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Hereditary Elliptocytosis Associated with Severe Haemolytic Anaemia and Malaria

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Summary. Two young children with hereditary elliptocytosis and severe haemolytic anaemia have been presented. Both had acute malaria infection when admitted to hospital. It is suggested that the acute malaria infection may have precipitated the severe haemolytic anaemia, though malaria could have contributed to the degree of anaemia observed in both children.

Résumé. On a amené deux enfants atteints d'une ellyptocytosie héréditaire et d'une anémie hémolytique sévere. Les deux enfants sont atteints d'une malaria aiguë quand ils sont admis à l'hôpital. On est de l'opinion que l'anémie hémolytique sévere pouvait etre précipitée par l'infection aiguë de malaria. Pourtant la présence de malaria aurait pu contribuer au stage d'anémie remarquée chez les deux enfants.

Hereditary elliptocytosis is usually an uncommon benign hereditary condition manifested by the presence of oval and elliptical erythrocytes in peripheral blood smears. The condition was first described by Dresbach in 1904 in a patient who did not present with any signs of haemolytic disease. Since then, a large number of similar cases have been published. Like hereditary spherocytosis, the anomaly of the red cell is hereditary and transmitted as a Mendelian dominant. Unlike hereditary spherocytosis, signs of overt haemolysis are found only in a small minority of individuals with elliptocytosis, and these have usually been recorded (Penfold & Lipscomb, 1943; Dacie, 1960; de Gruchy, Loder & Hennessey, 1962; Weiss 1963; Özer & Mills, 1964. Heilmeyer & Bergmann (1951) divided hereditary elliptocytosis into three clinical categories: (i) Asymptomatic, with no signs of increased haemolysis. (ii) Compensated, with signs of increased haemolysis but no anaemia. (iii) Elliptocytosis with haemolytic anaemia in which destruction of red cells exceeds maximum erythropoietic activity of the bone marrow. These clinical divisions are now generally accepted.

Two young children with hereditary elliptocytosis and exceptionally severe haemolytic anaemia were recently seen at the Pediatric department of the Korle Bu Teaching Hospital. Both had concomitantly acute falciparum malaria infection on admission.

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CASE 1

History

I.S., a 1-year 9-month-old male child, was referred to the Korle Bu Teaching Hospital because of fever, diarrhoea and severe anaemia. Four months prior to the present admission, he was seen in a polyclinic with a high fever. A presumptive diagnosis of malaria was made and he was treated with anti-malarial drugs. Haemoglobin recorded then was 5·7 g/100 ml. No further investigations or follow-up were carried out then. There was nothing significant in the family history to suggest a blood dyscrasia.

Physical findings

On admission, the patient appeared gravely and acutely ill. He was febrile, (temperature 101°F), lethargic and mildly dyspnoeic. The mucous membranes were extremely pale, and mild scleral icterus was present. Heart rate was 140/min. The liver was 3 cm below the right costal margin and the tip of the spleen was palpable.

Laboratory findings

Laboratory tests showed the following: Haemoglobin, 2·1 g; haematocrit, 9·0%; haemoglobin electrophoresis, AA; G6PD, normal; serum iron, 65 mcg; iron binding capacity, 200 mcg. A thin blood film showed marked anisocytosis and poikilocytosis, moderate hypochromia and polychromasia. A number of fragmented red cells, occasional spherocytes, nucleated red blood cells (10/100 WBC) and many elliptocytes were present (Fig. 1a). Coombs' tests both direct and indirect were negative. Malaria parasites were present on a Giemsa stained thick blood film.

A blood smear from the father showed marked elliptocytosis (Fig. 1b). A smear from the mother was negative for elliptocytes. The father showed no evidence of increased haemolysis.

Course

The child was transfused and the malaria treated with chloroquine. He made an excellent recovery. Two days after the transfusion, his haemoglobin was 7·6 g. A week later, his haemoglobin was 8·4 g and normoblasts were only rarely present on the smear. He was lost to further follow-up.

CASE 2

History

J.O., a 2-year-old girl, was referred to the Children's Emergency Ward, Korle Bu Teaching Hospital, because of fever, vomiting and severe anaemia. It was her first admission to a hospital. Nothing in her past history or in the family history suggested a blood dyscrasia.

Physical findings

The patient was critically ill on admission. She was febrile (temperature 101°F) and moderately dyspnoeic. Lung fields were clear to auscultation. Mucous membranes were extremely pale and the sclerae were mildly icteric. She was lethargic and did not respond

well to external stimulation. The spleen was not palpable but the liver was 6 cm below the right costal margin.

Laboratory findings

Laboratory findings showed the following: haemoglobin, 2·5 g; haematocrit, 9%; haemoglobin electrophoresis, AA; G6PD, normal; serum iron, 60 mcg%; total iron binding

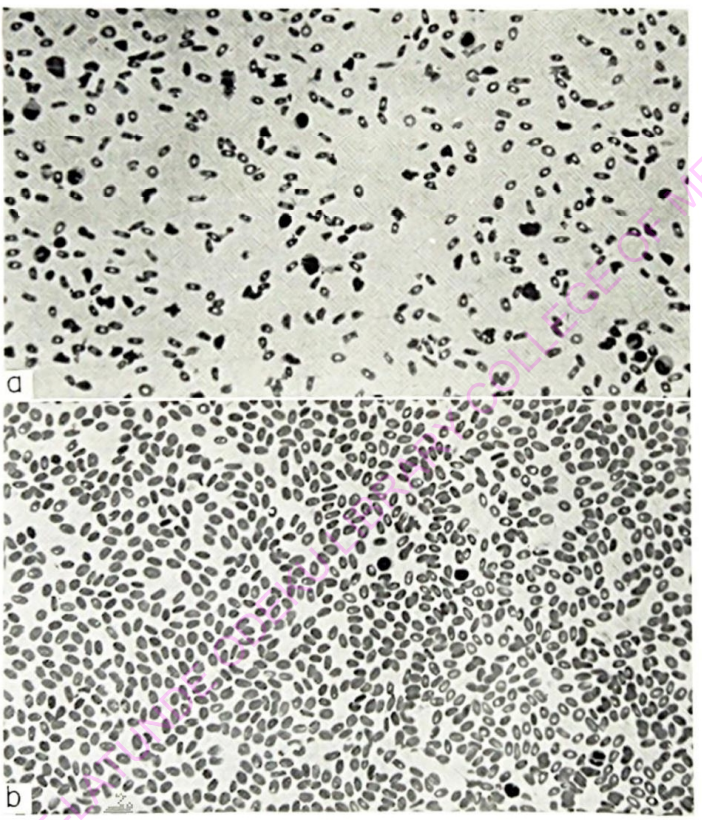

FIG. 1. (a) Microphotograph of a blood film of Case 1. × 180. (b) Microphotograph of a blood film of father of Case 1. × 180.

capacity, 180 mcg%. A thin blood smear showed many elliptocytes and many trophozoites of *Plasmodium falciparum*. Both elliptocytic and normal red cells were parasitized. Normoblasts (8/100 WBC) were present on the smear, as well as fragmented cells and a few spherocytes. There was marked anisocytosis, moderate polychromasia and hypochromia (Fig. 2a). Direct and indirect Coombs' tests were negative. A blood smear from the mother showed marked elliptocytosis and moderate hypochromia (Fig. 2b). A smear from the father was negative for elliptocytes. The mother was mildly anaemic (Hb 10·9 g%) but showed no signs of increased haemolysis.

Course

The patient was thought to be in early congestive heart failure and was given intravenous ethacrynic acid for prompt diuresis and then transfused. The malaria infection was treated with chloroquine. She made a remarkable recovery after the transfusion and anti-malarial treatment. She was discharged with a haemoglobin of 7·5 g. She was also lost to any further follow-up.

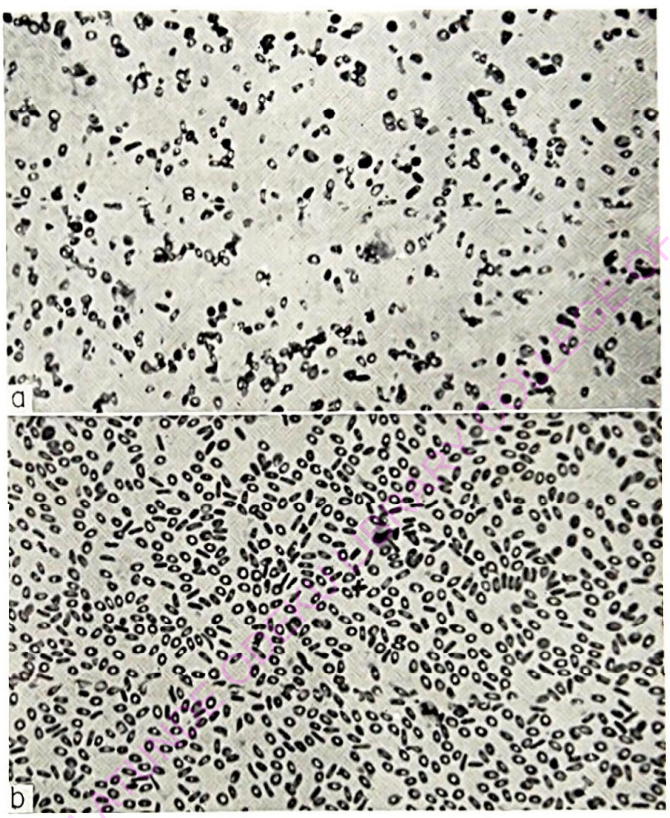

FIG. 2. (a) Microphotograph of a blood smear of Case 2. × 180. (b) Microphotograph of a blood smear of mother of Case 2. × 180.

DISCUSSION

The two cases described above both presented with severe haemolytic anaemia. The haemoglobin values were remarkably low and both patients were critically ill on admission. Both showed some signs of cerebral hypoxia and Case 2 was thought to be in early congestive cardiac failure. The diagnosis of hereditary elliptocytosis was made in each case on the basis of the characteristic appearance of the erythrocytes on the patient's peripheral blood films, and the presence of elliptocytosis in one of the parents.

It is generally agreed that hereditary elliptocytosis is in the majority of instances, a harmless trait. Why in a few cases this seemingly harmless trait becomes converted into a severe

uncompensated haemolytic anaemia is not clear (Dacie, 1960; de Gruchy *et al.*, 1962; Weiss, 1963; Ozer & Mills, 1964). Weiss (1963) suggested a genetic classification in an attempt to explain this variability in clinical expression of the trait and divided the disorder into four genetic groups: (1) All affected members of the family are asymptomatic, i.e. haemolytic disease absent. (2) Increased haemolysis in most of the affected family members—either frank haemolytic anaemia or evidence of compensated haemolysis, i.e. haemolytic disease present. (3) Sporadic haemolytic anaemia: In these families, the majority of the members with elliptocytic trait have no signs of either overt or compensated haemolytic disease. (4) Homozygosity, very rare and usually associated with haemolysis. A recent extensive pedigree study in Iceland supports this variability in clinical expression of the trait. Forty-five individuals with elliptocytosis were identified as having descended from a single ancestor. Clinical expression was, however, variable ranging from normal haematological status in the majority to frank haemolytic anaemia, although they presumably possessed the same gene (Jensson, Jonasson & Clafsson, 1967). Although complete family studies could not be obtained from the two patients described above, both may seem to fit within the third category of Weiss.

A number of red cell functional parameters have been studied by various investigators in patients with hereditary elliptocytosis. These have included osmotic fragility, mechanical fragility, autohaemolysis, and measurement of erythrocyte life span. The results have been variable and inconclusive. In individuals with asymptomatic trait, osmotic fragility and autohaemolysis are normal and in those with haemolytic disease, the results have been variable (Dacie, 1960; de Gruchy *et al.*, 1962; Weiss, 1963). De Gruchy *et al.* (1962) express the view that in patients with haemolytic disease, presence or absence of microspherocytosis determines the degree of osmotic fragility. In patients without microspherocytosis, the osmotic fragility is normal, and in those patients with microspherocytosis, osmotic fragility of both fresh and incubated blood is markely increased. Osmotic fragility tests could not be carried out on the two cases because of the urgency for transfusion or admission. Some spherocytes, however, were present on peripheral smears of both children. Studies of red cell survival in elliptocytosis by Mutulsky *et al.* (1954) using Ashby's technique of differential agglutination, and by Joseph & Avery (1955) and Dacie (1960) using radioactive chromium methods, indicate that when evidence of haemolysis is present, the red cell life span is shortened and that the life span is usually normal in asymptomatic individuals.

The basic erythrocyte abnormality in hereditary elliptocytosis is not known. Biochemical defects in the glycolytic pathway have been suggested (de Gruchy *et al.*, 1962; Weiss, 1963) but these have not been clearly defined. Zipursky *et al.* (1965) have described increased membrane permeability to sodium of the red cells of patients with non-haemolytic elliptocytosis. Their studies need confirmation both for non-haemolytic and haemolytic individuals with elliptocytosis. Both cases reported above had malaria parasites present on their peripheral blood smears. The clinical histories of fever, vomiting and diarrhoea are also compatible with acute malaria infection. Is it therefore possible that in these two children with hereditary elliptocytosis, acute malaria infection may in some way have precipitated the severe haemolysis encountered in them? Malaria alone is a common cause of anaemia in young children and in many cases, the anaemia is severe (Jilly & Nkrumah, 1964). However, the degree of normoblastaemia and the presence of many distorted and fragmented red cells seen on the peripheral blood smears of these two patients is unusual for just anaemia associated with malaria. Recently, Pryor & Pitney (1967) have reported severe haemolytic

anaemia in two young children with elliptocytosis from New Guinea. Both these children had acute malaria when admitted to hospital. They suggested the possibility that patients with elliptocytosis may be more susceptible to malaria than other individuals and that such malaria attacks could then exacerbate the degree of anaemia. However, an alternative and a more likely possibility is that malaria infection which normally causes some red cell destruction, may trigger a much more severe haemolysis in individuals with elliptocytosis. This view would conform with occasional observations where overt haemolysis in individuals with hereditary elliptocytosis has been associated with intercurrent infections (Dacie, 1960). Osler & Mills (1964) have suggested that associated biochemical abnormalities of red cells such as G6PD deficiency or other enzyme deficiencies may account for increased haemolysis in individuals with elliptocytosis. They documented two cases with overt haemolysis. One had decreased red cell glutathione and in the other G6PD deficiency was present. However, a family study by Pearson (1968) does not support this suggestion that interaction of genes for G6PD and elliptocytosis results in haemolytic anaemia. The father in this pedigree who had both elliptocytosis and low red cell G6PD enzyme levels did not have evidence of haemolysis. The propositus had haemolytic anaemia and normal G6PD. Red cell G6PD was normal in the two patients reported above.

The incidence of the elliptocytosis trait in Ghana is not known, though the trait is known to exist (Ringelham *et al.*, 1970). It is hoped that future mass blood smear surveys such as during a malariometric study, may allow the incidence of this uncommon but interesting hereditary trait to be determined. In malaria areas, the possible role of malaria in patients with elliptocytosis and haemolytic anaemia will need further study.

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