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Diagnostic considerations in ataxia-telangiectasia

JANINE M. JASON AND ERWIN W. GELFAND

Department of Immunology, Research Institute, Hospital for Sick Children, Toronto

SUMMARY 13 children with ataxia-telangiectasia were followed for 6 years. Unlike previously reported cases, these patients had progressive, debilitating neurological disease and slight pulmonary or infectious symptoms. Immunological dysfunction was variable and endocrinological defects were absent. Oculomotor findings, α -fetoprotein levels, and the incidence of chromosomal breakage were the most consistent parameters in the diagnosis of the condition. This disease should be considered in any patient with chronic ataxia, regardless of immunological findings or whether he has a history of infections.

Boder and Sedgwick (1957) presented the first thorough review of ataxia-telangiectasia (A-T) and stressed the prevalence of sinopulmonary symptoms. The incidence of pulmonary complications was considered sufficiently significant to include them as part of the syndrome—ataxia, oculocutaneous telangiectasia, and recurrent sinopulmonary infections. Since then, reports have shown that sinopulmonary infections occur in 45 to 81% of cases (Boder and Sedgwick, 1958, 1963; Peterson *et al.*, 1964; McFarlin *et al.*, 1972; Polmar *et al.*, 1972). Search for the possible cause or causes of this increased incidence of infection in A-T led to a series of articles describing a variety of immunological abnormalities including lymphopenia, decreased lymphoid tissue (Eisen *et al.*, 1965), significant deficiency or absence of IgA (Fireman *et al.*, 1964; Eisen *et al.*, 1965; Epstein *et al.*, 1966; McFarlin *et al.*, 1972; Polmar *et al.*, 1972; Kiran *et al.*, 1974), IgE deficiency (Ammann *et al.*, 1969; McFarlin *et al.*, 1972; Polmar *et al.*, 1972), presence of low molecular weight IgM (McFarlin *et al.*, 1972), decreased delayed hypersensitivity reactions (Eisen *et al.*, 1965; Epstein *et al.*, 1966), decreased E-rosetting and PHA responses (McFarlin and Oppenheim, 1969; McFarlin *et al.*, 1972; Kiran *et al.*, 1974), and variable failure of thymic development (Peterson *et al.*, 1964; Eisen *et al.*, 1965; McFarlin *et al.*, 1972). Unfortunately, there has been no direct correlation between the incidence of any of these defects and the occurrence of sinopulmonary problems.

Department of Pathology, Yale University, USA
JANINE M. JASON, clinical fellow of immunology
Department of Immunology, Research Institute, Hospital for Sick Children, Toronto
ERWIN W. GELFAND, professor of pediatrics

We were able to evaluate and follow up 13 patients with A-T. These patients differ significantly from those already described. The incidence of sinopulmonary infections was significantly lower and the extent of immunological defects much less severe. We describe the results of our evaluation and emphasise the heterogeneity of this disorder and the difficulties in diagnosis.

Materials and methods

Patients. All 13 patients were children seen at this hospital between 1972 and 1978. They were diagnosed as having A-T by meeting criteria of progressive cerebellar ataxia associated with eye movements simulating ophthalmoplegia, progressive oculocutaneous telangiectasia, and frequently, familial incidence. The population includes three sibships of two siblings in each.

Immunological testing

In vivo

Intradermal skin testing was done as previously described (Gelfand *et al.*, 1972), using *Candida albicans* extract, dermatophyton, diphtheria-tetanus, and streptokinase-streptodornase. A skin test was considered positive if >10 mm induration could be seen after 48 hours.

In vitro

Immunoelectrophoresis was carried out by micro-technique, and quantitative immunoglobulins by radial immunodiffusion. IgE levels were done by radioimmunoassay (Phadebas: Pharmacia, Montreal, Quebec). E-rosettes were determined by a modification of the method of Wybran *et al.* (1972).

Lymphocyte transformation assays were performed as previously described (Gelfand *et al.*, 1972).

Nonimmunological testing. Autoantibodies were sought by indirect immunofluorescence to nuclear factors, DNA, mitochondria, smooth muscle, thyroid, and glomerular basement membrane.

α -Fetoprotein levels were carried out by Dr T. Waldmann, NIH, Bethesda, Md, using a radio-immunoassay technique (Waldmann and McIntire, 1972). Chromosome studies were done on peripheral blood lymphocytes.

Results

Clinical data. Table 1 shows that all patients had pronounced ataxia and oculocutaneous telangiectasia. Neurological symptoms were generally noted in the first 2 years of life, but in one patient these were first seen as late as 5 years. Disease was present in 3 sibships; parents were consanguineous in one case. Most significantly, sinopulmonary symptoms were absent or were slight in all 13 patients.

Antibody-mediated immunity (Table 2). Four out of 12 patients had a selective absence of IgA. Low

molecular weight IgM was not detected on immunoelectrophoresis and absolute serum IgM levels were normal for age. IgE was present in normal amounts on repeated evaluation in all 11 patients tested. Functional evaluation showed a negative Schick test in 8/8 patients, indicating the presence of neutralising antibodies. One patient converted from a positive reaction after reimmunisation. Isohaemagglutinins were present in all patients. DPT-P booster injections were given to 7 patients, all of whom had significant increases in titres to these antigens.

Cell-mediated immunity (Table 3). Severe and persistent lymphopenia was present in one patient, moderate lymphopenia ($<1.5 \times 10^9/l$ lymphocytes) in 3 patients. Delayed hypersensitivity skin testing was positive to at least one antigen in 9/11 patients tested, equivocal in one (about 5 mm induration), and absent in one. E-rosettes were normal in 9/11 patients and slightly decreased in 2/11. PHA response was normal or only slightly decreased in 10/11 cases.

Nonimmunological data. One or more autoantibodies were weakly to strongly positive in 8/11 patients. Most significantly, α -fetoprotein levels were raised in

Table 1 *Clinical presentation*

	1	2	3	4	5	6	7	8	9	10	11	12	13
Ataxia*	4+	2+	+	3+	2+	4+	3+	3+	3+	2+	+	4+	+
Telangiectasia	+	+	+	+	+	+	+	+	+	+	+	+	+
Sinopulmonary infections†	0	‡+	1+	0	0	1+	0	0	0	0	1+	1+	0
Onset of symptoms (months)	12/12	9/12	15/12	14/12	13/12	14/12	14/12	24/12	10/12	60/12	12/12	12/12	14/12
Sex	F	M	M	F	M	M	M	F	F	F	M	M	M
Familial incidence	+ ↔ +			+ ↔ +		+ ↔ +							
	(Parents consanguineous)												

*1+ mild ataxia, 4+ pronounced ataxia.

†0 ≤ 4 episodes of URI symptoms per year; ‡+ > 4 episodes of URI symptoms per year, not requiring medical care; 1+ recurrent clinical or radiological documentation of sinusitis and/or ≥ 4 URIs per year requiring outpatient visits; 2+ chronic sinusitis or 2-3 episodes of pneumonia; 3+ ≥ 4 episodes of pneumonia; 4+ bronchiectases.

Table 2 *Immunological data*

B-cell function	1	2	3	4	5	6	7	8	9	10	11	12
IgG (mg/100ml)	1880	2000	800	570	900	940	445	850	800	1000	1081	800
IgA (mg/100ml)	0	0	40	50	0	130	150	115	70	0	125	180
IgM (mg/100ml)	260	480	200	300	86	225	200	190	150	175	200	222
IgE (ng/ml)	200	460	520	100	98	248	248	160	228	79	53	ND
Schick test†	-	-	ND	-	ND	-	-	-	ND	With boost	-	ND
Isohaemagglutinins												
Anti A:			1:32	1:32	1:256	1:128	1:64					
Anti B:	1:256	1:128	1:256	1:128	1:4	1:128	1:64	1:16	1:16	ND	1:32	ND
Blood type	(A+)	(A+)	(0+)	(0+)	(0+)	(0+)	(0+)	(A+)	(A+)		(A+)	

†Positive skin test to diphtheria toxin, indicating absence of neutralising antibody; - no reaction indicating presence of antibodies. ND = not determined.

684 *Jason and Gelfand*Table 3 *Immunological data*

<i>T-cell function</i>	1	2	3	4	5	6	7	8	9	10	11
Lymphocyte count ($\times 10^9/l$)	1.0	1.5	2.0	1.2	1.7	1.5	1.0	4.0	1.8	0.5	3.5
Delayed hypersensitivity	+	\pm^{**}	+	+	+	+	+	+	+	+	-
E-rosettes†	N	N	N $\rightarrow\downarrow$	N	\downarrow	N	N	N	N	N	N
PHA‡	N $\rightarrow\downarrow$	N $\rightarrow\downarrow$	N	N	N	N	N $\rightarrow\downarrow$	N	N	N $\rightarrow\downarrow$	$\downarrow\downarrow$

**This patient had a response to *Candida*, with 5 mm of erythema and induration.

†% E-rosettes was considered decreased (\downarrow) if percentages were within 1 SD of the mean for controls. (Laboratory controls for E-rosettes ranged from 50-65% of peripheral blood mononuclear cells with a mean of 55.)

‡PHA responses were considered to be decreased to within 1 SD (\downarrow) or 2 SD ($\downarrow\downarrow$) from the mean of control values (the mean control value was 33000 counts/min).

N = normal.

Table 4 *Nonimmunological data*

	1	2	3	4	5	6	7	8	9	10	11	12
Autoantibodies		+	+	+	+	+	-	-	-	+	+	ND
Liver function tests†		N	N	N	N	N	N	N	N	N	N	N
α -Fetoprotein‡		250	300	180	255	100	240	310	160	280	94	44
Glucose tolerance		N	N	N	ND	ND	N	N	N	ND	ND	N

†AST, bilirubin, alkaline phosphatase; ‡normal range ≤ 40 ng/ml.

Table 5 *Chromosomal abnormalities*

	1	3	4	5	6	7	8	9	10
No. of cells examined	56	6	52	50	50	50	32	53	39
No. of cells with breaks	35	2	6	6	6	4	5	3	2
% cells with breaks†	62	33	11	12	12	8	16	6	5
D-group affected (13-15)	+	+	+	+	+	+	-	-	+
Chromosome-14 affected	-	-	+	-	+	+	-	-	+
Chromosome-7 affected	+	+	-	-	-	-	-	-	-
Clones	+	-	+	+	-	-	-	-	-

†Normal = $< 6\%$ of cells with breaks.

11/11 cases. In one patient the level (44 ng/ml) was just outside the normal range (Waldmann and McIntire, 1972) (Table 4).

Chromosome breakage was present in 8/9 cases. Chromosome-7 was affected in 2 patients and chromosome-14 in 4. D-group involvement was present in 7 patients. Clonal expansion of aberrant chromosomes was noted in 3 cases (Table 5).

So far malignancy has occurred in only one patient (Case 6), who developed acute lymphoblastic leukaemia. Prolonged glucose tolerance tests were normal in all 7 patients tested. Electrolytes, thyroid function studies, and pituitary hormone levels (FSH, LH, growth hormone) were also normal in these patients.

Discussion

Since the complex of progressive cerebellar ataxia associated with bulboconjunctival telangiectasia was first reported in 1926, the multisystem nature of this disease has become clearer (Peterson *et al.*, 1964;

Ammann *et al.*, 1970; Paterson *et al.*, 1976). It is now known that involvement may include hepatic and endocrine organs, as well as neurological and immunological systems. The presence of debilitating sinopulmonary disease has been reported as a significant element of this syndrome (Boder and Sedgwick, 1957, 1958, 1963; Peterson *et al.*, 1964; McFarlin *et al.*, 1972). Correlations between pulmonary dysfunction and immunological abnormalities have been looked for without success (Boder and Sedgwick, 1963; Peterson *et al.*, 1964; Eisen *et al.*, 1965; Rosenthal *et al.*, 1965; Ammann *et al.*, 1969, McFarlin *et al.*, 1972).

Our patient population was distinctly different from those reported in the past in that the incidence of sinopulmonary disease was virtually nil. Several possible reasons for this difference may be considered. Firstly, it is possible that we have a genetically isolated population differing from others with this disease. This is unlikely, as our patients came from varied ethnic groups and from different parts of Canada. The second and most likely possibility is

that with increased awareness of this disease entity, less severe cases of A-T are now being diagnosed.

Immunological evaluation of our patients has shown similarly minimal dysfunction. IgA deficiency was present in 4/12 (33%) patients, a figure somewhat below those previously reported (Fireman *et al.*, 1964; Eisen *et al.*, 1965; Ammann *et al.*, 1969; McFarlin *et al.*, 1972; Polmar *et al.*, 1972; Kiran *et al.*, 1974). Interestingly, in one of our families, IgA deficiency was present in one patient and not the other, suggesting that the defect in this disease may not reflect a single gene phenomenon, or at least all deficits are not expressed in a simple recessive genetic fashion. IgE levels were found to be within the normal range in all patients. This is at variance with other reports of A-T (Epstein *et al.*, 1966; McFarlin *et al.*, 1972; Polmar *et al.*, 1972). Overall antibody function appeared to be adequate in these patients, as shown by a negative response to the Schick test, the presence of iso-haemagglutinins, and a normal booster response to antigen challenge. Similarly, T-cell function was grossly intact in these patients as suggested by delayed-hypersensitivity reactivity, E-rosette formation, and mitogen-induced lymphocyte proliferation. Significant lymphopenia was observed in only one patient. We could find no correlation between an immune defect and sino-pulmonary disease in our patients. Specifically, the 4 patients with most noticeable pulmonary symptoms had normal IgA and IgE levels, and lymphocyte counts. Delayed hypersensitivity reactions were absent in one of these patients, percentages of E-rosette forming T-cells were normal or only slightly decreased in all 4. The PHA response was within 1 SD of the mean for normal controls for 3 of these 4 individuals.

Levels of α -fetoprotein were raised in all these patients. This finding, first reported by Waldmann and McIntire (1972), may well become an invaluable diagnostic tool when the diagnosis of A-T is uncertain. Chromosome breakage was extensive in these patients, being present in 8/9 of our patients in whom an adequate number of cells could be obtained for examination. These breaks were of no specific type or unique pattern, although as in other reports (Cohen *et al.*, 1973; Hecht *et al.*, 1973; Nelson *et al.*, 1975), there was a high incidence of group-D involvement.

These findings suggest that the diagnosis of A-T should be considered in patients with moderate to severe neurological symptoms and less obvious involvement of cutaneous or pulmonary systems. We have found the pseudo-ophthalmoplegia in these patients a consistent finding and a useful aid in the diagnosis. α -Fetoprotein levels and evaluation for chromosome breakage have also proved to be

valuable diagnostic aids in evaluating equivocal cases of this syndrome. With further awareness of the full range of expression of A-T, more cases without a history of infections and with normal immunological findings will be recognised.

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Correspondence to Dr Erwin W. Gelfand, Department of Immunology, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.

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J M Jason and E W Gelfand

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