CONGENITAL AGAMMAGLOBULINAEMIA**REPORT OF TWO FURTHER CASES**

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Agammaglobulinaemia was first recognized in 1952 by Bruton as a distinct syndrome manifested by severe recurrent bacterial infections associated with an absence or severe deficiency of circulating gamma-globulin but a normal total serum protein. Since then several further cases have been reported in the world literature, and in 1955 the Medical Research Council set up a working party to collate the findings and advise on the problems arising in cases diagnosed in Great Britain. Nevertheless, there is still a lack of agreement on many points, and we therefore feel justified in reporting two further cases.

We agree with Firkin and Blackburn (1958) in defining agammaglobulinaemia as that condition in which circulating gamma-globulin is not demonstrable by the technique of electrophoresis, while recognizing that in many such cases very small amounts of gamma-globulin may be shown to be present by the more sensitive immunological method. The definition will usually exclude the physiological state, which occurs in the first few months of life, when the gamma-globulin commonly falls to between 300 and 600 mg./100 ml., although two cases have been reported in which it fell as low as 75 and 150 mg./100 ml., before beginning the climb towards the normal levels of 700 to 1,500 mg./100 ml., usually but not always reached by the age of 12 months. Also excluded by definition is the hypogammaglobulinaemia associated with hypoproteinaemia, such as occurs in nephrosis, where it has been suggested that the low gamma-globulin is at least partly responsible for the tendency to recurrent infection in that condition.

Recent evidence strongly suggests that the agammaglobulinaemia is itself a secondary effect of a more primitive, probably enzymatic, inborn error, as certain of the clinical features, notably the ability to accept homografts, do not seem to be dependent upon the lack of gamma-globulin (Medawar, 1955). Furthermore, it appears that some beta-globulins at least are also deficient. It is probably better to await further information on the nature of the primary defect, which may reside in the primitive reticulum cell, before embarking on a new terminology, among which immuno-globulinaemia and immune paralysis have been suggested.

Case 1

The patient was seen at the Walsall Manor Hospital on June 18, 1958, at the age of 11 months. In February he had developed an illness diagnosed as whooping-cough by the family doctor. Since then he had had a constant dry cough and his weight had fallen from 18½ to 16½ lb. (8.3 to 7.5 kg.). In March, and again in May, he had had two distinct febrile illnesses diagnosed as tonsillitis. For four days he had been vomiting and for two days had been passing watery stools, though this was tending to improve.

On examination he was pale and fretful. There were scattered rales in his lungs. His haemoglobin was 9.6 g./100 ml. Chest x-ray examination showed only a hilar adenitis and his tuberculin test was subsequently found to be negative. A rectal swab grew no pathogens. A simple sedative mixture was prescribed, and it was felt that he might indeed have had whooping-cough and two intercurrent illnesses before he had completely recovered from the original attack of pertussis.

On July 3 he was admitted as an emergency case. His cough was much more severe, the diarrhoea had returned, and for two days he had been running a high fever, which had not responded to antibiotics. He had lost a further 1½ lb. (567 g.) in weight, was toxic and dehydrated with a temperature of 105° F. (40.6° C.), and had a respiratory rate of 50. Again, only scattered rales were heard, but bronchopneumonia was diagnosed and penicillin and streptomycin were given intramuscularly. By next morning he was gravely ill. It was then found that his urine was loaded with sugar and his blood sugar was 250 mg./100 ml. He was given crystalline insulin 10 units at once and 5 units hourly until the urine became sugar-free 12 hours later and, by intravenous drip, a pint (570 ml.) of glucose-saline followed by half a pint (284 ml.) of half-strength plasma. At this stage we learnt that his total white blood cells were 850/c.mm., of which only 80 were granulocytes. In view of this, after further glucose-saline, half a pint (284 ml.) of blood was transfused.

He slowly improved, his temperature falling to between 99 and 100° F. (37.2 and 37.8° C.), but his distressing cough persisted and he was restless and miserable. Chemotherapy was discontinued on July 10. On July 16 his diarrhoea recurred, but it responded to neomycin. On July 20 he had a relapse of the bronchopneumonia, and on this occasion haemolytic streptococci were found in his cough swab. Meanwhile fibrocystic disease of the pancreas had been excluded and agammaglobulinaemia was considered. His blood group was A, and no iso-agglutinins could be detected in the serum. An electrophoretic strip showed the apparent absence of gamma-globulin, though Dr. Soothill, of the department of experimental pathology, University of Birmingham, was subsequently able to demonstrate a level of 80 mg./100 ml. Plasma cells being characteristically reduced or absent in agammaglobulinaemia, bone-marrow from a sternal puncture was carefully searched. No plasma cells could be found.

On July 26, the case having been accepted into their series by the Medical Research Council, intramuscular injections of gamma-globulin were started in alternate 17-week courses of 0.025 and 0.5 g./kg. of body weight. At the beginning of this treatment he weighed only 14 lb. (6.4 kg.) and, although there was no definite illness, he was not well. His subsequent general improvement was rapid and he put on weight. He has remained well, except for frequent episodes of upper respiratory catarrh and a short bout of diarrhoea in December, 1958, which responded readily to treatment. His circulating gamma-globulin is usually between 80 and 160 mg./100 ml.

Case 2

The patient was admitted to the George Eliot Hospital, Nuneaton, on January 23, 1958, at the age of 6 months. For two weeks he had been unwell with listlessness, cough, and pyrexia. On admission he was acutely ill; temperature 105° F. (40.6° C.), pulse 140, and respirations 48. He had respiratory distress and signs of a bilateral bronchopneumonia, which were more marked on the right. An x-ray film of his chest was reported as showing massive consolidation in the right lower zone. His distress was somewhat relieved by oxygen. Penicillin 250,000 units six-hourly and streptomycin 250 mg. 12-hourly, both given intramuscularly, were started.

His condition improved slowly, and when on January 27 his Mantoux was found to be positive isoniazid 15 mg. was given six-hourly by mouth in addition. On February 2 the

penicillin was discontinued, the other therapy being maintained until June 19. By February 19 he was very much improved and his chest x-ray picture was reported as showing advanced resolution of the pneumonic consolidation. His progress thereafter was punctuated by recurrent, acute though not severe, respiratory infections, shown clinically by a rise of temperature to the region of 103° F. (39.4° C.), signs of a bronchitis, and radiologically by basal pneumonic shadowing. His weight, which on admission was 13½ lb. (6.2 kg.), increased slowly, so that at the age of 12 months he weighed 18½ lb. (8.5 kg.).

By this time investigation of his contacts had shown his father to have open tuberculosis. His three siblings were found to have positive Mantoux reactions but radiologically no evidence of tuberculosis. Among other investigations of the patient, tubercle bacilli were not recovered in three pharyngeal swabs, and serial E.S.R.s (Westergren) gave the following results: January 29, 5 mm. in one hour; February 5, 2 mm., and February 8, 2 mm.

On July 17 electrophoresis of his serum had shown a complete absence of gamma-globulin, and a separate determination by Dr. Soothill gave a level of 3 mg./100 ml. On September 12, weekly injections of gamma-globulin were started under the same M.R.C. regime as in Case 1. Since then he has had coryza only occasionally, and one attack of diarrhoea during which no pathogenic bacteria or viruses were isolated from the stools. Levels of gamma-globulin have varied from 100 to 160 mg./100 ml.

In retrospect we feel that the tuberculous element in his illness was probably slight because of the rapidity of response, both clinical and radiological, to therapy and also because of the failure to recover tubercle bacilli.

Family History

It is generally stated that this condition depends upon the presence of a sex-linked recessive factor, which is transmitted by females and manifested in males, though this view is not universally accepted. The siblings of both these children have normal levels of gamma-globulin. Case 2 comes from a widespread Irish family, and unfortunately it has not been possible to determine this child's family history in detail. His father had seven siblings and one half-brother, and, so far as is known, all are alive and well. His mother had 10 siblings. One had died aged 7 years from pneumonia after an illness lasting two weeks and another at an unknown age, of "purple measles." Both were boys.

In the family of Case 1 there is nothing relevant on the paternal side. His mother comes from a large family, and it was possible to obtain the maternal pedigree in detail. His grandparents were only-children and unrelated. Of their 12 children, four boys and one girl died in early life. As the most recent death was in 1938, agammaglobulinaemia could not then have been considered, and the stated causes and ages at death were as follows: (1) epidemic enteritis—1 month; (2) prematurity—a few hours; (3) acute enteritis—10 months; (5) bronchopneumonia—12 months; (6) bronchopneumonia with measles—21 months. Agammaglobulinaemia could not have been a significant factor in II 2, as he lived only a few hours and II 3 was a female. II 7 has had a lobectomy for bronchiectasis, but his electrophoretic strip is normal.

In the third generation there has been one death, the son of II 4. This boy came under the care of one of us (J.M.G.) when he was admitted with bronchopneumonia to the Manor Hospital, Walsall, in December, 1957, at the age of 4 months. He was extremely ill on admission, initially requiring continuous oxygen. *Staphylococcus pyogenes* was isolated from a

cough swab. It was resistant to all the common antibiotics with the exception of erythromycin, to treatment with which he responded. He also had a systolic murmur consistent with a congenital lesion of the heart, to which the unusual severity of his illness was partly attributed. After his discharge from hospital contact with him was lost. He was admitted to another hospital

at the age of 11 months and died within an hour. The stated cause of death was bronchopneumonia, but unfortunately a post-mortem examination was not carried out.

This pedigree is not inconsistent with a sex-linked recessive mode of inheritance.

Discussion

The infections to which these children are peculiarly susceptible are those associated with the common pyogenic organisms, staphylococcus, meningococcus, pneumococcus, haemolytic streptococcus, and also haemophilus. In general, infections by Gram-negative organisms are withstood better than those by Gram-positive organisms. The occurrence of diarrhoea has been emphasized by Firkin and Blackburn (1958) and mentioned also by McKay and Richardson (1959). Case 1 had at least two such attacks and Case 2 had one. The response to tuberculous infections presents a striking contrast in that the acquired immune reaction to the tubercle bacillus seems to function normally, suggesting that tuberculosis differs immunologically from other bacterial infections. The case described by Elphinstone *et al.* (1956) had a positive Mantoux reaction, as also had Case 2.

On the whole these children withstand virus infections normally. Cases have been reported in which intercurrent attacks of rubella, rubeola, mumps, chicken-pox, infective hepatitis, and poliomyelitis have followed the usual course. Moreover, the acquired specific immunity after attacks of measles and chicken-pox has been shown, since further intimate contact with the same virus has failed to cause second attacks, in spite of the fact that specific antibodies have not been detected in the serum. Both of our cases failed to show a significant increase in antibody titre after an "immunizing" course of poliomyelitis vaccine.

In contrast to the normal clinical response to infections with these viruses, there have been reports of death from generalized vaccinia. Such reports include the case described by Keidan *et al.* (1953), which does not, however, appear to have been a typical case of congenital agammaglobulinaemia; and that described by Kozinn *et al.* (1955) is difficult to evaluate as the haemagglutination

inhibiting test was positive. There remain, however, the single cases described by Somers (1957), by Sédallian *et al.* (1957), and by Galloway and MacBean (1958). However, other authors—for example, Apt (1953-4)—report patients vaccinated without complications. One wonders whether secondary infection could have been a factor in the fatal cases. One is also surprised that Galloway and MacBean state that the overall mortality rate in generalized vaccinia is 90%, which does not agree with our small experience. Nevertheless, in our present uncertain state of knowledge we do not feel that vaccination is a justifiable procedure in the presence of agammaglobulinaemia.

It may be that agammaglobulinaemia is not such an uncommon condition as it seems. Good and Varco (1955) were able to collect six cases in 10 months, and three were seen at the Mayo Clinic in seven months (Hayles *et al.*, 1954). We have on many occasions before and since looked for it in children, who have had several attacks of pneumonia before their first birthday or in whom there is an appropriate family history, without finding a further example. The case of the son of II 4 (see above) suggests that they may go unrecognized at times when bronchopneumonia is epidemic. Obviously the more cases that are investigated the more examples will be found, but there seems nothing in the examination of the child with this condition particularly to draw one's attention to the correct diagnosis.

Margulis *et al.* (1957) have suggested that the chest radiograph may be of potential diagnostic importance when with extensive parenchymal involvement there is a paradoxical absence of hilar lymph-node enlargement. That these features, which are shown by the serial radiographs in Case 2, are not invariable was demonstrated in Case 1. As mentioned previously, his chest radiograph in June had shown a right hilar adenitis, which by the following month was so marked that the radiologist suggested that tuberculosis should be considered. The case described by Elphinstone *et al.* (1956) showed on one occasion "a little enlargement of the right hilar shadow only." His sibling, who also had agammaglobulinaemia, developed enlargement of the regional lymph nodes in response to B.C.G. vaccination.

The normal sedimentation rate of Case 2 at a time when one would have expected it to be markedly raised might in retrospect have been of some diagnostic significance. This was also found by Elphinstone *et al.* and has been commented upon by several other authors. Citron (1957), however, in describing a case of acquired agammaglobulinaemia in a girl of 12, where no gamma-globulin was detectable by paper electrophoresis, states that the sedimentation rate "was moderately raised during infection except in the last few weeks before death, when in spite of much pulmonary infection the E.S.R. was 3 mm. per hour or less." It is, however, not clear from his paper what the time relationship was between the raised E.S.R. and the discovery of the absence of gamma-globulin. It would perhaps be unwise at present to regard the low E.S.R. found in these cases as being due solely to low gamma-globulin, since the rate of sedimentation is known to be influenced also by the alpha-globulin and fibrinogen levels in the plasma.

Summary

Two cases of agammaglobulinaemia are described. Their family history is consistent with a sex-linked recessive mode of inheritance. The problems of diagnosis and the response of these cases to different types of infection are discussed.

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TOXIC EPIDERMAL NECROLYSIS

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The paper by Catto (1959) reporting a case of toxic epidermal necrolysis in a boy aged 3, has directed attention to the syndrome described by Lyell (1956) and by Lang and Walker (1956, 1957), and has again raised the question of aetiology. The available evidence indicates that the characteristic clinical picture is a response to a variety of circulating toxins or allergens, derived from drugs or possibly from foods—for example, snook liver—but the causative role of the suspected agents has not hitherto been definitely established.

In the cases reported below, known drugs are believed to have precipitated the typical syndrome on more than one occasion in persons who were already sensitive to them: these drugs were phenolphthalein and dapsone.

Case 1

In December, 1959, a deeply pigmented Nigerian woman, aged about 55, was admitted to the Uzuakoli Research Unit Clinic suffering from a widespread papular eruption of four days' duration. The illness had been ushered in by headache, nausea, and general malaise. The temperature and pulse were only slightly raised, and the patient's general condition was good. The skin presented the following picture: a purplish-black discoloration of the whole face, including the lips, but sparing the nose and the periphery; large macular hyperpigmented areas on the trunk roughly symmetrical in distribution; a diffuse slate-grey dyschromia of the skin of the limbs. The buccal, nasal, and meatal mucosae and the conjunctivae were unaffected. This hypermelanosis had appeared some months previously; during the present illness the areas involved had become acutely tender to the touch.