ATYPICAL CONGENITAL HAEMOLYTIC ANAEMIA

BY

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The most common type of congenital haemolytic anaemia found in Great Britain is familial haemolytic anaemia (chronic acholuric jaundice). A similar congenital haemolytic anaemia may be found on rare occasions in children in whom the red cells do not show spherocytosis, or increased osmotic fragility. The response to splenectomy is not very satisfactory and the syndrome does not fit into the established pattern of familial haemolytic anaemia. Cases of this type have already been described by Haden (1947), Crosby (1950), Kaplan and Zuelzer (1950) and by Dacie, Mollison, Richardson, Selwyn and Shapiro (1953). The following is a further example of this atypical (non-spherocytic) congenital haemolytic anaemia.

Case Report

A girl aged 7 was the fourth child in a family of five. Her mother died of metastases from a melanotic sarcoma a few months after the birth of her fifth child. The patient as a baby was noticed to be pale and on occasions mildly jaundiced. She failed to gain weight and walked late. On one occasion she was admitted to hospital with rickets from which she made a complete recovery. From the age of 6 she was noticed to be pale, listless, jaundiced and had definite abdominal swelling. She was admitted to hospital.

On examination the child had a definite mongoloid facies (Fig. 1). All the mucous membranes were pale and there was moderate jaundice. The cervical lymph nodes were slightly enlarged. No bony deformity resulting from rickets could be detected. The spleen was enlarged and the liver palpable. There was a soft, non-conducted mitral systolic murmur.

The haemoglobin was 34% Haldane (4.6 g./100 ml.), erythrocytes 1.32 million per c.mm., colour index 1.3, P.C.V. 15%, M.C.V. 94 cubic microns, M.C.H.C. 30%, leucocytes 4,100 per c.mm. (neutrophil polymorphs 62%, lymphocytes 35%, monocytes 3%), reticulocytes 17%, normoblasts=13/100 white blood cells. A film showed some macrocytosis, anisocytosis and polychromasia. There was no evidence of spherocytosis, fragmentation or bizarrely shaped erythrocytes. The osmotic fragility of erythrocytes (room temperature) was normal on repeated examination. The Coombs test was negative. The serum bilirubin was 3.75 mg./100 ml. Serological

tests for syphilis were negative. No auto-agglutinins or haemolysins could be detected in the serum and the titre of cold agglutinins was 1 in 8.

The bone marrow showed a marked normoblastic hyperplasia, 58.5% of cells belonging to the erythropoietic series.

General cardiac enlargement was seen on radiological examination of the chest but no evidence of pulmonary disease.

Radiographs showed bony changes in the skull. These changes were largely confined to the frontal and parietal regions of the calvarium and consisted of a great

FIG. 1.—Photograph of the patient showing the mongoloid-like facies.

thickening of the diploe with vertical striations and atrophy of the outer table (Fig. 2). The horizontal table of the frontal bones was thickened. No evidence of brachyphalangia or any change in the intimate bony structure was shown on radiological examination of the hands.

The spleen was removed in October, 1948.

Histological examination of the spleen did not reveal the changes normally associated with familial haemolytic anaemia. The lymph follicles were separated by a cellular but uncongested pulp. The splenic sinusoids were prominent and lined by large littoral cells. There

was an increase of reticulum cells with vesicular nuclei throughout the pulp cords with a slight increase of the connective tissue elements, but erythrophagocytosis and extramedullary haemopoiesis could not be demonstrated. Occasional haemosiderin-laden macrophages were present in the pulp cords but not in the supporting tissues.

The child has been observed for four years since splenectomy, during which time she has developed normally, has attended school regularly, and has engaged in the usual childhood pursuits. Anaemia has persisted although it is less marked than before operation (Table 1). Jaundice and hepatomegaly have remained but not increased. The apical systolic bruit is still present. The haemoglobin has varied between 57% (8.4 g./100 ml.) and 75% (11.1 g./100 ml.) and the erythrocytes between

significant change, and the jaundice did not deepen. A fluid retention hydraemia resulting from the cortisone therapy may have masked a true increase in the total number of circulating red cells which might have been expected in view of the reticulocytic response. There may have been a true increase in the total circulating red cell mass but blood volume studies were not made to confirm this.

Comment

From birth this patient had a severe anaemia associated with mild jaundice and splenomegaly. There were no episodes of crisis. The anaemia was haemolytic in character as evidenced by the constant reticulocytosis, the presence of normoblasts in the peripheral blood, the hyperbilirubinaemia and the normoblastic hyperplasia of the bone marrow. Spherocytosis of erythrocytes could not be demonstrated and the red cell osmotic fragility was normal on repeated testing.

The differential diagnosis from other congenital haemolytic anaemias was considered. The absence of crises, spherocytosis and increased osmotic fragility was thought to exclude familial haemolytic anaemia. No sickling of erythrocytes could be demonstrated. The anaemia was not hypochromic in character, target cells were not seen in the peripheral blood, and the osmotic resistance of the red cells was not increased as in Mediterranean anaemia. The possibility of a symptomatic haemolytic anaemia was also considered. In this condition, however, the blood picture resembles familial haemolytic anaemia and there is a definite relationship to an underlying disease such as leukaemia, Hodgkin's disease or neoplasm. Allibone and Collins (1951) recorded a case of severe haemolytic anaemia in a girl of 4 which was cured by the removal of a cystic teratoma from the ovary. In the present case clinical, haematological and radiological investigations failed to reveal any underlying disease to which the haemolytic anaemia could be considered as secondary. Consequently the condition was regarded as congenital non-spherocytic haemolytic anaemia.

The tendency towards the development of a facial configuration of mongoloid type was noted in this case and in those described by Kaplan and Zuelzer (1950). The presence of osseous changes was a marked feature. These changes consisted of a thickening of the calvarium of the frontal and parietal bones with a 'hair-on-end' appearance. The short tubular bones were unaffected. In previous reports the familial and hereditary nature of this disease has been described, but it could not be confirmed in this instance.

The response to splenectomy serves to differentiate

FIG. 2.—Radiograph of the skull showing the thickened diploe, 'hair-on-end' appearance and atrophy of the outer table.

2.25 and 3.05 millions per c.mm., with a high colour index. The M.C.V. has remained high but the M.C.H.C. normal. There has been a constant high reticulocyte count (18-39%) and a hyperbilirubinaemia. Normoblasts have been persistently in the peripheral blood and their number has been roughly correlated with the degree of reticulocytosis. Leucocytosis and thrombocytosis have marked the post-splenectomy peripheral blood findings.

A study of the survival of transfused erythrocytes in the patient was undertaken after splenectomy. This showed a steady decline in the transfused cells which were destroyed at the normal rate. The survival of the patient's cells in a normal individual was not undertaken.

Four years after splenectomy the child received a therapeutic trial of 150 mg. cortisone daily for eight days. Thereafter the dose was gradually reduced by 25 mg. every 48 hours. (The total dose given was 1.7 g. in 16 days.) This produced an entirely non-specific response with evidence of marrow stimulation, as shown by a leucocytosis, thrombocytosis, increased reticulocytosis and normoblastosis. However, the erythrocyte count per c.mm. of whole blood showed no

TABLE I
BLOOD PICTURE BEFORE AND AFTER SPLENECTOMY

Date	Haemoglobin (g./100 ml.)	Erythrocytes ($\times 10^6$ /c.mm.)	M.C.V. (c. micron)	Leucocytes (per c.mm.)	Reticulocytes (%)	Bilirubin (mg. %)	Normoblasts (per 100 W.B.C.s)
13/5/48	4.6	1.32	94	4,100	17	1.0	—
10/7/48	2.8	0.73	123	4,800	15	3.5	13
24/9/48	7.4	1.96	120	4,350	3	—	—
Splenectomy (October 29, 1948)							
18/11/48	10.1	2.83	114	10,700	—	—	—
25/5/49	9.8	2.95	100	9,100	18	2.5	6
29/4/50	9.5	2.65	102	17,750	30	1.6	6
5/12/51	8.4	2.47	106	11,400	30	1.25	12
3/10/52	9.6	2.36	113	8,500	25	2.5	7

this disease from familial haemolytic anaemia. Splenectomy in the latter condition is uniformly beneficial and is rapidly followed by a loss of all evidence of excessive haemolysis. In congenital non-spherocytic haemolytic anaemia removal of the spleen may be followed, as in this case and in one described by Dacie *et al.* (1952), by some improvement in the anaemia but the reticulocytosis, normoblastosis and bilirubinaemia persist. The macrocytosis was unaffected by splenectomy (Table 1).

In the post-splenectomy period cortisone therapy had no effect on the haemolytic anaemia. The response obtained was non-specific and similar to that produced in normal human beings. Cortisone treatment in familial haemolytic anaemia is not beneficial but in many cases of acquired haemolytic anaemia a profound, if temporary, improvement is obtained. This consists in a decrease in the severity of blood destruction with a rise in the haemoglobin and a fall in the reticulocyte and bilirubin level of the peripheral blood.

Despite the absence of any morphological change in shape of the erythrocytes it is considered that the defect in this condition is intra-corpuseular. This is inferred from the inability to demonstrate either circulating immune bodies in the serum of these cases or adsorbed antibody on the erythrocytes using the Coombs test. The demonstration that the survival of erythrocytes transfused from these

patients into normal individuals is markedly shortened whereas normal erythrocytes transfused into them survive normally (Crosby, 1950; Kaplan and Zuelzer, 1950) is further evidence in support of an intra-corpuseular defect.

Summary

A case of congenital non-spherocytic haemolytic anaemia is described.

Clinically the disease was characterized by anaemia, jaundice, hepatosplenomegaly, osseous changes and a mongoloid-like facies. Crises were absent.

The erythrocytes were macrocytic, showed no spherocytosis and had a normal osmotic fragility.

The anaemia improved following splenectomy although haemolysis continued. The post-splenectomy haemolysis was unaffected by cortisone therapy.

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