Familial dysequilibrium-diplegia with T-lymphocyte deficiency

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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 3.2 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 3.9 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 undersized. 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-

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TABLE I
Neurological findings: balance

Balance	Case 1	Case 2
Head control	4-5 m	8½ m
Sitting		
On slope	12 m	10 m
Independent	Never	3 yr*
Standing		
Held	10 m	8 m
Independent	Never	4½ yr*
Crawled	10 m	10-11 m
Walking		
Held	14 m	12 m
Few steps	Never	3½ yr
Independent	Never	Never

*Not stable for toilet functions at 5 years.

TABLE II
Neurological findings: hands

Hands	Case 1	Case 2
Reaching	5-6 m	Before 8 m
Lateral prop	Before 1 yr	Before 1 yr
Ataxia	No	Minimal tremor L hand
Thumb adduction	+	+
Clumsiness	+	+
		Poor pencil control, shaky writing, primitive grasp at 5 yr, never could tie bows

TABLE III
Neurological findings: lower limbs

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

dence was found of defective cell-mediated immunity, a 14-week fetal thymus was implanted (by Mr. D. G. Young) into the rectus abdominis muscle under local anaesthesia, but he died 10 days later without notable clinical or immunological improvement. Consent for necropsy examination was refused.

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 immunoglobulin standard.

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

Antiviral antibodies. Measured using preinfected 10³ 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/mm³ 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.

TABLE IV
Immunological investigation

Test	Case 2			Case 1
Skin tests (0.1 ml intradermal antigen)	Old tuberculin 1:100 Negative	Streptokinase Negative	<i>Candida</i> Negative	Old tuberculin 1:100 Negative
Dinitrochlorobenzene 5% sensitization	No response to primary application nor subsequent testing			Not done
Chest x-ray	No thymic shadow Bilateral bronchiectasis			Severe bronchopneumonia
Lymphocyte count (/mm ³)	Mean 390 (range 25-970)			450
Mitogen responses				
¹⁴ C-thymidine incorporated into DNA (counts/min per 10 ⁶ lymphocytes)	No mitogen	Test 1 482	Test 2 No	Not done
Immunoglobulins (mg/100 ml)	PHA 1642 PWM 1199	No detectable transformation		
	IgG 750 320 370	IgA 93 150 60	IgM 102 74 41	IgE 174 units/ml
Antibody titres	Bacteroides 1:4 Anti-A 1:16	<i>Esch. coli</i> 1:4 Anti-A ₂ 1:8	<i>Herpes simplex</i> 1:16 Anti-B 1:4	Total γ-globulin 1400 mg/100 ml
Isohaemagglutinins				Not done
Lymph nodes	Atrophic			Atrophic
Plasma cells in lymph nodes	Present			Present
Lymphocytes in thymus-dependent areas	Absent			Absent

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 paracortical 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' dysequilibrium nor an ataxic diplegia but is dominated by dysequilibrium without notable limb ataxia, that is, dysequilibrium-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 dysequilibrium 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

FIG. 1.—(a) Case 2. Mesenteric lymph node showing gross lymphocytic depletion in paracortical zone and poorly formed cortical lymphoid follicles. (H. and E. $\times 110$). (b) Appendix showing atrophic submucosal lymphoid tissue. (H. and E. $\times 40$.)

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 neuro-

pathology 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

FIG. 2—(a). Case 1. Mesenteric lymph node showing similar atrophic changes to sib in Fig. 1a. (H. and E. $\times 110$.)
(b) Spleen showing lymphocytic depletion in the perivascular sheath. (H. and E. $\times 110$.)

been identified 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),

TABLE V

Two autosomal recessive neuroimmunological disorders compared

	Dysequilibrium-diplegia syndrome	Ataxia-telangiectasia
<i>Neurology</i>		
Evolution	Static	Progressive (may be very slow)
Ataxia	±	+ → + +
Dysequilibrium	+ +	+ → + +
Diplegia	+ (4/4)	- (never)
Extensor plantars } Choreo-athetosis } Oculomotor apraxia }	-	+ → + +
<i>Neuropathology</i>	Neuronal dysplasia + heterotopia	Cerebellar atrophy
<i>Immunology</i>		
Humoral immunity	Normal	Selective impairment
T-cell function	Early severe incompetence (? static)	Progressive impairment

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.

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REFERENCES

- Cleveland, W. W., Fogel, B. J., Brown, W. T., and Kay, H. E. M. (1968). Foetal thymic transplant in a case of DiGeorge's Syndrome. *Lancet*, 2, 1211.

- Foroozanhar, N., Yamamura, M., Watson, G., Weaver, P., Belton, E. M., Lawler, S., and Hobbs, J. R. (1975). Successful thymus graft for T-cell deficiency in a 6-year-old boy. *British Medical Journal*, 1, 314.
- Graham-Pole, J., Willoughby, M. L. N., Aitken, S., and Ferguson, A. (1975). The immune status of children with and without severe infection during remission of malignant disease. *British Medical Journal*, 2, 467.
- Hagberg, B., Hansson, O., Lidén, S., and Nilsson, K. (1970). Familial ataxic diplegia with deficient cellular immunity. *Acta Paediatrica Scandinavica*, 59, 545.
- Hagberg, B., Sanner, G., and Steen, M. (1972). The dysequilibrium syndrome in cerebral palsy. *Acta Paediatrica Scandinavica*, Suppl. 226.
- Moore, M. J., Dikkes, P., Reif, A. E., Ramamel, C. A., and Sidman, R. L. (1971). Localization of theta alloantigens in mouse brain by immunofluorescence and cytotoxic inhibition. *Brain Research*, 28, 283.
- Peterson, R. D. A., and Good, R. A. (1968). Ataxia-telangiectasia. *Immunological Deficiency Diseases in Man, Birth Defects Original Article Series*, Volume IV, No. 1, p. 370. Ed. by D. Bergsma. National Foundation, New York.
- Terplan, K. L., and Krauss, R. F. (1969). Histopathological brain changes in association with ataxia-telangiectasia. *Neurology*, 19, 446.

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