Familial dysequilibrium-diplegia with T-lymphocyte deficiency

J. GRAHAM-POLE, A. FERGUSON,* A. A. M. GIBSON, and J. B. P. STEPHENSON
From the University Department of Child Health and Departments of Neurology and Pathology, Royal Hospital for Sick Children, and University Department of Bacteriology and Immunology, Western Infirmary, Glasgow

Graham-Pole, J., Ferguson, A., Gibson, A. A. M., and Stephenson, J. B. P. (1975). Archives of Disease in Childhood, 50, 927. Familial dysequilibrium-diplegia with T-lymphocyte deficiency. A second family is described with a combination of defective thymus-dependent immunity and cerebral palsy. The cerebral palsy comprised nonprogressive dysequilibrium and mild spastic diplegia without limb ataxia. This genetic entity of presumed autosomal recessive inheritance is clearly distinguished from ataxia-telangiectasia. Immunological abnormalities should be sought in other familial or unexplained cerebral palsy syndromes.

In 1970 Hagberg et al. reported as a new clinical entity the combination of ataxic diplegia and deficient cellular immunity in a brother and sister, both of whom died of overwhelming infection. The neurological picture of mild spastic diplegia with marked truncal ataxia was sufficiently well-defined to allow inclusion of the affected boy as Case 13 in the definitive paper on the dysequilibrium syndrome (Hagberg, Sanner, and Steen, 1972).

The evidence suggested a common genetic mechanism for the neurological and immunological disorder, but this inference was based on a single sibship. We report here a further family with the same combined affliction.

Case reports

The parents are unrelated and have had 4 children, the second and fourth of whom are entirely normal.

Case 1. The first-born, a girl, was born in 1963 after a normal pregnancy at 41 weeks' gestation, birthweight 3·9 kg. She had neonatal BCG immunization. She presented at 13 months because, though she had begun to crawl and stand holding on, she was unable to sit. She could not balance sitting on the flat and had a tendency to scissor gait with toes spread. At 21 months the picture was essentially the same, with minimal spasticity but inability to sit without props. Her parents felt that even when held sitting she was unsteady. She seemed to be a bright girl and had a few words of speech.

In her final illness she presented with foul bulky stools, weight loss, and cough. Oral thrush was followed by refractory pneumonia and she died at 23 months. A general post mortem only was carried out.

Case 2. The third sib, a boy, was born in 1966 of an uneventful pregnancy delivered at term, birthweight 3·2 kg, and was also immunized with BCG. His family doctor referred him at 8 months because 'he stands but cannot sit up, and has a tendency to let head flop forwards. Still some head lag'. Slight spasticity of the limbs was noted but was never striking. He began to crawl at 10 months and coast round his cot at one year, but like his sister he could sit only briefly on a slope and toppled backwards on the level. He began independent steps at 3 years, but lurched with knees bent and fell easily. At this time he could sit on the flat using one hand as a prop. He had tight heel cords and a tendency to tip-toe gait, but his main defect was one of balance and visuo-motor co-ordination. There was also some language delay and unco-ordinated phonation and articulation. Intelligence was assessed at 80–81 (Stanford-Binet Scale) at 4 years/10 months, 5 years/10 months, and 7 years. Tables I-III summarize the neurological findings in the 2 children.

Like his sister, he began to have loose foul stools in his third year, followed by recurrent antral and middle ear infections and persistent cough. Nevertheless, his tonsils and lymph nodes were always strikingly under-sized. He became increasingly listless and wasted, and suffered recurrent pneumonia. At the age of 7 years he developed an appendix abscess and peritonitis for which he required appendicectomy and hemicolectomy. Because functional and histological evi-
Graham-Pole, Ferguson, Gibson, and Stephenson

**TABLE I**

**Neurological findings: balance**

<table>
<thead>
<tr>
<th>Balance</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head control</td>
<td>4-5 m</td>
<td>8½ m</td>
</tr>
<tr>
<td>Sitting</td>
<td>12 m</td>
<td>10 m</td>
</tr>
<tr>
<td>On slope</td>
<td>3 yr*</td>
<td>3 yr*</td>
</tr>
<tr>
<td>Independent</td>
<td>Never</td>
<td>Never</td>
</tr>
<tr>
<td>Standing</td>
<td>10 m</td>
<td>8 m</td>
</tr>
<tr>
<td>Held</td>
<td>4 yr*</td>
<td>4 yr*</td>
</tr>
<tr>
<td>Independent</td>
<td>Never</td>
<td>Never</td>
</tr>
<tr>
<td>Crawled</td>
<td>10 m</td>
<td>10·11 m</td>
</tr>
<tr>
<td>Walking</td>
<td>14 m</td>
<td>12 m</td>
</tr>
<tr>
<td>Held</td>
<td>3½ yr</td>
<td>Never</td>
</tr>
<tr>
<td>Few steps</td>
<td>Never</td>
<td>Never</td>
</tr>
<tr>
<td>Independent</td>
<td>Never</td>
<td>Never</td>
</tr>
</tbody>
</table>

*Not stable for toilet functions at 5 years.

**TABLE II**

**Neurological findings: hands**

<table>
<thead>
<tr>
<th>Hands</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaching</td>
<td>5-6 m</td>
<td>Before 8 m</td>
</tr>
<tr>
<td>Lateral prop</td>
<td>Before 1 yr</td>
<td>Before 1 yr</td>
</tr>
<tr>
<td>Ataxia</td>
<td>No</td>
<td>Minimal L hand</td>
</tr>
<tr>
<td>Thumb adduction</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clumsiness</td>
<td>+</td>
<td>Poor pencil control, shaky writing, primitive grasp at 5 yr, never could tie bows</td>
</tr>
</tbody>
</table>

**TABLE III**

**Neurological findings: lower limbs**

<table>
<thead>
<tr>
<th>Lower limbs</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valgus ankles</td>
<td>+</td>
<td>? ('flat feet')</td>
</tr>
<tr>
<td>Tip-toe gait</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>'Tight' tendo achilles</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Spasticity</td>
<td>'No sign'</td>
<td>'Not easily detected'</td>
</tr>
<tr>
<td>Extensor plantars</td>
<td>'Not much'</td>
<td>'Very little' (7 yr)</td>
</tr>
<tr>
<td>Protective responses</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Investigations

**Differential white cell counts.** Performed with a Coulter Counter and Leishman's stain, counting 100 cells. 5% 2,4-dinitrochlorobenzene (DNCB) sensitization: 0·1 ml in acetone was applied to the volar fore-arm. Sensitization was evaluated after 3 weeks by applying 0·1% DNCB in acetone to the opposite forearm and reading daily for a week.

**Lymphocyte transformation.** Tested with phytohaemagglutinin (PHA-Wellcome) and poke-weed mitogen (PWM, Grand Island Biological Co.). Mitogens were used at concentrations known to give optimal responses in normal adults. The cells were incubated for 3 days and 14C-thymidine (0·2 μCi/culture) was added for the last 4 hours. Incorporation of thymidine into DNA of cultured cells was measured by extracting the DNA from each culture on a glass fibre filter and counting radioactivity in a liquid scintillation counter (Packard). Triplicate cultures were set up with PHA, PWM, and with no added mitogen, and results were expressed as counts/min per 10⁶ lymphocytes. Also, cytocentrifuge smears of cultured cells were stained with Leishman and blast cell transformation assessed morphologically.

**Serum immunoglobulins.** Assayed by single radial immunodiffusion using Hoechst tri-partigen plates and immunoglobin standard.

**Bacterial agglutinins.** Detected with disposable microtitre trays (Flow Labs).

**Antiviral antibodies.** Measured using preinfected 10⁹ Vero tissue culture cells and titrating by indirect immunofluorescence with serial dilution of serum samples.

**Results**

Table IV summarizes the functional and histological evidence for impairment of cell-mediated immunity in the 2 children. The limited investigation of Case 1 showed her to have a normal total γ-globulin level but a low lymphocyte count of 450/mm² and negative 1:100 Mantoux reaction, though she had had neonatal BCG immunization (without ill effect). Her brother showed failure of DNCB sensitization and negative skin tests, plus a persistent lymphopenia and minimal mitogenic responses (PHA: 1642-482=1160 cpm; PWM: 1199-482=717 cpm). In a group of normal children tested in the same laboratory, mean values for PHA and PWM minus control (no added mitogen) responses were 3900 cpm and 4200 cpm respectively, and values below 1000 cpm were found only in children with grossly defective cellular immunity (Graham-Pole et al., 1975). Circulating immunoglobulins in Case 2 were normal though they fell terminally and he had normal antibody production to bacterial, viral, and heterologous blood group antigens. These findings, together with radiological absence of a thymic shadow strongly suggested defective cell-mediated immunity.
Pathology. Fig. 1 and 2 show the histology of lymphoid tissues from the 2 children. A general necropsy only was performed on Case 1, which showed extensive haemorrhagic pneumonitis, probably viral. *Pneumocystis carinii* organisms were also identified in some areas. All lymphatic tissues were atrophic and lymphocytes were scanty, particularly in the para-cortical zone of the lymph nodes and the periarteriolar zone of the spleen. Nodular lymphatic tissue was atrophic and no germinal centres were seen, suggesting disturbed B-cell (thymus-independent) function also, though plasma cells were present in normal numbers. The state of the thymus was not recorded. The cerebellum was of normal size, but no neuropathological examination was made. In Case 2 the most striking feature was the paucity of submucosal lymphoid tissue in the terminal ileum and appendix. There was marked reduction of lymphocytes, with ill-defined lymphatic nodules lacking germinal centres. Plasma cells in the lamina propria were however normal. The mesenteric lymph nodes were identical to those of his sib. In summary, the histology of the lymphoid tissue was similar in the 2 sibs and supports a serious disturbance of T-cell function, with the virtual absence of germinal centres suggesting some B-cell dysfunction also.

Discussion

This report suffers from two handicaps. The neurology is largely retrospective and dependent on case notes and recollection by medical staff, therapists, and parents, aided by domestic photographs; and there is no neuropathology. The composite picture, however, strongly resembles that described by Hagberg *et al.* (1970), and this identity has been confirmed by G. Sanner (personal communication, 1974). The neurological syndrome is neither a 'pure' dys equilibrium nor an ataxic diplegia but is dominated by dys equilibrium without notable limb ataxia, that is, dys equilibrium–diplegia. Hagberg *et al.* (1970) showed the pathology to be neuronal dysplasia with heterotopia, implying abnormal neuronal migration in embryogenesis.

The immunological defect in our children is also identical to theirs, consisting of defective lymphocyte production and cellular immunity with essentially normal immunoglobulin levels and antibody production. Though IgG values were low terminally and the histological finding of absent germinal centres suggests a possible fault in the B-cell system, the prime defect is clearly one of cell-mediated immunity, almost certainly due to thymic dysplasia. The combination of deficient cellular immunity and dysplasia with autosomal recessive inheritance is also seen in the Louis–Bar syndrome, ataxia-telangiectasia. These patients usually have morphological and functional evidence of defective immunoglobulin production, however, and may have progressive decline in cellular immune competence in addition (Peterson and Good, 1968). Neurologically the distinction
between the two disorders is clear-cut (Table V). Diplegia with extensor plantars was recorded in all 4 children with dysequilibrium-diplegia, but is never a feature of ataxia-telangiectasia, while chorea, dystonia, and oculomotor apraxia, characteristic of the latter, have not been observed. The neuropathology of the Louis-Bar syndrome is also distinctive (Terplan and Krauss, 1969).

Both of these syndromes are intriguing models for studying the genetic basis of disordered neurological and immunological development. Some genetic loci responsible for brain antigen specificities have...
been indentified in the mouse (Moore et al., 1971), including the theta system, a pair of antigenic specificities present in high concentration only in thymic lymphocytes and in major white matter tracts of the brain, suggesting antigenic determinants common to thymus and nervous system.

In the dysequilibrium-diplegia syndrome the neurological handicap is sufficiently mild to justify attempts to restore immune competence. Cellular immunity has been successfully restored in Di-George's syndrome (Cleveland et al., 1968) and in pure T-cell deficiency (Foroozanfar et al., 1975),

**Fig. 2**—(a) Case 1. Mesenteric lymph node showing similar atrophic changes to sib in Fig. 1a. (H. and E. × 110.)
(b) Spleen showing lymphocytic depletion in the perivascular sheath. (H. and E. × 110.)
and could be anticipated in the patient described here. The fetal thymus was implanted terminally, however, and failure to achieve a rise in lymphocyte count or PHA-responsiveness is attributable to his poor constitutional state, recent surgery, and the presence of sepsis. We are continuing immunological screening of children with unexplained diplegia and dysequilibrium syndromes, who might benefit from fetal thymus implants at an early age.

We thank Professor J. H. Hutchison and Dr. D. Wallace for allowing us to report on this family under their care, the fetal tissue bank of the Royal Marsden Hospital (Director: Dr. S. Lawler) who supplied the fetal thymus, and Mrs. S. Aitken for technical help.

This paper was first presented by J.B.P.S. at the 9th International Study Group on Child Neurology and Cerebral Palsy (St. Edmund Hall) Oxford, 1974.

REFERENCES

TABLE V
Two autosomal recessive neuroimmunological disorders compared

<table>
<thead>
<tr>
<th>Neurology</th>
<th>Dysequilibrium-diplegia syndrome</th>
<th>Ataxia-telangiectasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evolution</td>
<td>Static</td>
<td>Progressive (may be slow)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>±</td>
<td>+ +</td>
</tr>
<tr>
<td>Dysequilibrium</td>
<td>+</td>
<td>+ +</td>
</tr>
<tr>
<td>Diplegia</td>
<td>(4/4)</td>
<td>(never)</td>
</tr>
<tr>
<td>Extensor plantaris</td>
<td>-</td>
<td>+ -</td>
</tr>
<tr>
<td>Chorea-athetosis</td>
<td>Neuronal dysplasia + heterotopia</td>
<td>Cerebellar atrophy</td>
</tr>
<tr>
<td>Oculomotor apraxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathology</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Immunology           |                                   |                             |
| Humoral immunity     | Normal                            | Selective impairment        |
| T-cell function      | Early severe incompetence (? static) | Progressive impairment |

Correspondence to Dr. J. B. P. Stephenson, Assessment Unit, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ.