HEREDITARY SPHEROCYTOSIS COMPLICATED BY THE INSPISSATED BILE SYNDROME

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Obstructive jaundice is uncommon in early infancy. It is characterized, as in later life, by enlargement of the liver and spleen, pale acholic stools, heavily bile-stained urine and accumulation of bilirubin glucuronide in the serum. Congenital obliteration of the bile ducts causes about two-thirds of the cases of obstructive jaundice in infancy. Much less common is obstruction from pressure on the biliary tract by cyst, tumour or glands. In one-third of cases, however, the biliary tract is normally formed and there is no evidence of extrahepatic biliary compression. Here, obstruction to flow of bile occurs in the liver through an ill-understood mechanism — accumulation of thickened secretions, swelling or necrosis of liver cells, excessive intrasinusoidal haematopoiesis, an immature biliary system, and dehydration, being variously incriminated.[1] Describing this picture in 1935, Ladd[2] used the term 'inspissated bile syndrome' for the first time.

In contrast to congenital atresia of the bile ducts, where jaundice gradually but steadily deepens and the outcome is invariably fatal unless surgical correction can be achieved, the inspissated bile syndrome is characterized by early onset of severe jaundice and a generally favourable outcome, provided that surgery is not attempted.[3]

The inspissated bile syndrome has often been found to complicate haemolytic disease of the newborn. Hsia *et al.*[4] in their well-known analysis of 156 cases of prolonged obstructive jaundice in infancy, listed 23 cases of erythroblastosis foetalis with this condition. Stempfel *et al.*[1] found

7 infants with obstructive jaundice among 83 cases of erythroblastosis due to rhesus incompatibility, suggesting that the complication may be commoner than was first thought. Presumably it may also result from ABO haemolytic disease.

The syndrome may also occur without evidence of haemolysis or other known cause of jaundice. In such cases, characteristic appearances, suggesting viral infection, are found on microscopic examination of the liver.[3,5] The term 'neonatal hepatitis' has been used for this picture. Recently Hsia *et al.*[6] analysed 59 families in which one or more offspring were affected with neonatal hepatitis. They point out that there may well be a hereditary component in the pathogenesis of this disease.

I found no references to other causes of the inspissated bile syndrome in the literature. The occurrence of this syndrome in a case of hereditary spherocytosis may therefore be of interest.

CASE REPORT*

History

Colin K. was born on 12 February 1957, the first child of healthy unrelated parents. One of his father's brothers and 2 sisters were known to have acholuric jaundice and his paternal grandfather had symptoms suggestive of this condition (Fig. 1). The father was not available for testing at the time of this child's illness but was later found to have spherocytosis and slightly increased osmotic fragility of the red cells, though free of symptoms.

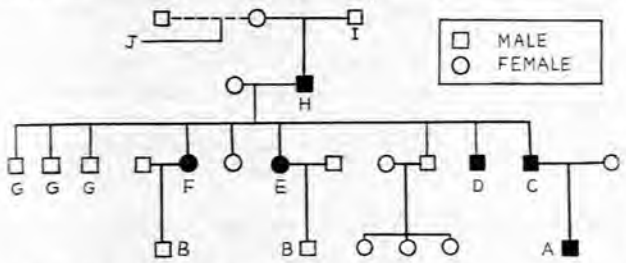

Fig. 1. Family tree of Colin K.

A = Colin K.
B = Clinically normal at birth.
C = Asymptomatic. Spherocytosis and increased fragility.
D = Spherocytosis. Splenectomy.
E = Spherocytosis. Anaemia.
F = Spherocytosis. Splenectomy. Gall stones.
G = Died of unrelated causes. (?)
H = Anaemia. Ulcers on legs.
I = Died in accident. (?)
J = Offspring of second marriage all normal.

The infant was delivered by forceps for disproportion at full term after a normal pregnancy. His weight at birth was 7 lb. 11 oz. He appeared normal at first but slight jaundice was noted at 4 hours, gradually becoming more intense. The liver and spleen were much enlarged. Stools consisted initially of dark meconium but changed to brown on the third day; thereafter they were clay-coloured. The urine became progressively more bile-stained. The jaundice deepened and the haemoglobin dropped rapidly to 8·5 g. per 100 ml. A simple transfusion of whole blood was given on the 12th day. There was considerable feeding difficulty and frequent vomiting, various formulae being tried.

Examination

The infant was first seen by me when he was 4 weeks old. Examination revealed an undernourished, chronically ill, icteric infant, the skin and mucosae being greenish-yellow in colour. He was only 1 oz. over his birth weight. No cataracts or retinitis were noted on ophthalmological examination. The liver was much enlarged and firm and smooth; the lower margin being felt 3 fingerbreadths below the costal margin. The spleen was easily palpable. No gastric peristalsis was visible and no other masses were detected.

Blood Investigations

RBCs, 3·2 million per c. mm.; haemoglobin 11 g. per 100 ml. (14·8 g. per 100 ml. = 100%); WBCs 8,200 per c. mm. with neutrophils 50%, lymphocytes 40%, monocytes 7%, and eosinophils 3%. There was some macrocytosis and there were small numbers of normoblasts. No microspherocytes were seen. The reticulocyte count was 3·5%. Saline red-cell fragility was within normal limits (Creed's method[7]). The blood groups of the mother and infant were ORh positive (D). The direct Coomb's test was negative. The serum bilirubin was 17·6 mg. per 100 ml. The Van den Bergh test gave an immediate positive direct reaction. The Kahn test was negative, and blood culture was sterile.

The stools were clay-coloured and the urine deeply bile-stained. Urobilin was found on some occasions. No galactose was present in the urine and repeated examination failed to reveal cells containing inclusion bodies. Studies on red-cell fragility in saline solutions were repeated, yielding a pattern within normal limits (Creed's method[7]).

Treatment

Instillation of concentrated magnesium sulphate solution into the duodenum produced several stools which were pale green in colour. This was repeated for 10 days without diminution in the bilirubinuria or the icterus. Some initial improvement in the feeding was not maintained later and the procedure was abandoned.

On these findings it was considered that atresia of the bile ducts was unlikely, the diagnosis resting between hereditary spherocytosis with a superimposed inspissated bile syndrome, and neonatal hepatitis. The persistent absence of spherocytes and the saline-fragility tests appeared, however, to militate against the former diagnosis. At 6 weeks of age treatment with cortisone was commenced, first by intramuscular injection (12·5 mg. *t.d.s.*) and later by mouth. There was immediate improvement in feeding and weight gain, but no diminution in the jaundice for the first month of treatment. By the sixth week of treatment, however, (age 3 months) the icterus had almost disappeared and the urine was clear during the day, though bile-stained on rising. The liver and spleen were still enlarged.

Progress

The child was not seen again until the age of 7 months. The mother then stated that his progress had been most satisfactory and that he appeared normal in all respects. His weight was 15 lb. 12 oz. and he showed good development. There was well-marked pallor but no jaundice. Two lower incisors had erupted and these were green in colour, a feature noted later in all the deciduous teeth. The liver was soft and of normal size, but the spleen could be felt 1 fingerbreadth below the costal margin.

On this occasion the following results were obtained on laboratory investigation: Haemoglobin 8·6 g. per 100 ml., RBCs 3·1 million per c. mm., WBCs 12,600 (differential count normal), no spherocytes or other abnormal cells seen, total protein 5·2 g. per 100 ml., albumin 3·0 g. per 100 ml., α_1 globulin 0·34 g. per 100 ml., α_2 globulin 0·60 g. per 100 ml., β globulin 0·53 g. per 100 ml., fibrinogen 0·27 g. per 100 ml., gamma globulin 0·47 g. per 100 ml., bilirubin glucuronide absent, total serum bilirubin 0·8 mg. per 100 ml., thymol turbidity 2 units, thymol flocculation 0, serum colloidal gold 0, zinc sulphate turbidity 2 units.

No improvement in the anaemia followed a course of intramuscular iron. At 10 months of age the haemoglobin had fallen to 5·4 g. per 100 ml. and the RBCs to 2·1 million per c.mm. The reticulocyte count was 6·8%. The erythrocytes were hypochromic and microcytic with considerable variation in size and shape. Polychromasia was prominent and there were 4 normoblasts per 100 leucocytes. No spherocytic cells were seen. A blood transfusion of 200 ml. of packed cells was given, raising the haemoglobin to 14·0 g. per 100 ml. At 11 months the haemoglobin had again dropped to 9·4 g. per 100

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ml. On this occasion a few microspherocytes were seen in a film of the peripheral blood. There was a reticulocytosis of 7%.

At 1 year of age the osmotic fragility test was repeated by Creed's method, and this time a slightly increased fragility to hypotonic saline solutions was demonstrated. The haemoglobin had dropped to 7·5 g. per 100 ml. and a further transfusion was given.

Splenectomy

The diagnosis of hereditary spherocytosis was at last considered established, and in view of the severity of the anaemia, splenectomy was performed at 13 months after adequate preparation. This procedure was withstood without incident and subsequent progress had been quite satisfactory, the haemoglobin being maintained at normal levels.

Microscopic examination of the spleen revealed no evidence of congestive splenomegaly, 'the picture being consistent with that of acholuric familial jaundice'.

At the time of writing the patient is 2 years 11 months of age and normal in every way apart from green discoloration of the teeth. Infections have not been a problem to date. A recent fragility test using the incubation technique revealed a normal pattern and no spherocytes were noted in the peripheral blood.

DISCUSSION

The occurrence of hereditary spherocytosis in infancy has recently been the subject of 2 excellent reviews.[8,9] The condition has been recorded before the age of 6 months in 40 patients,[9] but in less than 20 did symptoms become manifest in the first 2 weeks of life. In these neonatal cases, jaundice was a frequent feature, contrasting with older subjects where it is not often found. In 3 infants the jaundice was sufficiently severe to produce kernicterus[10-12] and exchange transfusions were performed to lower the serum bilirubin.[10,11,13] There is, however, no report of jaundice of the obstructive type such as in the case here described.

Although no liver biopsy was performed, the diagnosis of inspissated bile syndrome complicating hereditary spherocytosis would seem to be established beyond reasonable doubt, in view of the gradual disappearance of the obstructive jaundice and the eventual course of the anaemia. Yet the problems of diagnosis and management in the first 6 weeks of life were considerable. Faced with an ill, jaundiced and anaemic child, no haematological evidence of hereditary spherocytosis could be demonstrated. Haemolytic disease of the newborn due to rhesus or ABO incompatibility was ruled out, and atresia of the bile ducts could be excluded by the intermittent presence of urobilin in the urine and by the presence of bile-stained stools after intraduodenal instillation of magnesium sulphate. There was no evidence of septicaemia. The urine did not contain reducing substances; this excluded galactosaemia. Although congenital toxoplasmosis and cytomegalic inclusion disease could only be finally eliminated by liver biopsy, there was on the one hand no retinitis on fundoscopic examination and on the other no abnormal cells in the urine. There remained only neonatal hepatitis or haemolytic anaemia with superadded obstructive jaundice as likely alternatives.

Because of the reported beneficial effects of steroids in cases of 'idiopathic' inspissated bile syndrome,[3] a course of cortisone was given. Clinical improvement undoubtedly coincided with commencement of treatment but the significance of this is difficult to assess in view of the tendency to spontaneous improvement in this condition. Clinically and biochemically the liver appears to have suffered no lasting damage. Again, it is unfortunate that no liver biopsy was taken at the time of the splenectomy.

The more elaborate studies on red-cell fragility — incubated red-cell fragility, autohaemolysis and mechanical fragility[14]—were not performed in this critical early period. Although it has been held that the red-cell fragility may be normal at birth in cases of hereditary spherocytosis, the use of these recent techniques could prove this untrue. In 5 of 31 cases, however, the fragility using the standard method was normal when these cases were first examined and increased later.[8] In the present case the red-cell fragilities were repeated 1 year after splenectomy by Creed's method, using oxygenated heparinized blood, coupled with the thermal autohaemolysis test. It is of interest that no significant increase was detected compared with the control. Young *et al.*[14] found that in all of 11 patients with hereditary spherocytosis whom they investigated, the characteristic abnormalities of the erythrocyte persisted after splenectomy for the one or more years they were followed up.

The intraduodenal administration of magnesium sulphate as a cholagogue produced a definite response and was accompanied by no overt side-effects or diarrhoea. The use of parenteral bile acids would seem however to be safer and better.[15]

The importance of expectant treatment in this syndrome has been emphasized by Gellis *et al.*[3] who showed that mortality and morbidity were far commoner in cases explored surgically. The surgical management of neonatal obstructive jaundice has recently been reviewed by White.[16]

After subsidence of jaundice in the case here reported, the anaemia was severe enough to justify early splenectomy. This does not conform with the usual pattern of the disease in infancy.[9] Many infants have severe anaemia in the first few months of life, but, with transfusion therapy, the anaemia subsequently remains minimal. Splenectomy may therefore be deferred under a regime of careful observation. In view of the well-known danger of overwhelming infections in infants who have undergone splenectomy it is probably wise to delay the operation as long as possible.[8] This conclusion is however not supported by Laski and Macmillan[17] who claim to show that the incidence of serious infections in children after splenectomy is no higher than in a similar group after appendicectomy.

SUMMARY

Hereditary spherocytosis is a rare cause of jaundice in the neonatal period. A case complicated by the inspissated bile syndrome is described here. The obstruction cleared completely and splenectomy was later performed because of uncontrollable anaemia. The association of hereditary spherocytosis and the inspissated bile syndrome does not appear to have been previously reported.

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