Liver disease in infancy: a 20 year perspective

Giorgina Mieli-Vergani, Edward R Howard, Alex P Mowat

In Northern Europe and North America the majority of children with chronic or life threatening liver disease first develop features of liver disease in early infancy. They usually have a hepatitis syndrome characterised by conjugated hyperbilirubinaemia, abnormal biochemical tests of liver function, hepatomegaly with or without splenomegaly and partial or complete cholestasis. There may be features caused by malabsorption, particularly of fat soluble vitamin K. It is from this cohort that the majority of children requiring transplantation are drawn. Such liver disease may occur in as many as 1 in 2 500 newborn infants.

During the development of the paediatric liver service at King's, in fruitful cooperation with the adult Liver Unit, we have identified important differences in some aspects of the clinical and pathological features of chronic liver disease which occur in children and adults, such as autoimmune chronic active hepatitis and primary sclerosing cholangitis.12 Our major efforts, however, have been to identify and improve the treatment of those with progressive liver disease starting in infancy. These account for over 50% of patients referred, the numbers in the main categories being given in the Table. This review provides an opportunity to consider some developments in which we have participated in the last 20 years.

We highlight four advances which have had a major impact on the management of these disorders. Most important has been the observation that a large proportion of patients with biliary atresia could have prolonged survival with a good quality of life after successful porto-enterostomy. The second has been identifying the role of alpha-1-antitrypsin deficiency (PZZ) as a genetic factor associated with a particularly severe form of the syndrome frequently leading to cirrhosis. The third has been the developments in molecular biology which have led to the identification of rare genetic or congenital disorders presenting as neonatal hepatitis, gradually reducing the percentage of benign cryptogenic cases. Three will be considered: Niemann-Pick type 2, Zellweger's syndrome and Alagille's syndrome. Lastly, there has been the increased awareness of the importance of liver disease in children and the provision of improved treatment and research facilities which has come from the activities of the Children's Liver Disease Foundation.

Biliary atresia

In the last 30 years it has been confirmed that the underlying pathological process in this disorder is usually a destructive sclerosing inflammatory process. It initially causes atresia of all or part of the extrahepatic biliary system which in uncorrected cases extends into the major intrahepatic ducts. A biliary cirrhosis rapidly develops with a mean age of death of 11 months with less than 5% surviving beyond two years.3 Up to 25% of patients have congenital abnormalities in cardiovascular, gastrointestinal and genitourinary systems with up to 7% having a distinct constellation of abnormalities forming the polysplenia syndrome which may include situs inversus abdominis, preduodenal portal vein and intestinal malrotation as well as multiple or absent spleen.4 The aetiology of biliary atresia remains unknown. Those with other abnormalities may be a separate aetiological subgroup.

The vast majority of these infants are entirely well during the first four to eight weeks of life apart from jaundice. Their wellbeing often causes paediatricians and other health workers to dismiss consideration of this disorder until successful surgery is less likely, the process having destroyed the major intrahepatic bile ducts.5 Kasai and his coworkers in the late 1950's pioneered the operation of portoenterostomy.1 In this procedure an anastomosis is fashioned between the area of the porta hepatitis from which the inflamed bile duct remnants have been resected and a 30–40 cm Roux loop. This allows bile to drain from patent major intrahepatic bile ducts directly into the bowel. Before Kasai's work less than 15% of patients with biliary atresia were operated on at the stage in the development of the process in which the surgeon could identify a bile-containing duct at the porta hepatis and the surgeon was able to fashion a direct bile duct to bowel anastomosis. With this procedure a few patients cleared their jaundice and achieved longterm survival.

The portoenterostomy procedure was introduced only slowly into the surgical practice of Europe and North America.1 The first 32 patients seen between 1970 and 1973 in the newly established children's liver service at King's College Hospital all died of liver failure.6 Surgical experience with an experimental model of this condition in the pig, however, led to improvements in technique and the first longterm survivor (Fig 1) was treated in 1973.7 Since then it has been possible to obtain good bile flow with normal serum bilirubin values within one to six months in between 80% and 90% of infants if they are operated on by 60 days of age. In infants operated on later the percentage becoming jaundice free is between 20% and 35%. Results are less satisfactory in centres with less experience.8

Biochemical tests of liver function remain abnormal for many years after surgery. Hepatic fibrosis is usually well established at the time of surgery and is aggravated if ascending cholangitis occurs. Nevertheless in infants becoming jaundice free the 15 years survival with a good quality of life is now almost 90%.9 In infants in whom the bilirubin is not reduced the rate of progression to cirrhosis is not slowed. If bile drainage is
original cholangiopathy. For these patients and for those in whom surgery has not been effective in returning the serum bilirubin to normal liver transplantation is now possible. The morbidity and mortality of portoenterostomy (and the cost) is minor to that of transplantation, making portoenterostomy the initial procedure of choice in all except infants who have decompensated cirrhosis when they first present. Transplantation should be considered for the infant in whom portoenterostomy fails completely or for the longterm survivor with deteriorating liver function or life threatening portal hypertension. Sadly, biliary atresia remains the most frequent reason for transplantation in children in the United Kingdom because of delay in initial recognition of the possibility of serious hepatobiliary disease in infants remaining jaundiced after two weeks of age.

**Alpha-1-antitrypsin deficiency and liver disease**

Alpha-1-antitrypsin was isolated by Schultz and coworkers in 1955. An association with liver disease and alpha-1-antitrypsin deficiency was first identified in two brothers with cirrhosis. Since then genetic deficiency of alpha-1-antitrypsin has had a major impact in the clinical practice of paediatric hepatology. The deficiency state PIZZ (P=protease inhibitor, phenotype ZZ) which is inherited in an autosomal fashion is the second most common single diagnosis after biliary atresia in infants with the hepatitis syndrome in populations of European descent. Alpha-1-antitrypsin phenotyping, preferably by isoelectric focusing, is required for diagnosis. Serum concentrations, measured by immunological techniques, may be increased or decreased by associated diseases or drugs and therefore unreliable in making a diagnosis.

The deficient infant has an increased susceptibility to liver disease with 15% developing clinical features of a hepatitis. What initiates the liver damage is controversial. Alpha-1-antitrypsin is thought to inhibit tissue-damaging proteases. It inhibits a wide range of serine proteases, particularly neutrophil elastase. This enzyme functions as an extracellular protease. Its prime substrate is elastin but it also attacks many other proteins including a variety of proteins in the coagulation and complement cascades, E. coli cell wall components and all major components of extracellular matrix. In the deficient individual uninhibited action of proteases may cause progressive liver disease. The HLA status may contribute to the severity of liver injury.

Liver disease is most commonly identified in early infancy as a conjugated hyperbilirubinaemia with hepatitis in 11% or a bleeding state caused by vitamin K malabsorption in 2%. Up to 70% have abnormal biochemical tests of liver function in early infancy. The mean age at recognition of icteric hepatitis is between two and three weeks. Jaundice lasts on average for three months but may persist for as long as a year. The infants commonly have slow weight gain, some may show irritability or lethargy. They are at risk of sepsicaemia which can cause a devastating deterioration in liver function with marked pro-

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**Figure 1:** Fifteen year old boy with extra hepatic biliary atresia corrected at the age of 10 weeks.
longation of the prothrombin time. All have hepatomegaly and approximately 50% have splenomegaly. Those presenting with a severe bleeding episode do so at two to six weeks of age. The prothrombin time (prothrombin ratio) is greatly prolonged. It reverts to normal within six hours with intravenous vitamin K. Rarely the presentation is with ascites in the newborn period. The course of the liver disease is independent of the mode of presentation in infancy.

About 5% remain jaundiced, progress to decompensated cirrhosis and die in the first year of life. The remainder recover from the acute hepatitis and in approximately 25% the clinical and biochemical abnormalities gradually improve and results come within the normal range at ages ranging from three to 10 years. Survival into the third decade without features of cirrhosis has been recorded in such patients.

Approximately 25% have died from complications of cirrhosis at ages ranging from six months to 17 years. Death from liver disease occurs within two months to four years of the onset of complications. Haematuria and/or albuminuria as a result of glomerular lesions is a late complication which may predispose to severe systemic hypertension after transplantation.24

Approximately 25% survive through the first decade although they have histologically confirmed cirrhosis. A further 25% without liver biopsy evidence of cirrhosis have persistently abnormal liver function tests with or without clinical features of portal hypertension. In some of these without clinical abnormality, liver function test may eventually become normal but the outcome for those with clinical or biochemical evidence of liver disease is guarded.18 19 26–28

The management is that of chronic cholestasis and of cirrhosis.29 There is no specific treatment for liver disease associated with alpha-1-antitrypsin deficiency short of liver transplantation. It corrects the serum phenotype to that of the donor.30 The longest follow up is only 16 years making it too early to determine whether it will prevent emphysema.31 In up to 80% of children within a sibship the liver disease is of the same severity as the proband.32 Antenatal diagnosis of the PIZZ state initially possible only with fetal blood sampling33 now possible by examining the DNA of chorionic villus samples using synthetic oligonucleotide probes specific for the M and Z gene or by restriction fragment length polymorphism. With the polymerase chain reaction results can be made available within a few days of sampling at 11 weeks gestation. Preliminary studies confirm the validity of such techniques.34

In adults with emphysema it has been possible to bring plasma alpha-1-antitrypsin levels up to normal values with infusions of plasma derived alpha-1-antitrypsin. This has not been shown to modify the emphysema. Nor did it decrease to normal levels the raised serum transaminases values found in a few patients who were treated in this fashion.35

Direct gene targeting to the liver in vitro is another possibility having been used successfully to stimulate albumin production in analbumininaemic rats.36 The gene was contained in a plasmid which is targeted to the hepatocyte-specific asialoglycoprotein receptor and carried into the hepatocyte by pinocytosis. In this way the PIMZ state would be created. Another theoretical possibility is the correction of the hepatic secretory problem by insertion of normal tRNA which may facilitate secretion.37 38 Perhaps more immediately practicable and attractive, to paediatric hepatologist if not to pulmonary physicians, would be a trial of exogenous serum-derived alpha-1-antitrypsin, given iv at one to four weekly intervals, as is being used in emphysema but commencing as soon as significant liver damage is identified, perhaps in conjunction with a neonatal screening programme. It should be possible to conduct a trial of therapy lasting six to 12 months which in the course of at most a decade, and perhaps much shorter, would indicate whether such therapy was efficacious.

**TABLE**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients</th>
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<tbody>
<tr>
<td>Biliary atresia</td>
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<tr>
<td>Idiopathic hepatitis of infancy</td>
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<td>Alpha-1-Antitrypsin deficiency</td>
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<td>Choledochal cyst</td>
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**Niemann-Pick type 2**

The Niemann-Pick group of diseases are sphingomyelin-cholesterol lipidosis.39 Failure of lipid degradation causes abnormal lipid storage
with hepatosplenomegaly, the formation of foam cells in the bone marrow and in some forms progressive central nervous system involvement. In type I, alpha-1-antitrypsin deficiency or failure of the liver to metabolise the proteases, in the liver, is essential for characteristic cardiovascular, skeletal and ocular abnormalities (arteriohepatic dysplasia, syndromic cirrhosis) of the interlobular bile ducts). The syndrome is probably inherited in an autosomal dominant fashion with variable expression. The family history is positive in 15% of cases, although full expression of the phenotype may not be present in earlier generations.

Essential to the diagnosis is a decrease in the number of interlobular bile ducts seen in portal tracts (ratio <0.06). Such paucity may be found also in association with genetic disorders such as alpha-1-antitrypsin deficiency or failure of the liver to metabolise the proteases. The alpha-1-antitrypsin deficiency or failure of the liver to metabolise the proteases is characterized by paucity of interlobular bile ducts (intrahepatic bile duct hypoplasia) occurring in association with a range of characteristic cardiovascular, skeletal and ocular abnormalities (arteriohepatic dysplasia, syndromic cirrhosis) of the interlobular bile ducts). The syndrome is probably inherited in an autosomal dominant fashion with variable expression. The family history is positive in 15% of cases, although full expression of the phenotype may not be present in earlier generations.

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The Children’s Liver Disease Foundation

In the last decade paediatric hepatology in the United Kingdom has received a considerable boost from the activities of the Children’s Liver Disease Foundation. This organisation has as its aims the improved management of liver disease in children by provision of better facilities, promotion of research and teaching and by giving emotional support for the families of children affected. Parents and friends of children with liver disease have been largely responsible for collecting the magnificent sum of £1-2 million pounds which has been spent in furthering these aims. To them and to the trustees we owe a large debt of gratitude. At last there is increasing professional and public awareness of the problem of liver disease in children. We hope that the British Liver Foundation can achieve as much for adult hepatology.

36 Sanders RJA, van Roemond CWT, Schutgens RBH, et al.
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