small bowel aganglionosis occur in only 1–10% of various series. Total intestinal involvement is the rarest form of the disease.

Hirschsprung's disease is probably multifactorial in its causation (Bodian and Carter, 1963). However, in one strain of mice a similar condition appears to be inherited as an autosomal recessive (Bielschowsky and Schofield, 1962). If the family reported here and the 10 previously reported cases of total intestinal aganglionosis are combined (Lee, 1955; Boggs and Kidd, 1958; Bodian and Carter, 1963; Walker *et al.*, 1966; Ahmed *et al.*, 1971; Talwalker, 1976) 50% of sibs are affected, and none with a lesser degree of aganglionosis. In those reports which include a description of other sibs (Fig.), and allowing for failure to ascertain those families at risk in which no children have been affected, the pattern suggests that total intestinal aganglionosis may be a distinct entity, inherited as an autosomal recessive.

Summary

A case of total intestinal aganglionosis in a sib of a previously recorded patient is presented. The number of cases now reported is 9 in six families. The possibility that this condition is a distinct entity inherited in an autosomal recessive manner is discussed.

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References

- Ahmed, S., Cohen, S. J., and Jacobs, S. I. (1971). Total intestinal aganglionosis presenting as duodenal obstruction. *Archives of Disease in Childhood*, **46**, 868–869.
- Bielschowsky, M., and Schofield, G. C. (1962). Studies on megacolon in piebald mice. *Australian Journal of Experimental Biology and Medical Science*, **40**, 395–404.
- Bodian, M., and Carter, C. O. (1963). A family study of Hirschsprung's disease. *Annals of Human Genetics*, **26**, 261–277.
- Boggs, J. D., and Kidd, J. M. (1958). Congenital abnormalities of intestinal innervation. *Pediatrics*, **21**, 261–265.
- Ehrenpreis, T. (1970). *Hirschsprung's Disease*, p. 58. Year-book Medical Publishers, Chicago.
- Lee, C. M., Jr. (1955). Megacolon, with particular reference to Hirschsprung's disease. *Surgery*, **37**, 762–777.
- Talwalker, V. C. (1976). Aganglionosis of the entire bowel. *Journal of Pediatric Surgery*, **11**, 213–216.
- Walker, A. W., Kempson, R. L., and Ternberg, J. L. (1966). Aganglionosis of the small intestine. *Surgery*, **60**, 449–457.

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Idiopathic late-onset immunoglobulin deficiency with associated defect in cell-mediated immunity

Idiopathic late-onset immunoglobulin deficiency is a disease which is highly variable in severity, age of onset, and pattern of immunoglobulin deficiency. It is regarded as a heterogeneous group of syndromes (Geha *et al.*, 1974) and is designated 'common variable immunodeficiency' in the WHO classification. We describe a Southern Chinese boy who presented with recurrent respiratory infections and malabsorption and who has an associated defect in cell-mediated immunity.

Case report

The patient presented in January 1975 at the age of 8 years, after developing sudden weakness of the legs, preceded by a 2-month history of steatorrheic diarrhoea and fever for one week. Hypokalaemia was detected (serum K⁺ 2.2 mmol/l) and he was treated with Slow-K and referred to our hospital. His perinatal history was normal; he was breast fed and had full courses of BCG, DTP, and polio immunizations. Since early childhood he had had frequent upper and lower respiratory tract infections and episodes of loose stools. He developed uncomplicated measles when aged 7, after which he had persistent diarrhoea and productive cough. There was no family history of susceptibility to infection.

He was a small, thin boy (height 110.5 cm, weight 16.8 kg) with dry skin, clubbing of all digits, and small, discrete cervical and inguinal lymph nodes. Tonsils were of normal size. The chest was of normal shape with satisfactory expansion and occasional basal crepitations. The liver was palpable 1 cm and the spleen 2–3 cm below the costal margins (both were firm). Rectal examination was normal. The cardiovascular and nervous systems were normal.

Investigations. Hb 11.8 g/dl. White cell count 9850/mm³ (9.9 × 10⁹/l); differential count polymorphs 73%, lymphocytes 22%, monocytes 5%. Platelet count normal. Serum Na⁺ 139 mmol/l, K⁺ 2.9 mmol/l, alkaline phosphatase 160 μmol/min per l, bilirubin 10.3 μmol/l (0.6 mg/100 ml), SGOT 15 μmol/min per l, SGPT 13 μmol/min per l, albumin 40 g/l, globulin 17 g/l.

Serum immunoglobulin levels: IgG 2.78 g/l, IgM 0.13 g/l, IgA 0.37 g/l (all subnormal for age). Chest x-ray showed diffuse pulmonary mottling and peribronchial thickening. Bone age was 5–6 years.

Stools were yellow, foamy, and foul-smelling with no parasites or pus cells detectable; 24-hour faecal fat excretion was 50 g. Barium meal showed dubious 'cobble-stone' appearances of the duodenum; barium enema was normal. Urine excretion of Na^+ and K^+ was normal; glucose tolerance test was normal, and there was mild impairment of xylose absorption and BSP excretion.

Jejunal biopsy: mucosa showed normal villi and epithelial brush borders, nodular lymphoid hyperplasia, and heavy infestation with *Giardia lamblia*. Liver biopsy showed nonspecific inflammation only.

Progress. Diarrhoea subsided after treatment with metronidazole, and serum K^+ remained at 3–4 mmol/l without further supplements; a repeated faecal fat excretion was 21 g in 72 hours. The serum albumin level remained normal. In August 1975 bronchography showed no evidence of bronchiectasis, though pulmonary function testing showed a marked restrictive defect. He had two episodes of bronchopneumonia early in 1976 and a persistently wet chest. Hepatosplenomegaly remained unchanged. Although he has gained 5 cm in height in the 2 years since presentation, his weight has remained unchanged. He recently developed eczema of the hands and feet and also sterile arthritis of the knees. In November 1976, weekly injections of normal human gammaglobulin 25 mg/kg were begun. Subsequently there was marked improvement in his chest symptoms and clearing of the eczema. His current IgG level is about 4.0 g/l.

Special investigations.

Serum complement levels (CH50, C4, C5, and C6) were assayed by standard techniques. **Lymphocyte subpopulations** were determined using lymphocytes separated from heparinized venous blood over Ficoll-Hypaque. T cells were detected by the formation of 'E' rosettes with sulphhydryl-treated sheep erythrocytes (Kaplan and Clark, 1974). B cells were counted by (1) the formation of 'EAC' rosettes, and (2) the detection of surface-membrane-immunoglobulin by indirect immunofluorescence.

Delayed-type hypersensitivity (DTH) skin tests were performed by intradermal injection of four recall antigens; PPD (Tine Test, Lederle), PPD (CSL), Candida and Trychophyton extracts (Bencard), and SKSD (Lederle). **Lymphocyte blast transformation** was assessed by the stimulation of DNA synthesis (uptake of ^3H -thymidine) above controls by phytohaemagglutinin (PHA-P, Difco), concanavalin-A (Sigma) at optimal concentrations and pooled mitomycin-C treated lymphocytes from five donors (mixed lymphocyte reaction). 50 000

responder cells were cultured in quadruplicate in micro-T/C plates with and without the appropriate stimulant. Cultures were harvested semiautomatically at 3 and 6 days respectively.

Granulocyte function. Phagocytosis and killing of *Candida albicans* in the presence of autologous plasma was carried out by the method of Lehrer and Cline (1969). Killing of *E. coli* was assessed by the method of van Furth and van Zuet (1973). Chemotaxis of granulocytes under agarose was performed by the method of Nelson *et al.* (1975). Zymosan-activated human serum was the chemoattractant and migration was measured microscopically with the aid of a graduated eyepiece.

Results

Specific serum antibody activity. Anti-A isoagglutinin was weakly detectable in the serum (titre <1:2, red cells group B); antibodies to *Mycoplasma pneumoniae*, influenza A and B, adenovirus, and measles virus were not detectable. Neutralizing antibodies to poliovirus were present at titres of 1:4 and 1:8.

Serum complement. CH50, C3, C4, C5, and C6 were all normal.

Lymphocyte subpopulations and tests of cell-mediated immunity (Table). The proportions of T and B lymphocytes were normal as were the absolute counts. DTH skin tests were all negative. Mixed lymphocyte reactivity *in vitro* was absent and the responses to mitogens were low.

Table Lymphocyte subpopulations and tests of cell-mediated immunity

Investigation	Result	Normal range
T cells		
'E' rosettes'	72%	60–82%
B cells		
'EAC rosettes'	23%	12–25%
Surface Ig	23%	15–30%
Skin tests		
PPD		
5 TU	Negative	
100 TU	Negative (erythema only)	
Candida extract	Negative	
Trychophyton extract	Negative	
SKSD	Negative	
Lymphocyte transformation		
Concanavalin A (cpm/ 10^6 cells)	1 310	10 000–100 000
Phytohaemagglutinin	41 250	60 000–500 000
Mixed lymphocyte reaction	0	7 000–90 000

TU = tuberculin unit.

Phagocyte function. Blood granulocytes phagocytosed and killed *C. albicans* normally; phagocytic index 4.1 (normal 2–4); killing 33% (normal 20–42%).

Fig. Jejunal biopsy showing nodular lymphoid hyperplasia (H & E. $\times 30$.)

E. coli were also killed at a normal rate: $T_{\frac{1}{2}}$ 23.5 min (normal 12–25 min). The chemotactic response of neutrophils was brisk; 1950 μ m in 2 hours (normal 650–2000 μ m).

Discussion

This case of late-onset immunoglobulin deficiency in a Chinese boy was diagnosed on the basis of low serum levels of the major immunoglobulin classes, the onset of persistent diarrhoea and purulent bronchitis with recurrent pneumonia at the age of 7, and the finding of lymphoid hyperplasia of the small bowel (Fig.) and giardiasis. The child illustrates most of the clinical features of the disease as described in Caucasians (Hermans *et al.*, 1976) which usually presents in adult life, rarely in childhood. The heterogeneity of this disease has been emphasized (Geha *et al.*, 1974) and it has been postulated that this results from defects occurring at different stages in the maturation of B cells. Our patient showed a defect in T cell function, having negative DTH skin tests, no proliferative response of his lymphocytes to allogeneic cells in the mixed lymphocyte reaction and low lymphocyte responses to two T cell mitogens (Table). This could not be attributed to a selective loss of T cells into the gut, in that the absolute T cell count in the blood remained normal, as did the total lymphocyte count. An impairment of T cell function has been observed in approximately one-third of cases (Gajl-Peczalska *et al.*, 1973; Geha *et al.*, 1974). It is unclear whether this abnormality results from the essential defect in lymphocyte maturation, or whether it is secondary to persistent antigenic stimulation by bacterial infections and injections of homologous protein. Waldmann *et al.* (1974) have

shown that the immunoregulatory role of T cells may be disturbed leading to suppression of immunoglobulin synthesis.

Summary

An 8-year-old boy presented with idiopathic late-onset immunoglobulin deficiency manifested principally by recurrent suppurative chest infections and chronic diarrhoea with malabsorption. Nodular lymphoid hyperplasia and giardiasis were shown on small bowel biopsy. Investigation of the immune system showed low serum levels of IgG, IgM, and IgA, negative skin tests to four recall antigens, absent mixed lymphocyte reactivity, and impaired lymphocyte responses to mitogens *in vitro*. Serum complement and granulocyte function studies were normal. Maintenance therapy with gammaglobulin and antibiotics gave a good response.

References

- Furth, R. van, and Zwet, T. L. van (1973). *In vitro* determination of phagocytosis and intracellular killing by polymorphonuclear and mononuclear phagocytes. *Handbook of Experimental Immunology*, 2nd ed., Vol. 2, Ch. 36. Ed. by D. M. Weir. Blackwell, Oxford.
- Gajl-Peczalska, K. J., Park, B. H., Biggar, W. D., and Good, R. A. (1973). B and T lymphocytes in primary immunodeficiency disease in man. *Journal of Clinical Investigation*, **52**, 919–928.
- Geha, R. S., Schneeberger, E., Merler, E., and Rosen, F. S. (1974). Heterogeneity of 'acquired' or common variable agammaglobulinemia. *New England Journal of Medicine*, **291**, 1–6.
- Hermans, P. E., Diaz-Buxo, J. A., and Stobo, J. D. (1976). Idiopathic late-onset immunoglobulin deficiency. Clinical observations in 50 patients. *American Journal of Medicine*, **61**, 221–237.
- Kaplan, M. E., and Clark, C. (1974). An improved rosetting assay for detection of human T lymphocytes. *Journal of Immunological Methods*, **5**, 131–135.
- Lehrer, R. I., and Cline, M. J. (1969). Interaction of *Candida albicans* with human leukocytes and serum. *Journal of Bacteriology*, **98**, 996–1004.
- Nelson, R. D., Quie, P. G., and Simmons, R. L. (1975). Chemotaxis under agarose: a new and simple method for measuring chemotaxis and spontaneous migration of human polymorphonuclear leukocytes and monocytes. *Journal of Immunology*, **115**, 1650–1656.
- Waldmann, T. A., Durm, M., Broder, S., Blackman, M., Blaese, R. M., and Strober, W. (1974). Role of suppressor T cells in pathogenesis of common variable hypogammaglobulinaemia. *Lancet*, **2**, 609–613.
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