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Yeast opsonization defect and immunoglobulin deficiency in severe infantile dermatitis (Leiner's disease)

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SUMMARY The defect in Leiner's disease, which presents in early infancy with extensive dermatitis, diarrhoea, and failure to thrive, has been attributed to a defect of the fifth component of complement (C5). We report 2 brothers with extensive dermatitis and dysgammaglobulinaemia. Both died. The older showed symptoms of Leiner's disease: C5 tests were not performed. The younger had extensive dermatitis and was found to have the C5 defect. He developed normally, but died suddenly with pertussis. We postulate that the C5 defect is not the sole cause of Leiner's disease as has been suggested, but that hypogammaglobulinaemia or other lymphoid deficiency is also required for its expression.

Leiner (1908) described a disease of young babies characterized by extensive dermatitis, failure to thrive, and diarrhoea. Both boys and girls were affected, from the age of 5 weeks to 4 months. 60 years later Miller and his colleagues (1968) attributed the disease to a defect of opsonization. They found that plasma from their patient failed to support phagocytosis of yeast particles by normal neutrophils, and later (Miller and Nilsson, 1970) concluded that this was due to a functional defect of the fifth component of complement (C5) which was detectable by phagocytosis assay but not by immunodiffusion using anti-C5 antiserum. The defect of phagocytosis was corrected by the addition of purified mouse C5, but not by serum from mice congenitally deficient in C5.

A second affected boy was described by Jacobs and Miller (1972). He developed bloody diarrhoea at 2 weeks of age, followed by severe seborrhoeic dermatitis. Immunoglobulin levels showed IgG 4·3 g/l, at the lower limit of normal for this age (Stiehm and Fudenberg, 1966). 3 maternal cousins died young, 2 with unusual malignancies, which raised the possibility of a more generalized immune defect in the family.

The patients were successfully treated with regular infusions of fresh plasma on the basis that they provided active C5. Family studies showed the opsonization defect in the mothers of the patients, and in other family members, but it has been puzzling that the relatives, whose plasma showed an opsonization defect of equal severity to that seen in the babies, were fit and had no similar illness when they themselves were babies. The inheritance of the disorder has thus not been clear.

Scott *et al.* (1975) presented details of a third case with the clinical symptoms described by Miller. A girl of 2 months developed diarrhoea, seborrhoeic dermatitis, staphylococcal arthritis and osteomyelitis, and extensive histiocytosis with lymphocyte depletion at necropsy. The yeast opsonization defect was demonstrated and there was incomplete improvement with infusions of fresh plasma.

We have seen 2 brothers with extensive seborrhoeic dermatitis clinically resembling Leiner's disease. The first died with pneumonia. He also had dysgammaglobulinaemia with low IgG and high IgM, but the opsonization test was not performed. The second boy also had extensive seborrhoeic dermatitis but no diarrhoea and was progressing well, but died suddenly with a severe attack of whooping cough. He also had hypogammaglobulinaemia. His cord blood showed the opsonization defect and the abnormality was confirmed a month later. Family studies have shown variable results. On one occasion the boy's father showed defective opsonization; but later results were normal. The mother's yeast opsonization tests were normal, but immunoglobulins during the second pregnancy showed an imbalance. We suggest that in this family the clinical

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disease resulted from a combined deficiency state consisting of an opsonization defect together with immunoglobulin deficiency. Babies undergo a period of physiological hypogammaglobulinaemia during the early months of life. In some babies the fall in IgG may be more profound—the transient hypogammaglobulinaemia of infancy (Rosen and Janeway, 1966). Any baby with a pre-existing opsonization defect would become particularly susceptible to disease when his IgG levels fell in this way; but he would be able to compensate as IgG synthesis increased with age. Plasma infusions supply normal immunoglobulins as well as complement components, and the improvement shown by Miller's 2 patients with plasma infusions could be attributed as much to the immunoglobulin as to the postulated C5. This explanation would also account for the facts that Leiner's disease appears only in infants in the first months of life (because this is when IgG is low), that the babies can recover (as levels of IgG increase), and that adult family members with the opsonization defect are symptom free (because they have normal immunoglobulin levels).

Materials and methods

Immunoglobulins were measured by the radial immunodiffusion method using commercially available materials (Immunoplates, Hyland). Sera from Case 1 were retested after storage for 3 years at −20°C. Sera from the family and Case 2 were tested after 2 weeks to 20 months at −20°C. Plasma for the opsonization test on the baby was tested fresh by the method described by Miller *et al.* (1968) using neutrophils, from laboratory staff, previously shown to function normally. Later family tests were made using both neutrophils and plasma from patients and controls. In this test 0·2 ml of a leucocyte suspension (5×10^6 leucocytes/ml), 0·1 ml of a suspension of baker's yeast (1×10^9 yeasts/ml), and 0·1 ml of 10% plasma were mixed at 37°C for 30 minutes on a rotating wheel. The number of cells showing phagocytosis and the number of yeast particles ingested were counted on slides made from the suspensions, stained with Jenner-Giemsa. The test shows day-to-day variation, and only a marked difference from the control has been classed as abnormal.

Case reports

Case 1. A first child, born on 27 April 1972. After a normal pregnancy and delivery, he developed dry skin and started vomiting. Milk allergy was diagnosed and he was treated with a soya bean milk and corticosteroids orally and locally. He failed to respond and was transferred to Booth Hall Children's Hospital.

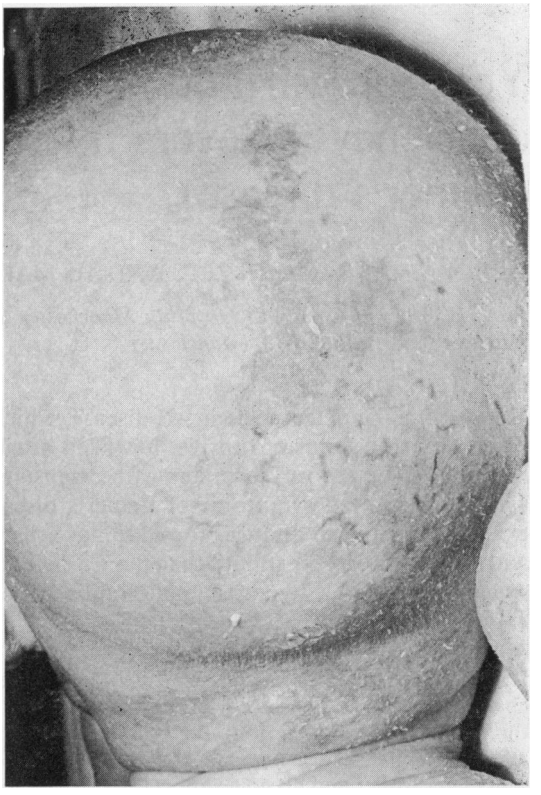

Fig. 1 *Case 1. Scalp showing dermatitis with atrophic areas.*

He had seborrhoeic dermatitis affecting the whole body including the scalp (Fig. 1), pitting oedema of the feet, and extensive lymphadenopathy. Oral moniliasis was present and responded to treatment with nystatin. Diarrhoea was not present. There was a constant polymorph leucocytosis. His condition deteriorated and the liver and spleen enlarged. Septic areas appeared on the arm and leg, which grew *Staph. aureus*, *Strep. faecalis*, and *E. coli*. Because of persisting leucocytosis the bone marrow was examined: it showed increased cellularity with increased granulocyte production. The granulocytes showed toxic changes. Lymphocytes were 20%. Myeloid/erythroid ratio 2·3/1. Serum immunoglobulins showed a low IgG of 2·58 g/l with IgA 1·26 g/l and high IgM 5·0 g/l.

In spite of treatment with gammaglobulin and antibiotics his condition deteriorated and he died at the age of 6 months, with a terminal neutropenia. Necropsy showed bilateral bronchopneumonia and lymphoid depletion in the gastrointestinal tract.

Degenerate but numerous Hassall's corpuscles were present in the thymus, with reduced macrophages, many leucocytes, and increased fibrous tissue and fat. The epithelial pattern was clearly visible, but atrophied. Subcapsular granulomas were present in the lymph nodes, which showed little follicle formation and loss of sinus pattern. The follicles showed few germinal centres. The tonsil showed a small amount of lymphoid tissue but no follicle formation (Dr. H. B. Marsden).

Initially it was thought that this was an immunoglobulin defect and the family was tested. The results are shown in Table 1.

Other investigations. Faecal trypsin: activity present to 1:160. Blood urea 44 mg/100 ml (7·3 mmol/l); serum Na 141 mEq/l (141 mmol/l), K 5·3 mEq/l, (5·3 mmol/l), Cl 107 mEq/l (107 mmol/l); serum bilirubin 0·3 mg/100 ml (5·13 μmol/l). Hb 9·6 g/dl, WBC $30{\cdot}5\times10^9$/l (polymorphs 39%, lymphocytes 45%, monocytes 5%, eosinophils 11%); ESR 17 mm/h. Faecal sugar chromatography, no sugar detected. Urine amino acid chromatography normal. Urine, protein nil, sugar nil, <20 WBC/mm^3.

Case 2. The second child was born on 16 August 1974 after a normal pregnancy. His cord serum was tested and showed defective yeast opsonization. The test was repeated at the age of one month and the abnormality confirmed. He too developed seborrhoeic dermatitis (Fig. 2) but no diarrhoea and was developing well. The skin condition fluctuated in severity but his progress was never in doubt. He was seen infrequently as an outpatient.

At 5 months he developed whooping cough but it was not thought severe enough for hospital admission. After a week his condition became suddenly worse with diarrhoea. The white cell count was 120×10^9/l, with 70% lymphocytes and 25% neutrophils. No localized infection was seen on chest *x*-ray.

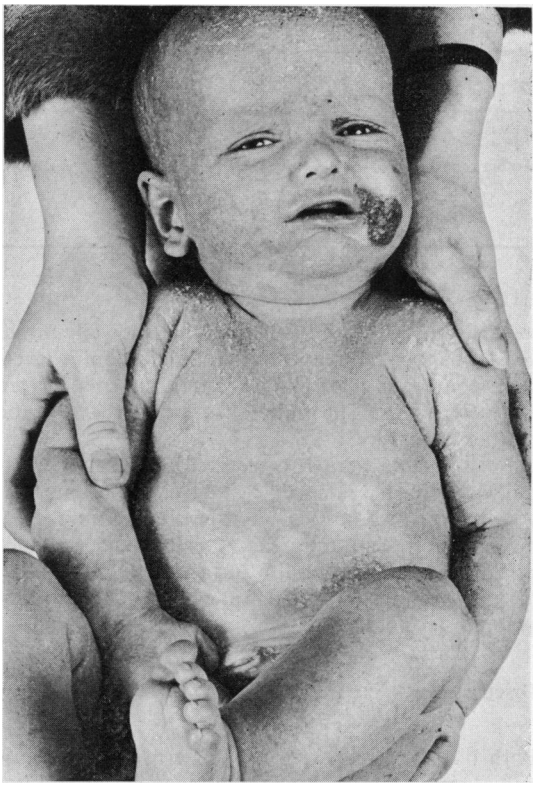

Fig. 2 *Case 2. Extensive eczema with scaling, and perioral lesion. Note adequate nutrition.*

He was given penicillin, gentamicin, digoxin, and intravenous fresh-frozen plasma without benefit. He developed fits, cardiac failure with a tachycardia of 200/min, and died the following day.

Family studies (Table 2) showed normal immunoglobulin levels in the father. The first test suggested that yeast opsonization was defective but subsequent

Table 1 *Immunoglobulin levels and antibodies*

		IgG	*IgA*	*IgM*	*IgE*				*Antibodies*				
	Date	*(g/l)*			*(ng/ml)*	*Blood group*	*Anti A*	*Anti B*	*Adeno-virus*	*CMV*	*Herpes simplex*	*Measles*	*Notes*
Father	19.9.72	9·69	2·27	1·56	—	B	1/64	—	1/10	1/10	1/10	1/20	
	13.1.75	10·0	1·4	0·7	189								
	29.10.76	10·22	1·65	1·72	—								
Mother	19.9.72	7·89	1·26	2·18	—	0	1/128	1/16	1/10	1/10	1/10	—	Tested during pregnancy
	16.8.74	6·0	3·2	0·4	290								
	13.1.75	3·6	0·31	0·27	209								
	29.10.76	8·87	1·0	1·11	—								
Case 1	4.9.72	4·6	0·62	4·6	650								
	19.9.72	2·58	1·26	>5·0	—								
	25.10.72	1·3	0·8	0·8	1050								
Case 2	13.1.75	0·5	0·33	0·38	209								
	9.3.75	0·68	0·52	0·5	350								

Table 2 *Yeast opsonization tests (100 cells counted)*

	Date	% of cells positive	No. of yeasts in 100 cells	Index	Source of cells
Father	9.10.74	2·5	3·5	0·04	Normal donor
	29.10.76	660	178	1·78	Normal donor
Mother	9.10.74	84	212	2·12	Normal donor
	29.10.76	36	94	0·94	Normal donor
Case 2	16.8.74 (cord)	26	64	0·64	Normal donor
	9.10.74	2	3	0·03	Normal donor

tests gave normal results. The mother showed normal yeast phagocytosis, but her immunoglobulin levels were abnormal in pregnancy though normal before and afterwards. The father has hay fever, but the mother is healthy.

Both parents were also seen by Professor J. Soothill who reported normal yeast opsonization, normal lymphocyte response to phytohaemagglutinin, normal E-rosette-forming cells (T cells), and lymphocytes with immunoglobulin surface markers (B cells) in the peripheral blood; and normal immunoglobulin levels.

Discussion

Both boys showed extensive seborrhoeic dermatitis and severe hypogammaglobulinaemia. It is not uncommon for babies with hypogammaglobulinaemia to have eczema and diarrhoea and initially we attributed the first child's illness to transient hypogammaglobulinaemia of infancy, though the raised IgM was unusual. When the parents had a second baby, we demonstrated the yeast opsonization defect in the cord blood and again a month later.

Miller's (Miller *et al.*, 1968) first baby weighed 1·98 kg at birth at 39 weeks' gestation and thus is likely to have had hypogammaglobulinaemia secondary to prematurity or low birthweight, though it is stated that immunoglobulin levels were normal. His second case weighed 3·8 kg at birth and had a low normal IgG of 4·3 g/l at the age of 7 weeks, and the authors mention the possibility of a more generalized immune deficiency. The patient of Scott *et al.* (1975) had abnormal immunoglobulins with raised IgM and low IgA and IgG. There were some features including lymphoid depletion, a low response to phytohaemagglutinin, and sparse Hassall's corpuscles in the thymus which the authors considered might be due to a primary immunodeficiency of lymphoid origin. Thus these 3 children presented with severe seborrhoeic dermatitis and intractable diarrhoea, recurrent infection, and failure to thrive. All 3 showed the yeast opsonization defect, but in 2 there was also a suggestion of lymphoid immunodeficiency, with low immunoglobulin levels. Our first case also showed lymphoid depletion and degenerate changes in Hassall's corpuscles, with low IgG and high IgM.

However, the yeast opsonization defect has been reported in otherwise fit family members of the affected cases, in 11 children who suffered from recurrent bacterial infections, and also in 4 of 73 normal individuals (Soothill and Harvey, 1976). Only 3 of these 11 children had diarrhoea and a rash in infancy. 8 presented within the first 6 months of life, and 5 within the first month. The opsonization defect was demonstrated later in life. Only 2 children were tested in the first 6 months of life: both at the age of 3 months when IgG and IgM were low. The brother of one case also had low immunoglobulins attributed to transient immunodeficiency, but patients with low immunoglobulins did not show the opsonization defect.

Miller and Koblenzer (1972) stressed the importance of diarrhoea for diagnosis of Leiner's disease. It is possible that diarrhoea itself might be associated with a protein-losing enteropathy and consequent deficiency of IgG and other proteins. Miller's (Miller *et al.*, 1968) first case was reported as having normal serum electrophoresis but the second had a serum albumin of only 2·7 g/l, and the case of Scott *et al.* (1975) also had hypoalbuminaemia. Our case, however, had no diarrhoea to explain the IgG deficiency.

Although all 3 cases with the features of Leiner's disease showed the yeast opsonization defect, it is clear that demonstration of the yeast opsonization defect is not synonymous with disease. Furthermore, since our case showed severe seborrhoeic dermatitis, but did not have persistent diarrhoea or failure to thrive, it must be possible to have a partial form of Miller's syndrome, and the statement of Miller and Koblenzer (1972) that 'a diagnosis of seborrhoeic dermatitis, no matter how severe, is not in itself enough to establish a diagnosis of Leiner's disease', needs to be modified.

The nature of the defect of yeast opsonization is

unknown. It is unlikely that a functional defect of C5 alone could explain Miller's findings, particularly now that Rosenfeld and Leddy (1974) have described a case with homozygous deficiency of C5 whose serum nevertheless supports opsonization of yeast normally. Yeast particles activate the alternate pathway directly and hence antibody concentration should be of minor importance in this system. Soothill and Harvey (1976) postulate that the yeast opsonization test may be sensitive to both the antibody-independent alternative pathway and the antibody-specific classical pathway. Some evidence for this is suggested by our case, whose cord serum (which we assume contained high levels of maternal IgG antibody) supported yeast opsonization better than serum collected a month later. However, Soothill and Harvey (1976) showed that serum from patients with hypogammaglobulinaemia supported yeast opsonization normally. We cannot believe that defective opsonization and a functional defect of C5 is the sole explanation for the disease seen in these children. In our first patient the illness could have been due entirely to severe immunoglobulin deficiency. Unfortunately the yeast opsonization test was not performed. The second child, who showed a clear defect of opsonization, had only a variable soborrhoeic dermatitis but showed no failure to thrive or persistent diarrhoea. His immunoglobulin levels were also very low, and his death was not necessarily related to the opsonization defect. If the yeast opsonization defect is present in normal individuals (Soothill and Harvey, 1976), in children with severe infection without dermatitis and diarrhoea, and in our case with dermatitis alone, it cannot be regarded in any way as specific for Leiner's disease, which may be due to other defects as yet unidentified. However, we cannot exclude the possibility that the yeast opsonization defect interacts with some other defect, possibly of lymphoid origin, to produce the full or a partially expressed form of the disease described by Leiner.

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