

Original articles

Hepatitis syndrome in infancy—an epidemiological survey with 10 year follow up

M C DICK AND A P MOWAT

Department of Child Health, King's College Hospital, London

SUMMARY Fifty four infants with hepatobiliary disease and conjugated hyperbilirubinaemia of more than two weeks' duration were identified in a defined area of south east England in a prospective study between January 1971 and December 1973. The overall incidence was one case per 2500 live births. The cases were regularly reviewed and all survivors except one were assessed at age 10 years.

Nine of 11 with extrahepatic biliary atresia died from liver disease by 2 years of age, one died at 5 years, and the survivor has cirrhosis with portal hypertension. Four out of seven with α_1 antitrypsin deficiency died aged 1 to 3 years from liver disease and one of the survivors has cirrhosis. All three infants with intrauterine infection and one with chromosomal abnormality died in infancy. Three children with other associated factors, choledochal cyst, galactosaemia, and rhesus isoimmunisation, recovered completely with no persisting liver disease. Two of 29 with cryptogenic hepatitis died, but only a further two have signs of persisting liver disease. Perinatal complications were more common in this group. Four of the 27 children surviving to the age of 10 years are educationally subnormal. Prognosis for infants with intrahepatic liver disease in the absence of known associated factors is good and every effort should be made to minimise the short term effects of cholestasis.

An increasing number of structural abnormalities, metabolic factors, and infective agents have been recognised in association with hepatobiliary disorders in early infancy.^{1,2} These factors clearly influence the prognosis for affected infants. The incidence of persisting hepatic abnormalities reported in children in whom no associated features were found is controversial ranging from 10 of 70 patients in Odievre's series³ to 21 of 59 in Danks' series.⁴ Such variation in outcome may be due to case selection, referral patterns, and completeness of follow up.

To assess the relative incidence of the various causes and factors associated with hepatobiliary disease in infancy and their influence on the long term prognosis, a prospective study of all such infants in a defined area of south east England was carried out between January 1971 and December 1973.⁵ The cases identified have been regularly reassessed up to the age of 10 years.

Patients and methods

The area studied was a NHS administrative region in south east England approximately 70 miles long and 50 miles wide. It includes a quadrant of inner London, the predominantly industrial southern shore of the Thames estuary, and a largely agricultural area extending down to the south east coast. The total population is approximately 3½ million, with 134 000 births during the three year period of the study. Criteria for inclusion in the study were (1) conjugated hyperbilirubinaemia lasting for more than two weeks in the first four months of life and (2) biochemical features of hepatocellular necrosis. The latter were confirmed by percutaneous liver biopsy performed in 90% of cases.

All 16 paediatric units in the region cooperated in the study by identifying and notifying cases. To ensure complete reporting, all units were visited and staff interviewed regularly. The paediatricians were

informed of the progress of the study by letters and clinical meetings. Forty per cent of patients were fully investigated in the peripheral paediatric unit, clinical responsibility being retained by the local consultant.

Appropriate samples for viral and bacterial causes of the syndrome, α_1 antitrypsin phenotype, galactosuria, and serum and urinary amino acids were taken in all patients. Where indicated chromosomal analysis, sweat electrolytes, and $^{1-131}$ Rose-Bengal faecal excretion were performed. Extrahepatic biliary atresia was confirmed at laparotomy. Patency of the extrahepatic biliary system in other patients was confirmed by subsequent clearing of the jaundice in all but two. One of these had operative cholangiography and in the other patient extrahepatic bile ducts were found at necropsy.

The frequency of clinical assessment with biochemical tests of liver function using standard laboratory methods was determined by the condition of the patient but occurred in all cases at 1, 3, 5, and 10 years of age. Follow up liver biopsies were only carried out in those children in whom there was clinical or biochemical evidence of continuing liver disease.

Results

The number of cases reported in each of the three years was 19, 20, and 15 giving an overall incidence of 1 case per 2500 live births. Details of diagnostic categories are given in Table 1. The three with intrauterine infection had cytomegalovirus, rubella, and toxoplasmosis, the latter infant also having Down's syndrome. For 29 of the 54 cases no cause or associated disorder was found, giving an incidence of idiopathic 'hepatitis' of 1 per 4800 live births.

Two girls with idiopathic hepatitis each have one sibling who also had hepatitis in infancy—one an affected brother, the other an affected sister. There was no parental consanguinity. None of the parents

were reported as having had hepatitis in infancy, although in 15 out of 54 families there was a history suggestive of acute viral hepatitis in one or both parents many years before.

The total series included 31 boys and 23 girls. The ratio in extrahepatic biliary atresia was eight boys to three girls; in α_1 antitrypsin deficiency, four boys to three girls; and in idiopathic hepatitis 17 boys to 12 girls.

Previous obstetric difficulties were more common in the mothers of those with idiopathic disease, five having had previous miscarriages or stillbirths and three having had terminations. There was one previous stillbirth in a mother of an infant with biliary atresia.

Preterm deliveries (five infants) and infants small for gestational age (11 infants) were common in the idiopathic group. Perinatal problems such as respiratory distress, hypoglycaemia, and convulsions occurred in 10 of the idiopathic group. There were no cases of preterm deliveries or infants light for gestational age in either the biliary atresia or the α_1 antitrypsin deficient groups. All the infants with intrauterine infections and chromosomal abnormality were light for gestational age.

Ventricular septal defect occurred in one infant with biliary atresia and one child with idiopathic hepatitis. Dextrocardia and pulmonary stenosis were detected in one other infant with biliary atresia, and congenital heart block in one infant with idiopathic hepatitis.

Bacterial infections occurred in all diagnostic categories. Three infants, including one with cytomegalovirus infection, had septicaemia, nine had a urinary tract infection, and nine had signs suggestive of infection which improved on antibiotic treatment, although bacteriological investigations were negative. In neither of these categories did antibiotic treatment clearly improve liver function. Pathogens were isolated in specimens from 13 other patients but none of these had symptoms or signs of infection. It is not known whether infection was causal or coincidental in any of these.

Outcome (Table 2).

Extrahepatic biliary atresia

Nine of the 11 cases died by 2 years of age after surgery had been ineffective. None had undergone portoenterostomy. One survived with partial bile drainage until 5 years of age. The sole survivor is aged 11 years and is leading a normal life, although mildly jaundiced with gross splenomegaly and abnormal liver function tests. He had an oesophageal resection for repeated haematemesis due to varices in 1976, and in 1984 required injection of varices because of recurrent bleeding.

Table 1 *Main diagnostic categories and incidence figures for neonatal hepatitis syndrome*

Diagnostic categories	Number	Incidence/ live births
Extrahepatic biliary atresia	11	12 200
Alpha ₁ antitrypsin deficiency (PiZ)	7	19 200
Intrauterine infection	3	45 000
Galactosaemia	1	134 000
Rhesus disease	1	134 000
Choledochal cyst	1	134 000
Trisomy 18	1	134 000
Idiopathic hepatitis	29	4 800
Total	54	2 500

Table 2 *Status of liver disease at 10 year follow up in all diagnostic categories*

<i>Diagnostic categories</i>	<i>Total</i>	<i>Alive</i>	<i>Dead</i>	<i>Liver disease</i>	<i>Not seen</i>
Extrahepatic biliary atresia	11	1	10	1	—
Alpha ₁ antitrypsin deficiency (PiZ)	7	4	3	1	1
Intrauterine infection	3	—	3	—	—
Galactosaemia	1	1	—	—	—
Rhesus disease	1	1	—	—	—
Choledochal cyst	1	1	—	—	—
Trisomy 18	1	—	1	—	—
Idiopathic hepatitis	29	27	2	2	—
Total	54	35	19	4	1

Alpha₁ antitrypsin deficiency

Four of the seven cases have died aged between 1 and 3 years, all with cirrhosis at death. Of the three surviving, one has cirrhosis, one has no clinical or biochemical evidence of liver disease, and the other is alive and well but is the only patient not seen at age 10 years. At 5 years he had marginally raised gammaglutamyl transferase activity but no other signs of liver disease.

Miscellaneous causes

The three patients with intrauterine infection and one with chromosomal abnormality all died during the first three months of life with other organs affected as well as the liver. The children with galactosaemia, choledochal cyst, and rhesus disease are all well with no biochemical signs of liver disease.

Idiopathic hepatitis

Two children have died in this group. Both were jaundiced with acholic stools which persisted until death at the age of 4 and 5 months respectively. One, who had no necropsy examination, had undergone a laparotomy at 5 weeks of age to exclude extrahepatic biliary atresia. The cause of death in this infant is uncertain. In the other infant necropsy showed pneumonia.

The duration of jaundice varied from two to 26 weeks with a mean and median of 10 weeks. Twelve had acholic stools but these persisted for over a month in only four patients. The two infants who died had acholic stools for more than one month but in other respects, such as presenting features and biochemical tests, did not differ from the remainder of the idiopathic group or from the others with acholic stools of more than one month's duration.

In the 27 survivors, jaundice gradually subsided by 1 year of age. At 1 year, two had hepatomegaly, six splenomegaly, and 12 still had a raised aspartate aminotransferase activity (greater than 40 IU/l), four of these being twice the upper limit of normal.

At 3 years, two had hepatomegaly and one had splenomegaly, all three having raised aspartate aminotransferase activity. Two others were below the third centile for both height and weight but these and the remainder had no clinical or biochemical features of liver disease.

At 5 years one had hepatomegaly, one had hepatosplenomegaly with raised aspartate aminotransferase, and one other had raised aspartate aminotransferase activity.

At 10 years one has hepatosplenomegaly and cirrhosis on liver biopsy and one has hepatomegaly, but none have abnormal biochemical tests of liver function. Repeat liver biopsies have been performed in five, two of whom had an affected sibling, the others having features of liver disease at 3 and 5 years of age. A liver biopsy at 8 weeks of age from one of those with an affected sibling showed severe cholestasis with moderate portal tract fibrosis and inflammatory cell infiltrate in the portal tract and hepatic parenchyma, with piecemeal necrosis. This persisted in repeat biopsies at 2 and 6 years of age, the most recent showing established post necrotic cirrhosis. The initial biopsies of the other girl with an affected sibling and the other three children were essentially similar to the above except two showed prominent giant cell transformation of hepatocytes, but the portal tract fibrosis was mild in all. Repeat liver biopsies at 8, 11, 11, and 12 years respectively showed no evidence of cholestasis, hepatocellular necrosis, or cellular infiltrate but all showed persisting mild increase in fibrosis both intralobularly and in the portal tract. The severity of liver disease in infancy in the two patients with persisting hepatic abnormalities when compared with the 25 who recovered completely was similar, as assessed by the duration of jaundice, period of acholic stools, and the degree of abnormality of biochemical tests of liver function. The initial biopsy in one of those with persisting liver disease had, as detailed above, increased fibrosis but in the other findings were similar to those who recovered completely.

Four of the 25 without liver disease, attend schools for the educationally subnormal. Two of these were light for gestational age and one was diagnosed as having congenital hypothyroidism at 6 months of age. One child is below the third centile for both weight and height and one is below the third centile for weight only. Both were light for gestational age. The remaining children are normally grown and leading normal lives.

Discussion

The stimulus to undertake this study was the observation that children referred with chronic liver disease have frequently presented in early infancy with jaundice associated with some form of 'hepatitis syndrome'. The frequency of this liver disease in infancy is clearly dependent on the criteria used in identifying these patients, modes of case ascertainment, and referral patterns as well as the frequency of genetic or environmental causes in the community studied. By including only infants who have had conjugated hyperbilirubinaemia for at least two weeks we hoped to identify infants who should be referred and who might develop chronic liver disease. Infants with transient cholestasis associated with treatable bacterial infections or metabolic disorders such as galactosaemia, which had been effectively treated would not necessarily have been included. The incidence of this disorder, 1 per 2500 live births, must be considered in respect of these criteria. Incidence figures quoted in other studies^{1 2 6} have ranged from 1 in 500 in the UK to 1 in 9000 in Norway. In the former study duration of jaundice was not indicated, so possibly included transient mild cases, while the latter was limited to infants with persistent complete cholestasis who were referred for consideration of biliary atresia.

Infective, genetic, and structural factors associated with hepatobiliary disease were identified in 25% of the cases in this series. The cause of liver disease in most is largely unexplained. Impaired blood supply to the biliary system⁷ may be one factor which initiates the inflammatory destruction of bile ducts in biliary atresia. Reovirus infection⁸ has been implicated in both intrahepatic and biliary disease. An increasing number of metabolic disorders and infective agents have been associated with liver disease but the mechanism of liver injury is uncertain. This is so even where the association with liver disease is strong as in α_1 antitrypsin deficiency in which only 50% have abnormal liver function as infants and only 10% have clinically evident liver disease.^{9 10}

The high incidence of obstetric problems, in-

trauterine growth retardation, and perinatal difficulties in those with idiopathic disease is striking, but whether the liver damage had the same primary cause or was a sequel to these problems could not be determined. Only two sibships with affected infants were identified in contrast to Danks' and Henriksen's series where familial occurrence was much higher.^{1 2} A high incidence of bacterial infection was observed in all diagnostic categories. It was impossible to ascertain whether the infection was causal, opportunistic, or coincidental. Unexpectedly, there was a high mortality in infants with systemic viral infection in contrast with the more favourable outcome in 22 infants reported by Danks, of whom only five died and three survivors had abnormal liver function.⁴ The dismal prognosis for infants with extrahepatic biliary atresia before the introduction of successful portoenterostomy¹¹ is reflected in this series, with only one of 11 surviving. Currently, with an experienced surgeon, over 70% of those operated on by 50 days of age may be expected to become jaundice free, and survival with a good quality of life into the third decade of life has been recorded.¹²

The high mortality in early childhood seen in the seven patients with α_1 antitrypsin deficiency is greater than that reported in the only other epidemiological study in which only three of 14 with prolonged neonatal cholestasis developed cirrhosis.⁹ In that study, however, liver biopsy was not used to assess the severity of liver disease and the incidence of cirrhosis may be underestimated. In two large series of cases presenting with jaundice in infancy, 25% had already died from cirrhosis by the age of 17 years, a further 25% had cirrhosis, while approximately 30% had persisting liver disease.^{13 14}

The prognosis of infants with cryptogenic intrahepatic disease has been encouragingly good with only two deaths and two with signs of persisting liver disease. A similarly low incidence of persistent abnormality has been reported in Japan,¹⁵ but other groups have reported more severe disease.²⁻⁴ In these series not only did intrahepatic disease carry a worse prognosis but those who also had a family history of the syndrome fared badly. In our series one of two infants from families with a positive history developed cirrhosis. It seems likely that the familial cases may be attributable to some unrecognised genetic or metabolic factor. No infants with intrahepatic bile duct hypoplasia, a cause of chronic liver disease, were identified, although possibly the two infants who died might ultimately have developed features of this disorder.

The prognosis in this series did not seem to be related to the duration or intensity of jaundice or the presence of acholic stools. Nor did it seem related to

the nature of the histological change in the early liver biopsy.

The possible deleterious effect of laparotomy on the long term prognosis of cholestatic liver disease in infants remains controversial^{3 16-18} and whether it contributed to the death of one of the two infants with intrahepatic disease in this series is uncertain. Laparotomy is now rarely required for diagnosis, which is fortunate, as the findings at laparotomy may be difficult to interpret¹⁹ and inappropriate destructive surgery undertaken.²⁰

None of the survivors in this series has symptomatic liver disease, although one has inactive cirrhosis on liver biopsy. Sixteen per cent have intellectual retardation, possibly related to perinatal problems. Of these, one child had congenital hypothyroidism. At the time of the study the association of hypothyroidism with conjugated hyperbilirubinaemia had not been recognised. The prognosis therefore for intrahepatic liver disease in the absence of known genetic, infectious, or structural factors or a positive family history is good and every effort should be made to minimise the short term effects of cholestasis with fat soluble vitamins and dietary supplements, and identify and ameliorate associated problems such as intellectual retardation.

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Correspondence to Dr A P Mowat, Department of Child Health, King's College Hospital, London SE5 8RX.

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