CASE REPORTS

ATROPHIC CIRRHOSIS OF THE LIVER

following

ICTERUS GRAVIS NEONATORUM

BY

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WITH PATHOLOGICAL REPORT

BY

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Cirrhosis of the liver is a comparatively rare disease in childhood. Poynton and Wyllie¹ describe seven 'types,' one of these being a type associated with icterus gravis neonatorum. They say:—

Pathologically, there may seem to be very little evidence in favour of grouping such cases among cirrheses of the liver. In affected infants dying in the first few days after birth . . . (there was) found no indication of increased connective tissue. . . . In the more chronic cases, however, as in the fourth child in Pfannenstiel's family which died on the 21st day, the liver was enlarged, coarse and dark green . . . Microscopically, the interstitial tissue of the liver was irregularly broadened and had an oedematous appearance, with here and there small collections of cells. The liver cells contained bile and the cell columns were very narrow; the bile ducts were widened at several points. These details are strongly suggestive of an early biliary cirrhosis, the fibrosis not commencing till after birth.

This thesis is supported by Hawkesley and Lightwood² in their clinical and pathological study of icterus gravis neonatorum. They found, in seven cases out of nine of more than five weeks of age, signs of hepatic fibrosis. The fibrosis was most conspicuous in relation to the portal tracts but an intercellular fibrosis was also observed. They suggest that survival from icterus gravis may be accompanied by cirrhotic changes in the liver and that infants so surviving may become the subjects of multilobular cirrhosis of the liver in early childhood.

Several cases of liver cirrhosis with a history of jaundice in the neo-natal period have been reported. The patient reported by Smith³ at the age of

four-and-a-half years was jaundiced in the first six weeks, Bossert's⁴ patient for seven weeks and Curtis's⁵ patient, age fourteen years, had a 'rather severe type of jaundice neonatorum but it cleared perfectly.' In de Lange's⁶ case which died at the age of seven months jaundice had been present from the third day of life. These authors either do not discuss the possible relation between the two conditions or suggest that some congenital defect of the liver may have been present. Bossert, for instance, thinks that the early icterus lends some support to this theory but feels that its disappearance makes acceptance improbable. But Hanau⁷, who gives the most detailed description of his case, discusses fully the type of the neonatal jaundice and its possible relation to the cirrhosis which developed. The main points in his case are these:—

The child was the eighth in a family of eight of whom only two survived. Of the others, two were stillborn, one died at seven weeks of convulsions, one died during the first year of some unknown cause and one was a premature still-birth. The maternal Wassermann reaction was negative. This child was jaundiced during the first three months of life and enlargement of the liver and spleen was noted during the first month. At one year and nine months, the liver and spleen were large, the abdominal veins distended and ascites was present. The course of the illness was then rapidly fatal. At autopsy, the liver was found to be nodular and the entire surface granular. The large bile-ducts were patent. Microscopically, the lobules were bordered by thick connective tissue in which were clumps of lymphocytes. There was fatty infiltration and degeneration of the liver cells. Hanau discusses fully the differential diagnosis of the neonatal jaundice and concludes that it belonged to the familial icterus gravis group. Although he could find no account of the fate of recovered cases of icterus gravis he considers it to be a possibility that the cirrhosis was a direct sequel to the icterus in his case.

The patient who is the subject of the present report is of interest because she first came under observation in the neonatal period suffering from icterus gravis and died at the age of three-and-a-half years from haematemesis due to multilobular cirrhosis of the liver.

Case Report

First admission. The patient, a female born on March 4, 1933, was admitted to the Children's Hospital at the age of four weeks with the history that since the age of three days she had been jaundiced and had passed colourless stools. She was the second child of healthy parents and the first child was healthy. On admission, her general condition was good and her weight was 8 lb. 11 oz. She was deeply jaundiced. The liver was enlarged and at this time the spleen was not felt. The stools were colourless. No umbilical sepsis or other abnormality was noted.

Laboratory Investigations

BLOOD. The van den Bergh test gave an immediate direct positive reaction, the indirect reaction showed 2.0 units of bilirubin. The fragility of the red cells was normal. The total red cells were 3.9 million, Hb. 74 per cent., C.I. 95, reticulocytes 5.8 per cent. (age 9 weeks), total white cells 11,500; polymorphs neutrophil, segmented, 16.5 per cent., non-segmented,

8 per cent.; eosinophil, segmented, 0.5 per cent., non-segmented, 1.5 per cent.; myelocytes 1 per cent.; metamyelocytes 0.5 per cent.; lymphocytes 70.5 per cent.; plasma lymphoblasts 0.5 per cent.; monocytes 1 per cent. The red cells stained well and were uniform in size; halometer reading $4.5=7.64\mu$ (at age 4 weeks).

STOOLS. Bile pigments were absent, bile salts present.

X-ray examination of the long bones showed no evidence of congenital syphilis. The maternal Wassermann reaction was negative.

FIG. 1.

Progress. On 18.4.33, the stools contained some bile pigment and from 25.4.33, when aged seven weeks, normally coloured stools were passed. The jaundice then gradually lessened. The baby maintained her good general condition and lost only 8 ounces during the first three weeks in hospital and then gained weight slowly. She was breast fed. On 4.5.33 she was discharged, still jaundiced and with the liver enlarged to the level of the umbilicus. Observed in the out-patient

department, the jaundice cleared steadily and completely, the liver remained large and the spleen became palpable at the age of five months. At eight months blood examination showed total red cells 4·3 million, Hb. 90 per cent., C.I. 1·04; total white cells 6,050 with a normal differential count. The general health and progress of the baby were good. In July, 1934, she had a severe attack of whooping-cough, complicated by pneumonia from which she made an apparently good recovery. At this time the liver was still enlarged and the spleen palpable.

Second admission. On 17.11.36 (aged 3½ years) she was again brought to the hospital because of enlargement of the abdomen which had become apparent in the previous fortnight. Until then her general health had been good and her physical and mental development normal. Examination revealed a marked enlargement of the abdomen with distended superficial veins (fig. 1). Much free fluid was present. The liver was now small, hard and nodular, felt in the intercostal angle below the xiphisternum but not felt under the costal margin in the mid-clavicular line. The spleen was palpable and the area of splenic dullness was increased. There was no jaundice at this time. There was no evidence of any lesion of the central nervous system. X-ray examination showed no abnormality of the bones.

Laboratory investigations

BLOOD. (23.11.36.) The van den Bergh test showed a direct negative reaction, indirect reaction 0·4 units of bilirubin; takata-ara reaction positive; albumin 2·94 per cent., globulin 1·65 per cent., calcium 8·9 per cent., phosphorous 4·2 per cent; phosphatase 18·0 mgm. P. liberated by 100 c.c. serum during three hours' incubation at 37° C. Intravenous glucose test (25.11.36) showed impaired tolerance.

URINE. (26.11.36.) Urobilin and urobilinogen in excess, bile pigments and bile salts absent.

STOOLS, average of three days. Dried faeces 66 gm.; total fat 32·1 per cent., unsap. fat 19·1 per cent., sapon. fat 13·1 per cent., free fatty acid 13·1 per cent., neutral fat 5·9 per cent., daily output 4·2 gm.

Progress. A suspicion of jaundice appeared on 27.11.36; on the two following days there was a sudden unexplained rise in temperature associated with diarrhoea. On 30.11.36, she had a severe haematemesis and died within twelve hours of its onset and within four weeks of the appearance of gross signs of liver failure

Pathological examination

The body was that of a three-and-a-half year old female child, well nourished with a slight excess of superficial fat. The skin and mucous membranes were extremely pale and slightly jaundiced. Prominent, tortuous veins were visible beneath the skin of the abdominal wall.

Both pleural cavities contained a small quantity of slightly bile-stained fluid. The lungs showed evidence of terminal congestion but no other disease. The remainder of the thoracic contents, including the heart, presented no abnormalities.

The peritoneum appeared healthy and contained a small quantity of bile-stained ascitic fluid. The liver was slightly enlarged, measuring 16·2 cm. by 10 cm. and 7·5 cm. in thickness. The whole organ was grossly nodular ('hobnail'), firm, and presented small granular nodules superimposed on the surface of the large knobs. The external surface was pale, with large gray streaks in an otherwise mottled surface, punctuated by scattered dark haemorrhagic areas (fig. 2 and 3). The gall bladder appeared

FIG. 2.

FIG. 3.

normal in size and contained normal bile. The cystic duct was patent and surrounded by an abnormal amount of fibrous tissue. All ducts were patent. The cut surface of the liver showed marked fibrosis with a multilobular distribution (fig. 4).

FIG. 4.

The spleen was slightly enlarged, measuring 10.5 cm. by 7.5 cm. and it was firm and moderately fibrotic (fig. 5).

The lower end of the oesophagus contained several dilated, tortuous vessels. The site of rupture of the varices which resulted in fatal haemorrhage could not be found (fig. 6).

FIG. 5.

FIG. 6.

The brain showed no evidence of bile staining. The bone-marrow of the femur was red, and appeared normal. Smears and sections of this showed no abnormality.

Microscopical examination of the liver revealed a coarse multilobular cirrhosis, with very little damage to the liver cells (fig. 7 and 8).

FIG. 7.

FIG. 8.

Discussion

The jaundice in the neonatal period was not due to sepsis for there was no evidence of sepsis, no haemorrhage and no disturbance of temperature and it was not due to congenital syphilis for the maternal Wassermann reaction was negative and the infant's bones showed no evidence of syphilis on x-ray examination. Nor was the good general condition of the baby consistent with either of these diagnoses. Because of the absence of bile from the stools in the early weeks the possibility of congenital obliteration of the bile-ducts had to be considered. Blood examination did not support this diagnosis and the fact that bile entered the intestine after the age of seven weeks and the jaundice then disappeared, ruled it out entirely. Familial icterus gravis may appear in a form which is not acute and may be associated with a temporary acholia, and it is to this category that the jaundice of the case under review belongs. There is no family history of icterus gravis for she was only the second child and as is usually the case the first child was healthy. Blood examination supports the diagnosis of icterus gravis in the increased amount of circulating bilirubin and in the presence of reticulocytosis. The colour index was still above unity at the age of seven months. The diameter of the red cells, at age four weeks, was 7.6μ as compared with van Creveld's normal average of 8.266μ at that age. A fall, more rapid than normal, in the size of the red cells in icterus gravis neonatorum has been noted by van Creveld and by Hawkesley². Subsidiary changes in the white cells were also present. The fragility of the red cells in icterus gravis is variable and in this case it was normal.

A temporary acholia in familial icterus gravis is an interesting fact. It was present in two of Hawkesley's cases in which early signs of liver cirrhosis were found and has been present in several cases under the care of one of us (F. B.). It was an outstanding feature in a patient who later developed generalized osseous dystrophy⁸. It was also present in another patient who has developed green teeth and in a baby now under observation. The explanation of its occurrence is not clear. It may be a direct result of excessive haemolysis whereby the bile channels or the liver cells are overtaxed with excretory work or the bile pigments accumulate in the bile capillaries. If that were so, one would expect to find a direct relationship between the extent of the haemolysis, as estimated by the degree of anaemia, and the absence of bile pigments from the stools. In our experience that is not so. In cases in which the red cells have fallen to one million or less acholia has not been observed and in those quoted above in which acholia has been a marked feature anaemia has not been severe. In the case under review the anaemia was slight and the fact that the spleen did not become palpable till the fifth month also suggests that haemolysis was not an urgent feature and not likely to be responsible for the acholia either by increasing the viscosity of the bile or by blocking the capillaries with pigment. Diamond, Blackfan and Baty⁹ who regard icterus gravis and the conditions allied thereto as a result of a congenital metabolic defect of the haematopoietic system, believe that the acholia is due to over-

crowding of the liver with haematopoietic foci which cause pressure of the liver cells sufficient to cause an obstructive as well as a haemolytic form of jaundice. If that is so, and if the view is confirmed that these foci may be sufficient to cause obstructive jaundice in cases in which haemolytic anaemia is not severe, then it would give support to the idea that the excess erythroblastic tissue is a primary condition and not secondary to the haemolysis, as is more generally believed at the present time.

The cause of the cirrhosis of the liver in this case is not to be found among the recognized causes of cirrhosis of the liver in childhood—syphilis, alcohol, malformation of the bile-ducts—but in the icterus gravis or rather in the etiological factor upon which the occurrence of icterus gravis depends and that is still a matter for conjecture. It is familial and it may be a hereditary or a congenital defect or both. Hawkesley² mentions one case in which hereditary transmission is apparent and in some of the reported cases already quoted associated congenital defects are noted. In Bossert's case⁴ bilateral congenital cataract was present, in the case reported by Curtis⁵ there was congenital dislocation of the left hip-joint and in the case reported by de Lange⁶ there was transposition of the viscera. It seems probable that there may be some link between liver cirrhosis following the familial condition of icterus gravis and juvenile familial cirrhosis, and the possible resemblance between 'kernicterus,' a complication of familial icterus gravis, and Kinnier-Wilson's familial disease, progressive lenticular degeneration¹⁰ associated with atrophic liver cirrhosis, has often been suggested. The course of the illness is variable in cases belonging to each of these groups but the type of the cirrhosis appears to be the same in all. In the case under review the liver was in the atrophic stage of multilobular cirrhosis, Bossert and de Lange considered their cases to be in the hypertrophic stage of atrophic cirrhosis, in the case reported by Curtis the liver was atrophic and in Smith's case the cirrhosis was interlobular in distribution. In Kinnier-Wilson's disease the cirrhosis is of this same type and this is true also of the cases of juvenile familial cirrhosis reported by Bramwell¹¹, and by Ruh and Albrecht¹² and Schuscik¹³, and by others. Bramwell's cases are of especial interest. Although nervous signs were absent and although the clinical course was short compared with the chronic illness in the former group, he considers that his cases are similar to those described by Kinnier-Wilson. Barnes¹⁴ supports this opinion in the group of cases which he reports. In two of his three cases belonging to one family haematemeses and gastro-intestinal disorders had actually occurred weeks or months before the nervous symptoms and, in the third case, gross signs of liver cirrhosis were present and at the time of the report evidence of a lesion of the central nervous system was absent. This makes the time factor in the appearance of the various signs in 'kernicterus' of less importance in relating that condition to progressive lenticular degeneration.

Parkes Weber¹⁵ places juvenile familial cirrhosis of the liver and progressive lenticular degeneration associated with cirrhosis of the liver among what he calls 'congenital-developmental disorders,' 'congenital' because the predisposition is in-born and 'developmental' because signs of the disorder appear at one or other stage of post-natal development. If further proof can be found to support the theory of Diamond and Blackfan that icterus gravis is due to some inborn metabolic defect of the haematopoietic system, then a relationship between icterus gravis with its sequels of 'kernicterus' and liver cirrhosis on the one hand and juvenile liver cirrhosis with or without progressive lenticular degeneration on the other hand might be established. They may be variations of a common 'congenital-developmental defect.'

Summary

(1) A case of cirrhosis of the liver following icterus gravis neonatorum is recorded.

(2) No lesion of the central nervous system or of the bones was present.

(3) The possible relation to juvenile liver cirrhosis and to progressive lenticular degeneration is discussed and it is suggested that familial icterus gravis may be classed with these as a congenital developmental defect.

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