Diagnostic considerations in ataxia-telangiectasia

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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, $\alpha$-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.

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 radioimmunoassay 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 (<1·5×10⁹/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 3  Immunological data

<table>
<thead>
<tr>
<th>T-cell function</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte count</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>1.2</td>
<td>1.7</td>
<td>1.5</td>
<td>1.0</td>
<td>4.0</td>
<td>1.8</td>
<td>0.5</td>
<td>3.5</td>
</tr>
<tr>
<td>(x 10^9/l)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>+</td>
<td>±**</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>E-rosettes†</td>
<td>N</td>
<td>N</td>
<td>N→</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>PHA‡</td>
<td>N→</td>
<td>N→</td>
<td>N→</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>ND</td>
</tr>
</tbody>
</table>

** This patient had a response to Candida, with 5 mm of erythema and induration.
† E-rosettes was considered decreased (↓) 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 (↓) or 2 SD (↓↓) from the mean of control values (the mean control value was 33000 counts/min).
N = normal.

Table 4  Nonimmunological data

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Liver function tests†</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>α-Fetoprotein‡</td>
<td>250</td>
<td>300</td>
<td>180</td>
<td>255</td>
<td>100</td>
<td>240</td>
<td>310</td>
<td>160</td>
<td>280</td>
<td>94</td>
<td>44</td>
<td>ND</td>
</tr>
<tr>
<td>Glucose tolerance</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>ND</td>
<td>ND</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

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

Table 5  Chromosomal abnormalities

<table>
<thead>
<tr>
<th>No. of cells examined</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>62</td>
<td>33</td>
<td>11</td>
<td>12</td>
<td>12</td>
<td>8</td>
<td>16</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>No. of cells with breaks</td>
<td>35</td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>% cells with breaks</td>
<td>62</td>
<td>33</td>
<td>11</td>
<td>12</td>
<td>12</td>
<td>8</td>
<td>16</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>D-group affected (13–15)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Chromosome—14 affected</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Clones</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

†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 isohaemagglutinins, 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 sinus-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 a-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. a-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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References


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