THYMIC ALYMPHOPLASIA: A CASE REPORT*

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Since Bruton[1] first recognized the association between hypogammaglobulinaemia and susceptibility to infection 18 years ago, advances in immunology have made possible a clearer understanding of clinically encountered immunological deficiency syndromes. In the light of current concepts of the immune response, the variable pattern encountered, depending on whether immunoglobulin production, cell-mediated mechanisms or both are affected, can be better appreciated. There is a wide measure of agreement on how these disorders may be classified.[2-6] The subject has been recently extensively reviewed.[7]

One variety of immunological deficiency recognized is associated with deficiency in small lymphocytes and almost absent thymic tissue. This has become known as 'thymic alymphoplasia'.[5] Recently an atypical form of this condition was reported in South Africa.[9]

In the patient described here, there were certain investigations which strongly suggested the diagnosis of thymic alymphoplasia during life. The clinical course, however, was dominated by severe, intractable diarrhoea due to proved malabsorption, which lasted nearly 8 months. Despite severe immunoglobulin deficiencies (particularly IgG and IgA), pyogenic, fungal or viral infections were not a major problem, except terminally. Defects in cell-mediated immunity were not fully assessed during life, but the autopsy findings were typical and confirmed the diagnosis.

CASE REPORT

History

E.E., 10 months old, was a White male, born 5 weeks prematurely. The parents were apparently quite healthy. Birthweight was 3 lb. 10 oz. The mother had had two previous abortions and one previous premature infant, who had survived only a few days. The present pregnancy was complicated by a threatened abortion and the mother was given hormone injections and a cervical stitch was inserted.

The neonatal period was uneventful and the infant was discharged from the nursing home weighing 5 lb. 2 oz. Feeding was commenced with a humanized milk mixture, and the infant thrived until the age of 4½ months. Immunization with triple vaccine was commenced and he was given oral polio vaccine, with no untoward effects. Vaccination was not performed.

*Date received: 22 January 1969.

At the age of 4½ months, he commenced having diarrhoea. This continued with very little abatement, until his death a few days after his first birthday. Stools were almost always watery with very little substance, 5 or 6/day, and always offensive. He had intermittent vomiting. He was always miserable and unhappy. Feeds were changed at various times with only temporary improvement of the anorexia and very slight weight gain. Mullsoy, Nutramigen and gluten-free diets were all tried, with no improvement.

On one occasion he was noted to have a fever, and an external otitis was diagnosed. He had mild eczema, which responded well to topical steroids. He was treated also with ampicillin and long-acting sulphonamides.

Investigations carried out before admission to hospital included numerous stool examinations, all of which showed neutral fat and fatty acid crystals; no parasites were found at any time. Coagulase-positive *Staphylococcus aureus* was isolated on occasion.

A tuberculin test was reported as negative and a Schwachman sweat-plate test was also negative. Tryptic activity of the stool was normal.

On the day of admission to hospital, he had become increasingly feverish and refused to take any fluids orally.

Examination

He was a small, unhappy baby, with a pale complexion. The rectal temperature was 104°F and his weight was 12 lb. 8 oz., which is well below the 3rd percentile for age. There was no skin rash and no adenopathy. The heart, lungs and genitalia were all normal. There was mild oral thrush. The central nervous system and ear, nose and throat were normal. Blood investigations showed a low lymphocyte count with an absolute number, ranging between 585 and 2,140/cu.mm. (Table I). Serum-protein electrophoresis showed that the total proteins were 5·4 G/100 ml. and gammaglobulin was 50 mg./100 ml. Subsequently this was shown to be due to almost absent IgG and IgA (Table II). Electrolytes and urea were satisfactory. The stool was bright yellow liquid with mucus. Microscopy showed blood and pus with a moderate growth of *Klebsiella aerogenes.*

Urine showed a pH 6, a trace of protein, 3 - 4 polymorphonuclear cells per high-power field and a profuse growth of coliform bacilli and coagulase-positive *Staphylococcus aureus,* insensitive to penicillin. The result

TABLE I. BLOOD INVESTIGATIONS

	22 Dec.	*8 Jan.*	*15 Jan.*	*29 Jan.*	*12 Feb.*	*15 Feb.*
Hb.	10·3		10·0	9·4	17·2	16·5
WBC	13·2	6·0	11·8	9·0	19·9	15·7
Total lymphocytes	1,580	1,260	2,140	585	1,520	750

TABLE II. SERUM PROTEINS

	22 Dec.	*4 Jan.*	*15 Jan.*	*23 Jan.*	*29 Jan.*	*5 Feb.*	*12 Feb.*
Total protein (G/100 ml.)	5·4	4·8	5·3	5·6	5·0	5·1	7·4
Gammaglobulin (G/100 ml.)	0·05	0·09	0·09	0·16	0·08	0·24	0·5
IgG (mg./100 ml.)		21	36	200	115	200	
IgA (mg./100 ml.)		10	10	13	10	23	
IgM (mg./100 ml.)		43	22	22	18	26	
Gammaglobulin given	1 ml.	7·5 ml.	6·5 ml.		200 ml. fresh-frozen plasma	200 ml. blood + 6 ml. globulin	

of a 5-hour D-xylose excretion test was only 0·2 G, the expected normal being 1·2 - 2 G/5 hours.

A glucose-tolerance test showed a flat curve, the fasting level being 28 mg./100 ml., rising to 29 mg. in 1 hour and reaching 75 mg. in 2 hours.

The blood group was B Rh negative. Anti A agglutinins were not demonstrable. An X-ray of the chest showed some localized inflammatory changes in the posterior segment of the right upper lobe. No thymus or hylar adenopathy was shown. A lateral X-ray of the nasopharynx showed no evidence of adenoidal tissue.

Tests for serum proteins and immunoglobulins, done on the parents, showed the father to be normal, while those of the mother were at the lower limit of normal (Table III).

TABLE III. SERUM PROTEINS IN THE PARENTS

Type of protein	*Mr E*	*Mrs E*
Total proteins (G/100 ml.)	7·0	6·2
Gammaglobulin	1·02	0·78
IgG (mg./100 ml.)	1,300	810
IgA (mg./100 ml.)	175	175
IgM (mg./100 ml.)	90	90

A Schick test was negative. There was no reaction to either the antigen or the control.

Course

The progress of the baby was characterized by the persistent watery diarrhoea. Feeding was commenced with 5% glucose and was continued with Mullsoy. Feeds had to be given by nasogastric tube. When the bacteriology of the urine and the stool became known, he was put onto cloxacillin. The pulmonary infection improved radiologically, but the diarrhoea persisted. Various non-milk feeds were tried, such as meat broth, meat puree, bone marrow, Casilan, butter fat and fructose, but there was no improvement.

When the results of the gammaglobulin estimations were known he was given first 1 ml., then 1 week later a further 7·5 ml., of commercial gammaglobulin. A repeat estimation after one week showed no improvement and there was no change in his clinical state. A further injection of 6·5 ml. of gammaglobulin resulted in a rise of the IgG to 200 G/100 ml., which fell to 115 G/100 ml. after one week. There was no change in the IgA or IgM. Therefore 200 ml. of fresh-frozen plasma was given, raising the IgG but not the other fractions (see Table II). Because of a falling haemoglobin concentration he was given 200 ml. of whole blood.

After 51 days he was transferred to another institution for metabolic balance studies. These showed a stool output of 28 oz./day which was reduced to 14 oz. after commencing Nutramigen feeds. Two days later, however, he had profuse diarrhoea requiring intravenous rehydration for the first time. The IVP was reported as normal, but he had a severe reaction to the contrast medium. A barium-meal X-ray was also reported as normal. Ten days after the admission to the second institution (61 days after initial hospitalization) he started to have even more profuse diarrhoea, with the passage of blood and mucus for the first time. Intravenous fluids plus Terramycin and Colistin were administered, but he became dyspnoeic and cyanotic, went into a shock state, passing blood in the stool, and then died.

Postmortem Findings

Necropsy was performed 18 hours after death. The following were the significant findings:

Thymus. The gland weighed 1·5 G. Histologically it consisted entirely of epithelial elements arranged in a lobular pattern in a loose, rather vascular, connective tissue stroma. In some areas a cortical zone could be defined by the presence of acinar gland-like structures. Elsewhere the cells were irregularly arranged and had poorly-defined cytoplasmic boundaries. Abundant PAS-positive amorphous material was present within cells, in free-lying aggregates and within the lumina of some acini. No lymphoid tissue was present, and neither small lymphocytic cells nor Hassall's corpuscles could be found. These features accord closely with those recorded by Blackburn and Gardon[10] in 4 cases of thymic alymphoplasia, and resemble the embryonic human thymus at about the 30-mm. stage.

Lymphoid tissues. Six lymph nodes were identified along the splenic vessels and at the aortic bifurcation. They were

conspicuously absent from the mesentery of the small intestine. Microscopically the nodes all showed severe lymphoid depletion. While occasional moderately dense aggregates of lymphocytes were present, there were no follicles or germinal centres. The paucity of lymphocytes was equally striking in the spleen, which was of normal weight. There were no peri-arteriolar aggregates or Malpighian bodies. Peyer's patches could not be identified, and lymphoid aggregates were not found microscopically in the small or large intestine. Plasma cells were not found in any of the sections from the various lymphoid tissues described above. The sternal bone-marrow was moderately cellular with representatives of granulocytic and erythroid series present, as well as megakaryocytes.

Intestine. A severe ulcerating enterocolitis was present. The jejunum and proximal ileum showed superficial loss of mucosal cells, with some villous atrophy. More distally there was total loss of the villous pattern, with ulceration of the mucosa and its replacement by a layer of necrotic cell debris and fibrin. In the distal ileum, ulceration extended to the muscularis mucosae, and the terminal 10 cm. showed grossly and microscopically the features of pneumatosis intestinalis.[11] The latter was also present at the caecum and ascending colon. Throughout the large intestine there were discrete and confluent ulcers with relatively normal intervening mucosa. Microscopically, some of the ulcers extended deeply into the outer muscle layers. The inflammatory cell response throughout was not prominent. Histiocytes, a few polymorphs and scanty eosinophils and lymphocytes were noted. Cultures for bacterial intestinal pathogens (including staphylococci and clostridia) and for yeasts were negative.

Lungs. Microscopically these showed areas of pneumonic consolidation, congestion and oedema and a fibrinous pleurisy over the right lower lobe. Histologically the picture was varied, and included:

1. Areas of typical pneumocystis carinii pneumonia in which the parasites were demonstrated by methenamine-silver staining.
2. An area of syncytial giant-cell pneumonia.
3. Bronchopneumonic areas of probable bacterial aetiology.
4. Intra-alveolar haemorrhage.

Evidence of infection was lacking in other organs and there were no other significant findings.

The pathological findings were typical of thymic alymphoplasia. Ulcerative bowel lesions are a well-recognized association and their severity explains the dominating clinical features of this patient's terminal illness. Lung infections of multiple aetiology were also evidently a late manifestation.

DISCUSSION

In the original case described by Bruton a deficiency was noted in gammaglobulin.[1] With the further breakdown of gammaglobulin into the respective immunoglobulins, it has now become apparent that there are a number of distinct syndromes associated with deficiency of either all (classical Bruton type) or only certain of the immunoglobulin fractions. It has also been found that in certain of the cases there are deficiencies in lymphocyte production, giving a quite distinct type of immunological deficiency. This syndrome was first recognized by Glanzmann and Riniker[7] in 1950, and was called 'alymphocytosis' by Donahue.[12] Its hereditary nature was subsequently noted by Hitzig *et al.*[13] and the condition has been well reviewed.[14]

In the series of cases reported by Gitlin and Craig[5] those suffering from thymic alymphoplasia all succumbed in infancy to uncontrollable infections. Of the 6 patients reported in this group, 4 had severe diarrhoea and, of the other 2, one had a terminal oesophago-gastroenterocolitis, while the other had a malabsorption syndrome. On autopsy examination all these patients had almost absent thymic tissue with very abnormal structure and cytology of the remnant. It was found that the residual thymuses consisted of excess fibrous tissue with no Hassall's corpuscles.

In studying the case history of the patients with immunoglobulin deficiencies, it is apparent that severe diarrhoea is an important part of their symptomatology.[15] Immunoglobulin deficiency should be considered in the differential diagnosis of chronic diarrhoea and malabsorptions even though it is very rare.[16] In the case here reported, intractable diarrhoea was the presenting symptom and a major problem in management.

Why diarrhoea should be such a prominent symptom is not exactly understood. Whether malabsorption is the primary defect is not known. As IgA is produced in the lamina propria of the normal small intestine[17] it would be thought that diarrhoea would lead to considerable loss. In studies using radioactive ^{131}I-labelled gammaglobulin it has been shown that this is not ordinarily the case, though there is an increased breakdown and intestinal leak.[18] However, in the patient with the classical Bruton type of immunoglobulin deficiency the half-life of radioactive globulin is prolonged as compared with that of a normal person.

IgM deficiency has been noted in coeliac disease,[19] while some patients with steatorrhoea have hypogammaglobulinaemia or even selective IgA deficiencies.[20] When both IgA and IgM are deficient the patients always have a severe diarrhoea.[21] In one patient with a hypogammaglobulinaemia a secondary malabsorption was proved to be the cause of the diarrhoea.[22]

In the patient here presented, diarrhoea was the major problem, dominating the clinical picture, and was probably the ultimate cause of death. The features which suggested the premortem diagnosis of thymic alymphoplasia were chiefly the low lymphocyte count, gammaglobulin less than 100 mg./100 ml. with selective IgG and IgA deficiency, the absence of anti-group A agglutinins and the failure to demonstrate adenoidal or thymic tissue radiologically.

There were, however, a number of unusual features. Severe systemic infections were not a problem. Though diarrhoea is well recognized, it is not usually the presenting symptom. Also, the onset (at 4½ months) was later than average, most cases manifesting themselves before 3 months of age.

Malabsorption was proved by a D-xylose absorption test and a glucose-tolerance test. One patient with hypogammaglobulinaemia previously reported was shown to have diarrhoea due to malabsorption[22] but immuno-assay was not performed. Subsequent balance studies showed an incredible stool loss. Steatorrhoea did not seem to be present but could not be proved, as initially sufficient stool could not be collected for a fat-balance test.

Typically, these patients have a marked lymphopenia (less than 1,000/cu.mm.), but this is not invariable.[9,23] In this patient the absolute count varied from 585 to 2,140/cu.mm. Absence of radiologically demonstrable adenoidal tissue also occurs with Bruton's type of immunoglobulin deficiency, and so this feature was also not diagnostic.[23]

The serum proteins were relatively normal, but the gammaglobulin fraction was less than 100 mg./100 ml. This now does not seem to be invariable.[9] Immuno-assay showed severe deficiency of immunoglobulin, particularly IgG and IgA (Table II).

The familial nature of the thymic alymphoplasia is well recognized and a number of families have been described.[5,22,24,25] It is generally stated to be an autosomal recessive and sometimes sex-linked.

In the patient here described, there was no family history of other affected siblings, though the mother did have a previous infant who died shortly after birth because of prematurity. On examining the parents' immunoglobulins it was found that the father was normal (Table III) but the mother had a low IgG. It is felt that the mother was, in fact, the carrier, probably as a result of an isolated mutation.

The treatment of thymic alymphoplasia has been very unsatisfactory and all the cases so far reported have died. Attempts at supplying the deficient immunoglobulins have not made any substantial difference to the ultimate fatal outcome. Commercial gammaglobulin which provides mainly IgG[26] also had no significant clinical effect in all the patients reported. This is in contrast to the Bruton type which responds well to gammaglobulin administration.[3,6] Fresh-frozen plasma provides IgA and IgM and has been used successfully in secondary hypogammaglobulinaemia.[27] In this patient, gammaglobulin administration did cause a rise in IgG from 21 mg. to 36 mg. and later to 200 mg./100 ml. after a total of 14 ml. had been given, but there was no significant change in the clinical status. Fresh-frozen plasma raised the total gammaglobulin to 240 mg., also with no improvement.

It would thus seem that though the gammaglobulin can be raised with large doses of commercial gammaglobulin and fresh-frozen plasma, this does not necessarily affect the clinical picture.

The logical treatment would be to restore cellular function by supplying the missing cells. Attempts at implantation of foetal thymuses[13] has been unsuccessful though skin transplants are not rejected.[28] The best immunological restoration so far has been the infusion of suspended thymic cells of a 12-week foetus and also of the liver cells from another foetus.[29] This resulted in the appearance of plasma cells and small lymphocytes and is obviously a method to be tried in future cases.

Recently a case has been reported from Holland, that was successfully treated with transplantation of foetal thymus and histocompatible bone marrow.

SUMMARY

A case is presented of a patient with severe immunoglobulin deficiency and postmortem findings characteristic of thymic alymphoplasia. The clinical course was a little unusual in the relatively late onset of symptoms, the severity of the intractable diarrhoea, and the absence of infections as important clinical events. Special investigations during life strongly suggested the clinical diagnosis. Infections were only evident terminally when they were due to multiple agents as judged histologically. Parenterally administered commercial gammaglobulin and fresh-frozen plasma, though raising the serum gammaglobulin slightly, failed to influence the clinical course.

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