year had suffered from 14 attacks of acute pulmonary infection. Previously she had been well. Her serum gammaglobulin was only 0.2–0.3 g. per 100 ml. Her mother was quite well, but had a marked increase in serum gammaglobulin (2 g. per 100 ml.). The serum proteins of the patient's father and sister were normal. This observation adds further support to the suggestion that in some cases of acquired idiopathic agammaglobulinaemia (hypogammaglobulinaemia) the abnormality of gamma-globulin production is genetically determined.

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AGAMMAGLOBULINAEMIA

REPORT OF TWO ADULT CASES

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The clinical and laboratory findings in patients with deficiencies or absence of gamma-globulin in their serum have been described only in the past few years. Most of the cases have been in children (Bruton, 1952; Fried and Henley, 1954; Elphinstone *et al.*, 1956), but a number of examples of the condition have been recorded where the deficiency has not appeared until adult life (Grant and Wallace, 1954; Wall and Saslaw, 1955).

The purpose of this paper is to record the findings in two further adult female patients in whom this deficiency was present.

Case 1

A single woman, born in 1907, was perfectly well until 1933, when she had a chronic cough for a few months. In 1937 she had her first attack of pneumonia, two more attacks following in 1943. She was admitted to hospital in 1949 for investigation of diarrhoea of one year's duration, and was found to have a mild degree of steatorrhoea (4–8 g. of faecal fat on a 50-g. daily fat intake). Her blood count showed: red cells, 4,460,000 per c.mm.; haemoglobin, 9.9 g. per 100 ml.; M.C.V., 96 cubic microns; M.C.H.C., 25%; white cells, 7,400 per c.mm., with normal differential; and serum proteins: albumin, 4 g. per 100 ml.; globulin, 1.2 g., with gamma-globulin 0.04 g. (alcohol precipitation method—G. Thomas, 1954, unpublished observation). The serum bilirubin, alkaline phosphatase, cholesterol, empirical tests of liver function, and pancreatic enzymes were normal. Chest radiographs showed no abnormality.

Over the next two years she had pneumonia on four further occasions and her diarrhoea increased. In 1951 she complained of severe attacks of abdominal pain, on account of which an exploratory laparotomy was performed by Mr. B. N. Brooke. A swollen pink pancreas was seen, but no other abnormality.

For the next three years she continued to have recurrent attacks of pneumonia and constant diarrhoea of up to 10 stools a day, and in 1954 she was readmitted to hospital. Estimations of faecal fat then showed an excretion of 10–20 g. a day. The serum amylase fluctuated between 183 and 370 units per 100 ml., with one period of a week during which it rose steadily to 670 units per 100 ml. On admission serum electrolytes showed: sodium 146 mEq, potassium 2.9 mEq, chloride 106 mEq per 100 ml. The blood count, serum proteins, bilirubin, alkaline phosphatase, cholesterol, and empirical tests of liver function showed no significant change from 1949. Gamma-globulin was estimated at 0.05 g. per 100 ml. by alcohol precipitation method and 0.1 g. per 100 ml. by paper electrophoresis (Dr. Hardwick), but none was shown by the Tiselius method (Dr. Kekwick). Serum tested by the immunochemical method (Gell, 1955) for gamma-globulin showed that some was present in amounts approximating to 10% of that in the normal control serum. A routine blood grouping at this time showed absence of iso-agglutinins. She was treated with a high-protein and low-fat diet and pancreatin, 12 g. daily with meals. Her diarrhoea improved on this regime, though she continued to excrete 10–20 g. of fat daily. She was discharged relatively well after two months in hospital.

During the past 18 months the patient has had one further attack of acute bronchitis, which subsided within a week in response to antibiotic therapy. In order to raise her gamma-globulin level before the winter 1 litre of fresh plasma was transfused in October, 1955. The last estimation of gamma-globulin, in July, 1956, by paper electrophoresis, showed it to be 0.3 g. per 100 ml.

Case 2

A single woman born in 1916 was well until the age of 20, when she began to suffer with severe nasal catarrh and repeated "colds" each winter. In 1947, at the age of 31, she had her first attack of pneumonia, followed by further attacks in 1948 and 1949, when she was admitted to hospital for drainage of an empyema. In 1950 and 1951 she had further attacks of pneumonia, and in 1952 she was admitted to another hospital, where she underwent a resection of her right middle lobe for bronchiectasis. This, however, did not prevent her from having a further attack of pneumonia in 1953. In 1954 she had another attack, and later in that year (October) was admitted to hospital for investigation and treatment of her chronic nasal catarrh by Mr. Stirk Adams. A routine blood grouping disclosed at this stage an abnormality in her iso-agglutinins which suggested an absence of gamma-globulin.

Examination of the serum proteins showed albumin 4.1 g. and globulin 1 g. per 100 ml. No gamma-globulin was revealed by the alcohol precipitation method, but paper electrophoresis showed 0.3 g. per 100 ml. The immunochemical method showed the presence of gamma-globulin in quantities below that present in normal control serum. Blood counts, serum bilirubin, alkaline phosphatase, and empirical tests of liver function were within normal limits. Shortly before her intended discharge she again developed pneumonia, which responded to penicillin, but two days after discontinuation of the therapy she had a second attack and, whilst convalescing, a third.

During this period the white blood cells rose from a normal level of 7,000 to 19,000 per c.mm., with 12,000 polymorphs per c.mm. No alterations in the levels of the serum proteins were detected. As no gamma-globulin was available at this

time it was decided to raise the level of her serum gamma-globulin by the transfusion of fresh plasma, 300 ml. being administered every three days until a total of 3 litres had been given. This resulted in a rise of gamma-globulin to 0.6 g. per 100 ml. as assessed by paper electrophoresis, but it gradually fell over the next 14 days to 0.3 g. per 100 ml., at which level it seemed to be relatively stationary. She was therefore given a further boosting transfusion of 600 ml. of plasma and discharged. Before the winter of 1955 1 litre of fresh plasma was transfused, which again raised the gamma-globulin level from 0.3 to 0.6 g. per 100 ml. Apart from one short attack of pneumonia aborted by antibiotic therapy during the summer of 1956, the patient has remained well.

Examination of blood from all her living relatives by paper electrophoresis and blood-grouping techniques failed to show any evidence of a deficiency in gamma-globulin and there was no history of recurrent infections.

Diagnosis

The condition, although attracting much attention, is rarely found with the present methods for detection. Nearly all cases, however, including the two reported above, have a history of recurrent infection, pneumonia being particularly frequent.

The deficiency of total gamma-globulin may be readily picked up by paper electrophoresis or by using the alcohol precipitation method, but techniques for detecting important partial deficiencies have not yet been developed. The immunochemical method is one such improvement which may allow the detection of some of the many protein fractions necessary for protection against infection.

The simple procedure of blood grouping, performed with care, will in most cases produce a result indicating an abnormality in the protein moiety of the serum that should invite further investigation. The pattern obtained in both of the above cases was more or less identical. The first case grouped by cell grouping as group O, but at first no alpha- or beta-agglutinins were identified in the serum, a finding usually associated with group AB. Further investigation of the serum at different temperatures (4° C., 20° C., and 37° C.) against A and B cells showed that at 4° C. group A cells were agglutinated up to a titre of 2, whereas group B cells showed hardly any agglutination at all. In spite of the fact that several high-titre group O sera did not agglutinate the patient's cells, it was thought necessary to exclude a possible subgroup of B, analogous to A2 or A3. Grouping-serum of moderate potency was incubated at room temperature for two hours with an equal volume of packed cells from the patient and with control group O cells, no difference being found. Interestingly enough, an indirect Coombs test performed with the serum from the patient against group A and group B cells at low temperature gave a weakly positive result against A cells only. Investigation for the presence of other immune antibodies gave a negative result, using a fairly large number of test cells. Later, when the serum contained some gamma-globulin, the abnormal grouping results had rectified themselves somewhat, and both group A and group B cells were now agglutinated at room temperature to a titre of 4, and, if anything, group B cells showed better agglutination than group A cells.

The diagnosis in the second patient was, as pointed out, actually suggested by a routine blood grouping. Again the cells grouped regularly, group A this time, and one would have expected the serum to contain beta-agglutinins. However, neither group A nor group B cells were agglutinated at either 22° C. or 4° C. To exclude a low-grade B antigen absorption experiments were performed with completely negative results. To exclude the possibility of a "blocking" anti-B antibody giving no reaction in saline media an indirect Coombs test was performed, using group B cells. Also trypsinized cells and cells suspended in albumin were used. A uniformly negative result was obtained. About six weeks later, when the patient had had treatment for some time, a little activity was demonstrated, but this only to a titre of 2. From the findings obtained in both patients and others (Janeway *et al.*, 1953; Grant and Wallace, 1954; Sanford *et al.*, 1954; Wall and Saslaw, 1955; Kuhns *et al.*, 1956) it would appear that careful blood groupings might in all cases of group O, A, or B give an indication of agglutinin abnormality which should invite further investigation. Group AB patients would in this respect be at a disadvantage, as no iso-agglutinins are normally present in their serum.

Treatment

Once the condition is detected the use of antibiotics will control most infections, but it may also be necessary to raise the plasma gamma-globulin level. If fractionated gamma-globulin is not available in adequate amounts, this can be done temporarily by the transfusion of fresh plasma. Both of the above cases appeared to derive benefit from this form of treatment.

Discussion

The absence of gamma-globulin in the serum of young children has been ascribed to a hereditary defect resulting from a sex-linked recessive characteristic (Janeway *et al.*, 1953; Gitlin, 1954; Good, 1954). It is less likely, however, that such a concept holds good where the condition is first detected in adult life, such as the two cases reported here. In neither patient was there evidence of any unusual or recurrent illness in infancy and childhood. The familial occurrence of the condition was sought for in Case 2, but was not detected. In neither case was there any evidence of liver dysfunction, and, with the exception of the gamma-globulin, the other serum proteins were normal on all occasions, findings which support the view that gamma-globulin is not formed by the liver.

It is of interest that three further cases at least (Sanford *et al.*, 1954; Saslaw and Wall, 1954; Good 1954) have been reported somewhat similar to Case 1 in having a sprue-like syndrome. Some diminution in gamma-globulin, usually in conjunction with a general diminution of serum proteins, has been noted in a number of our patients with steatorrhoea due to varied causes, but in Case 1 the recurrent respiratory infection preceded the symptoms of steatorrhoea by at least 10 years, and it seems more likely that the pancreatitis and steatorrhoea were secondary to the agammaglobulinaemia.

The condition of agammaglobulinaemia in the two patients reported here would appear to be phasic, and it may well be that the administration of fresh plasma is adequate to tide them over any temporary crisis.

Summary

Two further cases of agammaglobulinaemia are described; both had recurrent attacks of pneumonia and one also had recurrent pancreatitis and steatorrhoea. The method of diagnosis, with particular reference to the blood-group screening test, is discussed. Transfusion of fresh plasma is recommended as a means of combating recurrent acute infection in these cases.

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