots in six.

Immunological findings: The absolute lymphocyte count was under 2000 per cmm in 54.5 % of the patients (17/31), in 29 % of the

* Kindly determined by Dr. Henry J. Smith.

parents-siblings (8/27) and in 18 % of the control children (4/22). The absolute lymphocyte counts were significantly low ($p<0.01$) in patients when compared with controls and parents-siblings.

Skin tests: The percent of negatives in each group tested were compared (Table I). The phytohemagglutinin (PHA) skin test was negative in 36.6 % (11/30) of A-T, in 8 % (2/25) of parents-siblings and in 19 % (4/21) of controls. The results were significant between patients and controls ($p<0.05$) but not significant between controls and parents-siblings ($p>0.05$). The candida skin test was negative in 76.6 % (23/30) of A-T, in 28 % of (7/25) parents-siblings and in 47.6 % (10/21) of controls. The Streptokinase-streptodornase (SK-SD) skin test was negative in 46.6 % (14/30) of A-T, in none of parents-siblings, in 19 % (4/21) of controls. PPD was negative in 100 % (30/30) of A-T, in 32 % (8/25) of parents-siblings and 76.2 % (15/21) of controls. All the results were significant ($p<0.05$–$p<0.001$) between A-T and parents-siblings, A-T and controls.

In vitro lymphocyte studies showed that fifteen of 30 patients (% 50) had a low response to stimulation with PHA (Table II and Figure 1). This was statistically significant between patients and controls ($p<0.001$); patients and parents-siblings ($P<0.05$).

Sixty-five percent (17/26) of A-T, 16.6 % (3/18) of parents-siblings and 33.3 % (7/21) of controls had low in vitro lymphocyte response to candida stimulation. (Table III and Figure 1) This was statistically significant when compared with controls ($p<0.05$) and also with parents-siblings ($p<0.001$).

Eighty percent (16/20) of A-T, 44.8 % (8/18) of parents-siblings and 23.6 % (5/21) of controls had low in vitro lymphocyte response to SKSD stimulation. (Table IV and Figure 1) These figures were significantly low in A-T in comparison to parents-siblings and controls ($P<0.05$).

Eleven out of 15 patients with A-T had a good MLC response. There was no significant difference between A-T and control groups. (Table V).

Forty percent of the patients' plasma caused an inhibition of 50 % or more in the in vitro response of normal lymphocytes to PHA.

T cell rosettes were significantly lower in percentage in A-T in comparison to controls ($p<0.01$) (Table VI, Figure 2).

The serum immunoglobulins and β_1C levels are seen in Table VII. Serum IgA was low in 13 out of 31 patients (42 %) and 3 out of 25 parents-siblings (12 %). Serum IgM and IgG levels were within normal range in A-T with the exception of one case for each, respectively.

TABLE I

SKIN TESTS (PERCENT OF NEGATIVES)

	PHA-P (10 µg/0.1 ml	Candida (50 PNU/0.1 ml)	SKSD (50 and 12.5 UNITS/0.1 ml)	PPD (3 UNIT/0.1 ml)	Total Negatives (%)
A-T Patients (30 Cases)	11/30 or (36.6 %)	23/30 or (76.6 %)	14/30 or (46.6 %)	30/30 or (100 %)	65
Parents and Siblings (25 Cases)	2/25 or (8.0 %)	7/25 or (28.0 %)	0/25 or (0 %)	8/25 or (32.0 %)	17
Healthy Controls (21 Children)	4/21 or (19.0 %)	10/21 or (47.6 %)	4/21 or (19.0 %)	15/21 or (76.2 %)	40.5
Patients-Controls	$P > 0.05$	$P < 0.001$	$P < 0.05$	$P < 0.001$	$P < 0.001$
Parents-Sib-Controls	$P > 0.05$	$P > 0.05$	$P < 0.01$	$P < 0.001$	$P < 0.001$
Patients-Parents	$P > 0.05$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$

TABLE II

IN VITRO RESPONSE OF LYMPHOCYTES TO PHA (CPMx10^3/10^6 LYMPHOCYTES)

		PHA	Unstimulated	Stimulation Index (SI)	Number with Low Response (SI < 20) and Percent
A-T Patients	Mean	55.2± 98.3	4.87±20.25	51.3± 62.4	15/30 50 %
(30 Cases)	Range	(0.042–218.6)	(0.105–111.6)	(0.3–212.7)	
Parents and Siblings (21 Cases)	Mean	151.6±137.9	2.28± 2.24	96.7± 94.7	None
	Range	(16.6 –283.4)	(0.11 –11.05)	(26.7–424.7)	
Healthy Controls	Mean	189.5±174.3	1.64± 2.28	171.6±141.6	None
(20 Children)	Range	(11.96 –708.7)	(0.16 – 10.8)	(28.5–650)	
Patients-Controls	P < 0.001				
Parents-Siblings-Patients	P < 0.05				
Parents-Siblings-Controls	P < 0.05				

TABLE III

IN VITRO RESPONSE OF LYMPHOCYTES TO CANDIDA (CPMx10^3/10^6 LYMPHOCYTES)

		Candida	Unstimulated	Stimulation Index (SI)	Number with Low Response (SI<2) and percent
A-T Patients	Mean	10.6 ± 27.9	82.9 ± 183.8	2.25 ± 2.81	17/26 or 65.3 %
(26 Cases)	Range	(0.021–138.5)	(0.014–76.9)	(0.01– 9.5)	
Parents and Siblings	Mean	50.1 ± 61.3	10.4 ± 17.8	8.3 ± 6.9	3/18 or 16.6 %
(19 Cases)	Range	(0.014–188.2)	(0.014–85)	(0.1 –23.2)	
Healthy Controls	Mean	17.1 ± 36.7	5.3 ± 9.9	6.5 ± 7.8	7/21 or 33.3 %
(21 Cases)	Range	(0.22 –165.9)	(0.17 –39.7)	(0.2 –28)	
Patients-Controls		$P < 0.05$			
Parents-Siblings-Patients		$P < 0.001$			
Parents-Siblings-Controls		$P > 0.05$			

TABLE IV

IN VITRO RESPONSE OF LYMPHOCYTES TO SKSD (CPMx10^3/10^6 LYMPHOCYTES)

		SKSD	Unstimulated	Stimulation Index (SI)	Number with Low Response (SI <2) or percent-
A-T Patients (20 Cases)	Mean	36.8 ± 152.7	82.9±183.3	1.25 ± 1.15	16/20 or 80 %
	Range	(0.021–685.3)	(0.014–76.9)	(0.1– 3.6)	
Parents and Siblings (18 Cases)	Mean	26.7 ± 49.3	10.4 ±17.8	5.40± 7.0	8/18 or 44.4 %
	Range	(0.013–212.2)	(0.014–85.1)	(0.2–22.7)	
Healthy Controls (21 Children)	Mean	22.8 ± 46.9	5.3 ± 9.9	7.5± 12.6	5/21 or 23.6 %
	Range	(0.042–204)	(0.13 –39.7)	(0.2–55.4)	
Patients-Controls		P < 0.05			
Parent-Siblings-Patients		P < 0.05			
Parents-Siblings-Controls		P > 0.05			

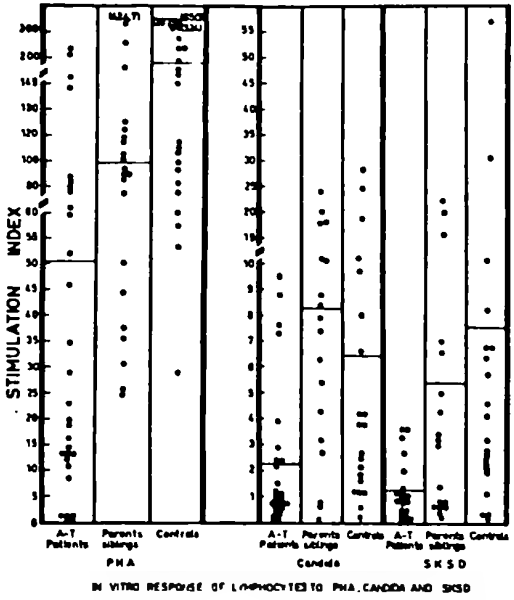

Figure 1

TABLE V

MLC IN A-T PATIENTS (CPMx10^3/10^6 LYMPHOCYTES)

Case No:	$Pt+C_m$	$Pt+\bar{0}$	SI	$C+Pt_m$	$C+\bar{0}$	SI
1	0.35	0.14	2.5	1.56	0.33	4.8
2	0.37	0.24	1.5	2.47	0.33	7.5
4	6.43	0.28	22.7	36.57	4.08	8.9
5	0.91	0.20	6.2	13.20	2.75	4.7
6	3.60	0.37	9.8	30.91	2.76	11.2
7	2.36	0.22	10.7	9.94	2.75	3.6
12	10.28	0.71	14.2	22.61	1.21	18.7
13	7.18	0.39	1.9	13.49	1.21	11.1
14	0.35	1.52	0.2	11.12	1.21	9.2
20	2.57	0.53	4.9	19.82	1.86	11.0
21	4.54	0.09	48.0	16.64	0.81	20.5
25	14.49	0.69	20.9	1.52	6.52	0.2
28	1.32	0.11	12.6	1.47	0.58	2.5
29	13.00	68.19	0.2	6.17	0.48	12.7
31	1.46	0.37	3.9	1.39	0.32	4.4

$Pt+C_m$: Stimulation of the patients lymphocytes by the mitomycin C treated control lymphocytes

$Pt+\bar{0}$: Unstimulated lymphocytes of the patient

$C+Pt_m$: Stimulation of the control's lymphocytes by the mitomycin-treated patient's lymphocytes

$C+\bar{0}$: Unstimulated lymphocytes of the control.

SI : $\frac{\text{CPM of responding x stimulating lymphocytes}}{\text{CPM of responding unstimulated lymphocytes}}$

Response: SI > 2.5

TABLE VI

T CELL ROSETTES (PERCENT)

	Mean	Range
A-T Patients (25 Cases)	33.4 ± 10.7	14–58
Parents and Siblings (20 Cases)	38.5 ± 11.4	17–64
Healthy Controls (21 Cases)	44.4 ± 13.1	27–69
Patients-controls	$P < 0.01$	
Patients-parents-siblings	$P > 0.05$	
Controls-parents-siblings	$P > 0.05$	

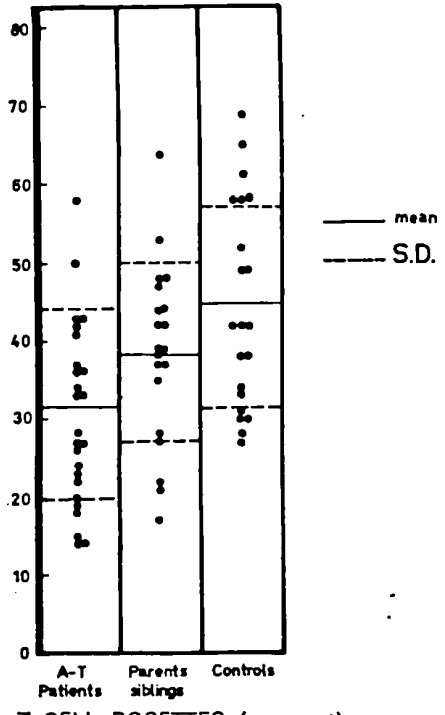

Figure 2

Salivary IgA was determined in 15 patients and the levels were within the normal range in 11 (2 mg % - 11.3 mg %). It was absent in 4 patients. Of these 4, three had low serum IgA levels.

TABLE VII

IMMUNOGLOBULINS AND B_1C (mg/100 ml)

		IgG	IgM	IgA	B1C
A-T Patients	Mean	1162 ± 356	161.4 ± 44	104.2 ± 71.9	115.4 ± 47.3
(31 Cases)	Range	(75–1700)	(25–233)	(5–220)	(33–222)
	Percent low	(3 % or 1/31)	(3 % or 1/31)	(42 % or 13/31)	(22.5 % or 7/31)
Parents and Siblings	Mean	1208 ± 239	148 ± 44	229 ± 76	130 ± 40.1
(25 Cases)	Range	(975–2100)	(76–230)	(60–420)	(47–183)
	Percent low	(None)	(None)	(12 % or 3/25)	(4 % or 1/25)
Controls	Mean	1190 ± 350	114 ± 34	232 ± 58	120 ± 31
(Kiran and Say[24])	Range	(600–2200)	(36–150)	(40–420)	(80–150)

Adenosine deaminase levels were normal in the 9 patients studied. IgE levels were studied by radio immunoassay in 9 patients and were low in seven.

Discussion

A-T is a primary immunodeficiency disorder transmitted in an autosomal recessive manner and characterized by telangiectasia, progressive ataxia, sinopulmonary infections and a variable immunodeficiency involving the antibody or the cellular immune system, or both.

In our study 36.5 percent of the children from 20 families had A-T, confirming an autosomal recessive inheritance. This figure was 29 percent and 25 percent in previously published series.[25, 26]

A high consanguinity rate of the parents (85 %) in our series is attributed to the common practice of intermarriages in this country. In fact, the incidence of intermarriages in Turkey was reported to be varying between 21.4 and 28.4 percent.[27, 28] In the previous study from our laboratory 60.8 % of the parents were related.[13]

In our series, ataxia was the first symptom which has been noticed by the family. Fifty-eight percent of our patients had sinopulmonary infections. Sinopulmonary infections and otitis were seen in 50 % – 85 % of patients with A-T.[3, 25, 29]

Careful analysis of our patients revealed no association between the severity of infections and the duration of illness; or the severity of infection and the degree of ataxia. In five patients with severe ataxia, infections were mild or non-existing.

Impairment in cellular immunity of varying degrees is reported in patients with A-T.[29] In this study the absolute lymphocyte count was low (less than 2000 per cmm) in 54.5 % of patients and severe lymphopenia (less than 1000 per cmm) was observed in 6 patients. In some patients blood counts were repeated during infections and no increase from the previous values was observed. Absolute lymphocyte counts were reported to be low from 30 % to 70 % in patients with A-T.[25, 29, 30] Eight of the parents-siblings (29 %) had low absolute lymphocyte counts which was not significant when compared with normal controls.

Delayed hypersensitivity responses (skin tests) to various antigens were reported to be negative in the majority of the patients.[25, 29, 31] Peterson and Good found the skin tests to be negative in 70 % of the patients.[30] Seventeen percent of the parents-siblings had negative skin tests with the above tested antigens.

Epstein et al observed no skin test response to DNCB and NDMA in 14 and 17 respectively, of the 19 patients with A-T. Of the 46 parents-siblings, 25 and 13 responded to the skin test with DNCB and NDMA antigens in their series.[32] In our series the skin tests were significantly negative (in 65 % of the patients) with PHA, Candida, SKSD and P.P.D. antigens.

The lymphocytes of A-T patients have low response to the stimulation with PHA[7,8,25,29,30] pokeweed mitogen[29] and streptolysine-O.[29] This low response is attributed to an inhibitory factor present in the patients' plasma.[9, 29] The addition of the patients plasma causes some inhibition in the response of the normal lymphocytes to PHA. The use of normal homologous plasma corrects the in vitro lymphocyte response to PHA.[29, 33] We observed a low response of the lymphocytes to PHA in 50 percent of our patients. In fourty percent, the addition of their plasma inhibited the blastic transformation response to PHA to fifty percent or more.

All of the parents-siblings had normal in vitro response of their lymphoytes to the stimulation with PHA.

The patients' lymphocytes showed significantly low blastic transformation response to in vitro stimulation with candida and SKSD antigens when compared with parents-siblings and controls.

Despite a low response to PHA and antigens (candida and SKSD), lymphocytes in 11 out of 15 patients showed a normal response to in vitro stimulation with allogeneic lymphocytes. In the one way mixed lymphocyte culture system the patients lymphocytes were also able to stimulate the normal individuals lymphocytes. This may be due to the presence of subpopulations of T lymphocytes responding differently to antigens (candida and SKSD) and allogeneic lymphocytes. This type of response (low response to PHA, but normal response in MLC) has also been reported in some patients with severe combined immunodeficiency.[34, 35]

T cell rosettes were low (under 25 %) in 9 out of 25 patients tested. The mean value of T cell rosettes in 25 patients (33.4 %) was significantly low ($p<0.01$) when compared with the control group. This finding is opposite to that reported by Bach, who found a normal percentage of T rosettes in 7 cases of A-T examined.[36] Twenty parent-siblings had a normal mean value of T cell rosettes (38.5 %).

In ataxia-telangiectasia, disturbances in humoral immunity have also been reported. The most consistent abnormality is the presence of a low or absent serum IgA.[5, 6, 25, 29, 30] This was present in 46 % to

72 % of patients.[29, 30] We found the serum IgA to be low or absent in 42 percent of our patients. One patient had a low IgG and another patient had a low IgM level. In the parents-siblings group, serum IgA was low in only 3 out of 25 tested. Levin and Perlov found dysgammaglobulinemia in 5 out of 7 parents tested.[25] Eisen et al, examined the serum of 16 parents-siblings and they found a low serum IgA in only one.[31] Serum complement was low in 7 out of the 31 patients we tested. The parents-siblings had normal serum complement levels. Salivary IgA was absent in 4 out of 15 patients. Of these 4, three had low serum IgA values. South and coworkers reported the absence of salivary IgA in 8 out of 22 patients with A-T. Of these 8, only one had low serum IgA.[37]

Serum IgE levels were low in 7 out of 9 patients tested in our series. It was reported to be low in A-T patients[38] and association of low serum IgA and IgE was suggested as the possible cause of sinopulmonary infections in these patients. In our series we found low IgE in 7 patients who had normal serum IgA. In one patient both serum IgA and IgE were normal. In another one serum IgA was low, but IgE was normal.

Recently erythrocyte adenosine deaminase (ADAse) deficiency has been reported in some patients with severe combined immunodeficency.[39] We found normal red cell ADAse levels in 9 patients and their parents.

We checked the correlation between the low in vitro PHA response of the lymphocytes and the duration of the illness and found no such correlation. Also no correlation existed between the degree of ataxia and duration of the illness. We analyzed the combination of low serum IgA, lymphopenia, negative skin tests and low PHA response of the lymphocytes in order to see their effect on the respiratory infections. Different combinations of these abnormal immunological tests were seen in patients in this series. However, we were unable to correlate the severity of infections with these tests alone. Our study shows that cellular immunity is deficient in different degrees in A-T patients and IgA deficiency is not the only factor responsible for sinopulmonary infections. We believe further immunological tests (such as interferon, etc) should be developed to investigate the cause of different clinical pictures for infections in A-T patients.

Summary

Thirty-one patients with A-T from 20 families, were subjected to clinical evaluation. Various tests for cellular and humoral immunity were carried out on these patients, their four healthy siblings and on 23 of the parents. Twenty-two healthy children of the same age were also

subjected to similar tests. The consanguinity rate among the parents was 85 %. The absolute lymphocyte count was low in 54.5 %, and delayed hypersensitivity responses to five different skin test antigens were imparired in 65 % of the patients.

In vitro response of the lymphocytes to PHA, Candida and SKSD antigens were low in these patients with respective values of 50 %, 65 % and 80 %. Mixed lymphocyte culture response was good in 11 out of 15 patients studied. T cell rosettes were significantly low. Serum IgA deficiency was present in 42 % of the patients and serum IgE was low in 7 out the 9 patients investigated. Salivary IgA was low in 4 out of 15 examined patients. The red cell ADA'se levels were normal in 9 patients studied. No correlations between a consistent pattern of tests and/or the severity of infection in these patients was observed.

Acknowledgement

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