Intrahepatic Cholestasis in the Newborn

L. HAAS

From the City Hospital, Exeter; Torbay Hospital, Torquay, Devon

Hitherto little attention has been paid to cholestatic jaundice in the newborn which occurs in the absence of rhesus incompatibility. 4 such cases, among a consecutive series of 24 newborns with prolonged neonatal jaundice occurring in the Devon and Exeter clinical area since 1960, are here described in detail to demonstrate that their clinical and histological picture, and their prognosis, is quite distinct from that of other forms of prolonged obstructive neonatal jaundice. Attention is drawn to a possible relation between cholestatic jaundice in the newborn and absence of the intrahepatic bile-ducts in later infancy, and to the place of steroid therapy in the management of cholestatic jaundice.

Case Reports

Case 1. Male: born January 1, 1964, after 35 weeks' gestation, weighed 2.95 kg. (5 lb. 2½ oz.). The mother had had a Shirodkar suture inserted early in the pregnancy, and this was removed when the membranes ruptured three days before the birth of the baby. The labour and delivery were uneventful. Because of the early rupture of the membranes, penicillin and streptomycin were administered prophylactically. Jaundice first became apparent on the second day of life. The stools were pale and the urine contained large amounts of bile. At the age of 5 weeks the liver was palpable two fingers below the costal margin, and was firm in consistency. He was still jaundiced. Results of liver function tests are set out in Table I.

At 7 weeks of age, an operative cholangiogram and an open liver biopsy (Mr. Dendy Moore) was undertaken. The liver was enlarged but macroscopically normal. The external biliary apparatus was normal. An operative cholangiogram showed the medium to pass freely into the duodenum.

The liver biopsy showed severe bile retention, both in the liver cells and as bile thrombi. The normal architecture was preserved but the portal tracts were infiltrated with eosinophils, plasma cells, and round cells. Bile-ducts were present, empty, and slightly dilated (Fig. 1a, b, and c).

At 9 weeks of age treatment was started with prednisone 10 mg. daily, which was continued for 6 weeks.

Within 4 days the clinical jaundice had disappeared completely. At the time of discharge at the age of 10 weeks the liver was still palpable three fingers below the costal margin. Unfortunately, he developed acute gastro-enteritis at the age of 3 months. He was admitted to another hospital and died 3 days later. No necropsy was carried out.

Case 2. Male: born February 8, 1964, after 38 weeks' gestation. The pregnancy had been normal and two elder sibs were alive and well. The birthweight was 3.7 kg. (8 lb. 4 oz.). Jaundice was noted on the second day of life and persisted, though it fluctuated in intensity. The stools were colourless and the urine was dark. He was admitted to hospital at the age of 4 weeks. He was jaundiced and the liver edge was palpable to three fingers below the costal margin. The spleen was not palpable. His stools continued to be clay coloured and the urine dark. The results of liver function tests are set out in Table I.

Liver biopsy at 3½ weeks showed an obstructive jaundice of some standing, with evidence of bile retention as bile thrombi, and bile pigment in liver cells and Kupffer's cells. The liver cells were normal. There

TABLE I
Liver Function Tests of 4 Patients with Intrahepatic Cholestasis during Period of Clinical Jaundice

	Case 1	Case 2 (on admission)	Case 3	Case 4
<i>Proteins (g./100 ml.)</i>				
Albumin	3.10	4.05	2.8	2.85
Globulin	2.2	1.85	2.7	2.16
Total	5.3	5.9	5.5	6.01
A/G ratio	1.41 : 1	2.20 : 1		1.78 : 1
<i>Bilirubin (mg./100 ml.)</i>				
Total	9.26	5.5	2.2	4.85
Direct	6.30	3.85	1.6	4.0
Indirect	2.97	1.7	0.6	0.85
<i>Alkaline phosphatase (King Armstrong units)</i>	26.9	28.8	50	61.5
<i>Transaminases</i>				
SGOT (units/ml.) ..	74	162	88	
SGPT (units/ml.) ..	42	90	64	

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FIG. 1.—(a) A portal tract widened by a dense infiltrate of eosinophils, plasma cells, and round cells; the bile-duct is present, empty, and slightly dilated. (H. and E. $\times 46$.) (b) The liver parenchymal cells are shown in greater detail. The normal liver architecture is preserved, but there is severe bile retention. (H. and E. $\times 115$.) (c) Lymphocytes and plasma cells in the portal tract. (H. and E. $\times 115$.)

was chronic inflammatory cell infiltration by round cells, plasma cells, and eosinophils in the portal tracts (Fig. 2).

At the age of 2 months an operative cholangiogram (Mr. Dendy Moore) showed a normal extrahepatic biliary tract with no extrahepatic obstruction.

Following this, treatment with prednisone 10 mg. daily for 10 days was given, after which the dose was reduced to 5 mg. and continued for 6 weeks. On this regimen his jaundice faded rapidly and his liver function tests returned to normal.

At the age of 1 year he was admitted to hospital for

FIG. 2.—Liver biopsy at 4 weeks. Low-power view of liver biopsy, showing normal liver architecture with bile stasis. (H. and E. $\times 74$.)

TABLE II

Results of Liver Function Tests on Case 2 aged 1 year

<i>Proteins (g./100 ml.)</i>					
Albumin	..	..	..	..	4.55
Globulin	..	..	..	..	2.05
Total	..	..	..	..	6.60
A/G ratio	..	..	..	..	2.20 : 1
<i>Bilirubin (mg./100 ml.)</i>					
Direct	..	..	..	..	0.7
Indirect	..	..	..	..	0.27
Total	..	..	..	..	0.34
Electrophoresis of proteins	..	..	..	..	Normal pattern
Cephalin cholesterol	..	..	..	..	Very weak positive

reassessment of his clinical condition. He was then free from symptoms. The liver edge was palpable three fingers below the costal margin and was firm in consistency. Results of liver function tests at this time are set out in Table II.

A second, percutaneous, liver biopsy (Fig. 3a and b) showed infiltration of the portal area with plasma cells, lymphocytes, and eosinophils, bile thrombi in the canaliculi and in a duct, and bile retention in the parenchymal cells and Kupffer's cells. The changes were less severe than those seen previously but still indicative of biliary obstruction.

At the age of 15 months he had a severe attack of

haemophilus meningitis, from which he made an uneventful recovery.

He is now 4 years old and free from symptoms. His liver is still enlarged to three fingers below the costal margin. The edge feels firm, though not stony hard, and is regular. There has been no recurrence of jaundice and his liver function tests are normal. The bilirubin is 0.4 mg./100 ml., and flocculation tests are within the normal range. The alkaline phosphatase is 13 KA units.

Case 3. Male: born May 11, 1967, was a full-term infant born by breech delivery. Two elder sibs were alive and well. His birthweight was 3 kg. (6 lb. 13 oz.). Jaundice was first noted soon after birth and persisted, and at the age of 6 weeks he was admitted to hospital for investigation.

On admission the infant was yellow. The stools were colourless and the urine dark. The liver edge was palpable three fingers below the costal margin. The spleen could not be felt. The relevant investigations are tabulated in Table I.

Liver biopsy showed a slight degree of cholestasis but no other abnormality.

The patient was started on prednisone 10 mg. daily for 2 weeks followed by 7.5 mg. daily for 1 week. Over the following 3 weeks the dose of the drug was gradually reduced and finally omitted.

Four days after starting treatment the jaundice had disappeared and the total serum bilirubin was 0.9 mg./100 ml. One month later the bilirubin level was 0.5 mg./100 ml. and the liver size had returned to normal.

FIG. 3.—(a) Second liver biopsy taken at the age of 1 year, showing bile stasis and infiltrate of portal tract. (H. and E. $\times 50$.) (b) High-power view showing normal liver cells, intracellular bile stasis, and infiltrate of portal tract. (H. and E. $\times 125$.)

The infant continued to thrive and there has been no recurrence of jaundice.

Case 4. Female: born March 15, 1966, was the second of non-identical twins. The pregnancy had been complicated by toxæmia of pregnancy and an ante-partum hæmorrhage. Her birthweight was 2 kg. (4 lb. 6½ oz.).

She was admitted to hospital when she was 9 weeks old with a history that she had always looked a 'darker' colour than her twin brother. The stools had always been pale and the urine dark. Two elder sibs were alive and well.

On admission she was jaundiced, with pale stools and dark urine. The liver edge was felt two fingers below the right costal margin. The relevant investigations are tabulated in Table I.

Liver biopsy was inconclusive: though 2 cm. long liver tissue was procured no portal tracts whatsoever were included. However, the liver tissue showed bile retention.

The child was not treated with prednisone, but in spite of this continued to make an uneventful recovery over the course of 6 weeks. At the time of discharge she was free from symptoms and her bilirubin had dropped to 2.00 mg./100 ml., direct 1.97 mg./100 ml., indirect 0.03 mg./100 ml. She has since continued to thrive normally and is now quite well.

Other Causes of Neonatal Obstruction

Since 1960 we have investigated 24 newborns suffering from prolonged neonatal jaundice, occurring in the Devon and Exeter area. Some of these infants had classical biliary atresia, in only one of which was an anastomosis possible and successfully performed. 9 infants had cholestatic jaundice complicating rhesus incompatibility. In all these, high direct serum levels were present on the second day of life, all were treated with exchange transfusion and in addition received oral prednisone; one died at 3 weeks and was found to have blood in the alimentary canal, and a bile-stained liver; no histology was undertaken. 3 patients had obstructive

jaundice of uncertain origin; in 2 liver biopsy was unhelpful, and in the third, liver biopsy was not performed, but he responded well to prednisone, and at 5 years was well and without signs of hepatic disease, though liver function tests were abnormal. The history and course of this infant were very similar to the 4 cases described in detail.

Discussion

The 4 patients described in detail all had liver biopsies, and their main features are summarized in Table III. Two of these patients also had laparotomies, with operative cholangiograms showing up a perfectly normal and patent extrahepatic biliary system. The liver biopsies in both these patients showed similar if not identical changes (Fig. 1, 2, and 3). There was severe bile retention in the liver cells, and bile thrombi. The portal zones showed marked cellular proliferation, with round cells, plasma cells, and eosinophils. No giant cells or disturbance of the liver cell architecture were seen. Both these cases responded well to treatment with steroids. One patient died of an intercurrent infection elsewhere and there was no necropsy. One patient, however, is alive and well at the age of 4 but hepatosplenomegaly persists. His liver function tests are normal. The features of the liver biopsy obtained by the percutaneous method when he was 1 year showed the same changes as those in the neonatal period. Thus, in spite of the excellent clinical condition his disease cannot with absolute certainty be regarded as fully cured.

Untreated intrahepatic cholestasis in early infancy may well have further long-term consequences. Cotton (1960) reports the case of a boy who developed jaundice during the first week of life. Laparotomy was performed at 5 months. A normal but empty gall-bladder was found and small extrahepatic ducts were identified. Biopsy showed a normal lobular

TABLE III
Summary of Findings in Cholestatic Jaundice

Case No.	Age at Onset of Jaundice	Duration of Jaundice (mth.)	Serum Bilirubin (mg./100 ml.)		Diagnosis	Treatment	Histology	Outcome
			Total	Direct Fraction				
1	2 days	2	9.26	6.3	Cholestatic hepatitis	Steroids	Cholestasis + obstruction	Recovered, but died at 3 mth.
2	2 days	4	6.67	4.33	Cholestatic hepatitis	Steroids	Cholestasis + obstruction	Recovered
3	Since birth	2½	2.2	1.6	Cholestatic hepatitis	Steroids	Cholestasis	Recovered
4	Since birth	4	4.85	4	Cholestatic hepatitis	Nil	Cholestasis	Recovered

architecture and normal liver parenchymal cells. Bile accumulation was seen in the bile canaliculi and in the macrophages adjacent to the liver parenchyma. There was increase in the portal area of lymphocytes and of macrophages. The picture was that of interlobular biliary obstruction, and this biopsy appears to be very similar to biopsies of our cases of cholestatic hepatitis. Cotton's patient survived without steroid therapy but jaundice persisted to the age of 21 months. Thereafter it gradually faded and the serum bilirubin levels returned to normal. Stercobilin in small amounts appeared in the stools. He continued, however, to show evidence of disturbed liver function, as shown, clinically, by pruritus, skin xanthomata, and gastro-intestinal haemorrhages; and, pathologically, by raised alkaline phosphatase levels, high serum cholesterol, and excess bilirubin in the urine. Smooth liver enlargement was always present. The serum transaminases remained raised. A second laparotomy was carried out at the age of 6 years and 8 months. Portal venogram and portal pressures were both normal. The gall-bladder was small but contained bile-stained mucus. A cholangiogram confirmed the patency of the extrahepatic biliary system communicating normally with the duodenum. Liver biopsy showed absence of intrahepatic portal bile-ducts. There was no increase in portal fibrous tissue or infiltration. Thus, the histological picture had undergone a remarkable change, and now resembled that of intrahepatic biliary atresia, as first described by Ahrens, Harris, and MacMahon (1951), Sass-Kortsak, Bowden, and Brown (1956), and later reviewed by Haas and Dobbs (1958).

The aetiology of this form of intrahepatic biliary atresia still remains obscure, but Cotton's case sheds further light on this problem. It clearly proves that intrahepatic biliary atresia can be preceded by intrahepatic cholestasis. Thus, the inflammatory process in the portal areas seen in cholestasis, if untreated, may in time cause the complete disappearance of intrahepatic bile-ducts. If this sequence of events is to be prevented treatment with steroids appears to be indicated.

Intrahepatic cholestasis must be differentiated from other forms of obstructive jaundice in the newborn. Giant cell hepatitis, as described by Bodian and Newns (1953), is histologically quite different from the four cases described in this paper. In this condition there is variation in the size of the liver cells, with distorted multinucleated giant cells scattered throughout the liver substances. We saw no examples of this in our series. Recent evidence suggests that it is caused by an autosomal recessive

gene and not by any infective agent (Hsia *et al.*, 1958; Danks and Bodian, 1963).

Haemolytic disease of the newborn may be complicated by obstructive jaundice. Originally this was thought to be due to inspissation of bile in the canaliculi (Lightwood and Bodian, 1946). Dunn (1963, 1965) has now provided good evidence to show that in addition to cholestasis, hepatic cell damage is also present, which may be already evident at birth and thus originate *in utero*. He has shown that the obstructive jaundice in these infants is due to a hepatitis. In this way the obstructive jaundice found in a small proportion of severe cases of haemolytic disease differs from the cholestatic jaundice described in this paper, in which there was no evidence of liver cell damage.

In the absence of any real explanation for the occurrence of apparently idiopathic intrahepatic cholestasis in the newborn it is not possible to explain the favourable response of this condition to steroid drugs. There are, however, many precedents for this form of therapy in other forms of obstructive jaundice and of hepatitis (Summerskill *et al.*, 1961; Williams and Billing, 1961). It has been used with success in the treatment of obstructive jaundice complicating haemolytic disease (Dunn, 1963), so that its empirical use seemed justified in the condition under discussion. Clinical observation in this small number of cases seems to support the view that steroid treatment is beneficial and it seems possible that further damage to bile-ducts may well be prevented. In the light of present knowledge the treatment of intrahepatic cholestasis with oral steroids is recommended.

Summary

Four newborn infants with idiopathic intrahepatic cholestasis have been described, and their clinical progress and their liver histology have been compared and contrasted with that of 20 other newborn infants who have been investigated for obstructive jaundice. The possibility of a relation between this condition and of absence of the intrahepatic bile-ducts has been discussed, and the value and place of steroid therapy for this condition have been mentioned.

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