CONGENITAL AGAMMAGLOBULINAEMIA

A CASE REPORT

W. S. WINSHIP, M.B., CH.B. (CAPE TOWN), *Durban*

Agammaglobulinaemia or hypogammaglobulinaemia has been reported frequently since Bruton,[1] in 1952, first described the absence of a gamma-globulin peak in the electrophoretic pattern of a child suffering from severe recurrent infections.

It is now apparent that agammaglobulinaemia is but one effect of some still unknown primary defect, of which the absence of plasma cells from bone marrow, lymphoid tissues and bowel, and the inability to accept homografts, are other features. Deficiency of some beta-globulins has also been found in this condition, which shows itself as an inability to combat bacterial infections. Moreover, it is evident that several different forms of this deficiency occur and these have been the subject of recent reviews.[2-5]

Controversy has arisen over the use of the term agammaglobulinaemia, since the development of more sensitive methods[6,7] of determining levels of circulating gamma-globulin has shown that, in the majority of cases in which gamma-globulin is undetectable on the electrophoretic pattern, a small amount is, in fact, present. In an attempt to clarify the position, Firkin and Blackburn[4] defined agammaglobulinaemia as that condition in which gamma-globulin is not demonstrable on the electrophoretic pattern, thus perpetuating Bruton's original description, while recognizing that in many such cases very small amounts may be present. Good *et al.*[5] supported this definition as did Garvie and Kendall,[8] who considered that no change in terminology should be made until the nature of the primary defect is known.

The following is a classification of the types of agammaglobulinaemia which have been described:

1. *Primary agammaglobulinaemia* with normal total serum protein:
   - (*i*) Congenital sex-linked recessive form occurring in males.
   - (*ii*) Congenital form, so far only reported in females.
   - (*iii*) Acquired form occurring after early childhood or in adult life.
   - (*iv*) Transient self-limiting agammaglobulinaemia of infancy, occurring as an extension of the decline

in the gamma-globulin level normally found in infants between the second and sixth months of life.

II. *Secondary agammaglobulinaemia*:

(*i*) Associated with hypoproteinaemia, as found in the nephrotic syndrome.

(*ii*) Associated with neoplastic conditions, such as multiple myelomatosis and leukaemia.

It is the purpose of this paper to report a case of congenital agammaglobulinaemia, which is possibly of the sex-linked recessive form.

CASE HISTORY

C.R., a European male, now aged 3 years and 5 months (June 1961), was delivered at term by Caesarean section for disproportion. His mother was a primiparous woman aged 37 years. His birth weight was 6 lb. and his neonatal period of life uneventful. The pregnancy had been complicated by hyperemesis, and on 4 occasions between the 12th and the 24th weeks by transient vaginal bleeding. There was no known exposure to viral infections or radiation. He is the only child of unrelated parents.

At the age of 4 months he was vaccinated against smallpox and had a severe local reaction accompanied by high fever, but otherwise uncomplicated.

From the age of 6 months he suffered from repeated respiratory and enteral infections. At 15 months he became ill with diarrhoea and was treated with chloramphenicol, 125 mg. 4-hourly for 8 days. The diarrhoea stopped, but he became progressively more ill, with a persistent high fever despite the use of aspirin 4-hourly. On the eighth day of this illness he was admitted to a nursing home where he was found to have a complete absence of neutrophils in a total leucocyte count of 5,700 per c.mm. Treatment with chloramphenicol was stopped, since it was thought to be the cause of the neutropenia, and erythromycin was substituted. He remained critically ill for a further 3 days, during which time he developed several paronychiae of the fingers, a perianal abscess and bleeding from his gums. The temperature exceeded 106° F. on several occasions. He recovered after another 10 days, when his leucocytes totalled 15,150 per c.mm., of which 43% were neutrophils.

He first attended the Outpatients' Department of Addington Children's Hospital at the age of 17 months, since when he had the following illnesses:

22 May 1959 — upper-respiratory-tract infection and gingivitis.

14 July 1959 — upper-respiratory-tract infection and left otitis media, which failed to respond to treatment with penicillin, but responded to oxytetracycline after 8 days of treatment.

30 July 1959 — gastro-enteritis, which responded to treatment with neomycin and succinylsulphathiazole.

25 August 1959 — upper-respiratory-tract infection, which did not respond well to treatment with dosulphin.

On 2 October 1959, at the age of 1 year and 10 months, he was admitted to the Addington Children's Hospital with another upper-respiratory-tract infection, because he was again found to have a complete absence of neutrophils.

Examination

Physical examination in October 1959 revealed a boy 33 inches tall and weighing 27 lb. He was flushed and had a thick yellow nasal discharge. His throat was inflamed, but the tonsils were small, and there was no lymphadenopathy. His liver edge was palpated 2 inches below the costal margin, but it was soft and non-tender.

His temperature was 101·6° F., pulse rate 120 per minute and respiratory rate 24 per minute.

Laboratory Investigations

The haemoglobin was 13 G. per 100 ml., leucocytes totalled 13,000 per c.mm. (neutrophils 0%, lymphocytes 83%, monocytes 15%, eosinophils 2%), and there were 145,000 platelets per c.mm.

The bone marrow was markedly hypoplastic. Erythropoiesis was normoblastic, but depressed. All stages of myelopoiesis were present, but there was a generalized reduction in the whole series. Megakaryocytes and platelets were diminished.

The liver-function tests were normal. Zinc turbidity was 1 unit, and the serum proteins totalled 5·7 G. per 100 ml. (albumin 4·2, globulin 1·5; A:G ratio 2·8:1).

The electrophoretic pattern showed a complete absence of gamma-globulin. Descending starch-gel electrophoresis revealed a decrease in the beta-globulins as well.

His blood group was O Rhesus positive. No isoagglutinins were detected.

Family History

There is no relevant history on the paternal side, but several deaths in infancy have occurred on the maternal side,

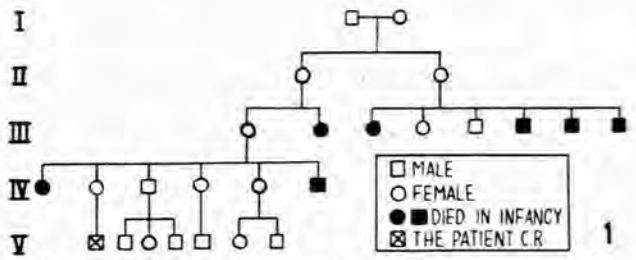

Fig. 1. Genealogical table of patients' maternal family over 5 generations (I - V).

as shown in the genealogical table (Fig. 1).

The patient's great-grandmother had only one sibling, a sister who had 6 children. Of these, a girl died at 9 weeks, and a boy at 7 years after prolonged illness following 'infantile paralysis'. The death of the girl at 9 weeks cannot be attributed to agammaglobulinaemia, nor is it likely that agammaglobulinaemia was a factor in this boy. Two other boys, however, died at the ages of 18 months and 2 years of pneumonia, and fever with convulsions, respectively.

In the direct line, his grandmother had one sister who died at the age of 3 months, the cause of death being unknown to us, but agammaglobulinaemia is unlikely to have been a factor here because of her age and sex. Of the 6 children born to his grandmother, the first was a stillborn girl, but a boy suffered from recurrent respiratory infections and discharging ears from the age of 8 months until his death from pneumonia at 13 months.

Of the fifth generation shown in the table all are still children. Our patient is the only one living in Durban, but it is known that all the others are well, and the only other male infant has a normal electrophoretic pattern.

Treatment

From admission the child was treated with oral penicillin, which was ineffective in controlling his infection. Repeated nasal and throat swabs revealed a variety of organisms, none of which predominated. When the result of the electrophoretic pattern became known, treatment was commenced with pooled human gamma-globulin intramuscularly. Penicillin was continued and recovery took place within a few days.

The dosage of gamma-globulin was based on the work of Martin,[6] who estimated the gamma-globulin fluid compartment to be approximately 12% of the body weight. Since plasma volume is roughly 5% of the body weight, between 55% and 60% of gamma-globulin is distributed in cells and interstitial fluid, the intravascular and extravascular compartments being in equilibrium. Janeway and Gitlin[3] have found that levels of over 100 - 150 mg. are sufficient to keep agammaglobulinaemic patients free of infection, and several studies[6,7,9] have shown the half-life of gamma-globulin to be between 30 and 35 days. Maintenance of a satisfactory level can therefore be achieved by giving an injection of 0·3 - 0·4 ml. per lb. body weight of a 16% solution of gamma-globulin at 4-weekly intervals. Apart

TABLE I. SHOWING THE MARKED VARIATION IN THE NEUTROPHIL COUNT OVER A PERIOD OF 2 YEARS

Days of observation	1	3	5	8	26	109	114	147	185	188	189	191	195
Total neutrophils per c.mm.	0	0	1,431	6,300	1,590	140	320	1,520	0	600	240	0	180
Days of observation	196	198	206	220	252	282	310	348	404	468	645	716	744
Total neutrophils per c.mm.	210	1,600	1,760	3,740	0	0	1,540	720	220	0	4,080	1,440	8,840

from the advantage of less frequent injections, one large dose results in a more rapid attainment of protection and longer periods of higher circulating antibodies than do smaller weekly injections.[3] Accordingly, this child was given 0·7 ml. per lb. body weight initially, and thereafter 0·35 ml. per lb. body weight at 4-weekly intervals.

In addition, a prophylactic dose of 0·5 G. of sulphadimidine daily has been given in an attempt to prevent the upper-respiratory-tract infections to which he is particularly susceptible.

Progress

The child has been observed for 18 months since the diagnosis was made and his progress has been satisfactory. His weight gain over this period has been 7 lb. and he has grown 4 inches in height.

He has required medical attention on only a few occasions. A paronychia of the right index finger and a small post-traumatic abscess of a foot both responded rapidly to the appropriate treatment. Recently, on the day after receiving an injection of gamma-globulin, he developed acute bacillary dysentery (*Shigella sonnei*). This responded well to treatment with neomycin and succinylsulphathiazole at home. Gamma-globulin given intramuscularly takes 3 days to reach its maximum concentration in the circulation, thus the onset of dysentery occurred at a time when his gamma-globulin level was probably at its lowest.

Gingivitis and bleeding from his gums, which had been observed before admission to hospital, recurred on 3 occasions. No other evidence of a bleeding tendency was found, and his platelet count was normal. Treatment with vitamin C produced rapid improvement, and discontinuation resulted in recurrence of the bleeding. A prolonged course of vitamin C was given with an excellent outcome. His dietary intake of vitamin C at that time was very poor, whereas his intake of sweets was excessive.

During his stay in hospital, and whenever possible since his discharge, leucocyte counts, with particular reference to the neutrophils, have been made. These as well as counts done before his admission to hospital are presented in Table I. Although the number of recordings is small and over varying intervals of time, he appears to have long periods of profound neutropenia alternating with periods in which the neutrophils approach the normal number. His liver-function tests have been repeated on 4 occasions. On each occasion zinc turbidity has been 1 unit, and all other tests normal.

DISCUSSION

Cases of the congenital sex-linked recessive form of agammaglobulinaemia have been reported more often than the other forms, and a distinct clinical syndrome is apparent. It occurs in males and appears to be transmitted by females as a recessive trait. The lymphoid tissues are poorly developed in them, and absence or gross deficiency of plasma cells in the bone marrow, lymphoid tissues and bowel is a feature of these patients. There are frequently associated haematological abnormalities, the most common of which is neutropenia.[2,10,11] The neutropenia may be aregenerative or occur as cyclical or transient episodes, and is considered to be a reflection of some underlying disturbance of haemopoietic function associated with agammaglobulinaemia.[5] Lymphopenia, thrombocytopenia, and complete absence of eosinophils have also been reported.

A second type of congenital hypogammaglobulinaemia has been described affecting females.[5,12] These patients present with the same inability to combat infection. Their gamma-globulin levels, when estimated by the more sensitive immunochemical[6] or antiglobin-inhibition[7] techniques, are slightly higher than those found in the sex-linked form. There is enlargement of the lymphoid tissue including the spleen, and associated haemolytic anaemia has been described. No familial incidence has been discovered in the few cases reported so far.

In the case presented here several features suggest that the patient may have the congenital sex-linked form of agammaglobulinaemia. He is a male, his lymphoid tissues are poorly developed, and he has periodic episodes of neutropenia. Unfortunately, plasma cells were not sought for when his bone marrow was examined, and it has not been possible to repeat this examination.

It is of interest that when neutropenia was first discovered in this child it was thought to have been caused by chloramphenicol. The possibility of repeated infections or the repeated use of antibiotics causing neutropenia has been suggested, but Good and Zak[2] described a patient with agammaglobulinaemia with neutropenia, studied from birth, in which no antibiotics had been used.

Some patients with agammaglobulinaemia have succumbed to homologous serum jaundice, to which they seem particularly susceptible. Good *et al.*[5] advocated that all syringes and needles used on these patients should be of the disposable variety.

SUMMARY

A case of congenital agammaglobulinaemia, possibly of the sex-linked recessive form, is reported.

Associated periodic neutropenia is a feature of this case.

Regular monthly treatment with intramuscular injections of pooled human gamma-globulin has been effective in averting serious illness.

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