Liver and biliary disease in infancy

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What's new?

- Recent review on biliary atresia
- Genetics in hereditary cholestasis
- Longitudinal analysis on liver disease in Alagille's syndrome

Abstract
Liver disease in infancy is a relatively rare but serious cause of morbidity and mortality. Since jaundice is a common finding in the neonatal period, the immediate priority is to differentiate between unconjugated hyperbilirubinaemia, which is generally a benign developmental phenomenon, and conjugated hyperbilirubinaemia (conjugated fraction >20%), which is always pathological. Conjugated hyperbilirubinaemia, suggested by yellow urine and stools that are not yellow or green in an infant of any age, is pathognomonic of liver parenchymal or bile duct disease and warrants prompt investigation since some of its causes require urgent treatment and/or genetic counselling.

Keywords Alagille's syndrome; alpha-1 antitrypsin deficiency; biliary atresia; infantile liver disease; progressive intrahepatic cholestases

Infantile cholestasis/neonatal hepatitis syndrome

The terms hepatitis syndrome of infancy or neonatal hepatitis syndrome were initially used to describe a group of disorders causing clinical and biochemical liver dysfunction, of which the most distinct is conjugated hyperbilirubinaemia. The term hepatitis was chosen because of the frequent presence of inflammatory changes on liver biopsy; however, the cause is only occasionally infective (Table 1). 'Infantile or neonatal cholestasis' is probably a better name to describe this entity.[1] The reported incidence of neonatal cholestasis is approximately 1:2500 live births, the most common causes being, in order of frequency, biliary atresia, idiopathic infantile cholestasis and α_1-antitrypsin deficiency.

Bile production is dependent on active transport of bile acids and other osmotic compounds into the bile canaliculus and subsequently on a passive process of movement of water into the canaliculus. Active transporters both at the hepatic basolateral membrane and the canalicular membrane play an important role in this process. Genetic defects of these transporters are recognized and identify a range of familial intra-hepatic cholestatic diseases (see below). In liver disease and sepsis, the expression of the transporters helps to protect the hepatocyte from the cytotoxic effect of the bile acids. In the fetus and newborn, both immature bile acid synthesis and bile acid transport result in decreased bile flow. Cholestasis leads to bile acid and conjugated bilirubin retention, apparent as jaundice, hypercholesterolaemia and pruritus, and to decreased bile excretion into the intestine resulting in malabsorption of dietary long-chain fat and fat-soluble vitamins.

Clinical presentation

The majority of babies with infantile cholestasis present with prolonged jaundice, dark urine and pale stools within the first 4 weeks of life, but may occasionally present as late as 4 months of age.[2] The second most common presentation is spontaneous bleeding, usually secondary to vitamin K deficiency associated with fat malabsorption, which may also cause failure to thrive and rickets. Less commonly, babies present with hypoglycaemia or hypoalbuminaemia. Review of the perinatal records, pregnancy, family and past medical histories is helpful in determining the possible role of intra-uterine infections, exposure to toxins, drugs or prolonged intravenous nutrition, familial, genetic or metabolic conditions or consanguinity. On clinical examination hepatomegaly and splenomegaly are common. Facial dysmorphic features or other stigmata of syndromic disorders, evidence of congenital heart disease, manifestations of intra-uterine infections or cutaneous haemangiomata are of diagnostic value.

Management

Urgent investigations are necessary to identify disorders for which there is a specific treatment and to prevent complications (Table 2). Standard tests of liver function are seldom helpful in the differential diagnosis. Infective, metabolic and endocrine causes must be excluded urgently, since the prognosis may be modified radically by early treatment. Galactose and fructose must be excluded from the diet until the results of enzymatic studies for galactosaemia and fructosaemia are available. If the baby has received a blood transfusion, parents need to be tested for heterozygosity for galactosaemia, because the enzymatic defect is detected in red blood cells.

Fat-soluble vitamins (A, D, E and K) must be prescribed to avoid deficiencies and their complications. They can be given orally, but in persisting cholestasis intramuscular supplements on a monthly basis are recommended. The nutritional management of infantile cholestasis requires a high-calorie diet containing 120–150% of the estimated average daily requirement with an increased percentage of fat as medium-chain triglycerides (MCT). As mentioned above, a lactose-free formula should be used until the diagnosis of galactosaemia has been excluded.

The second priority is to identify infants requiring surgical correction of bile duct pathologies such as biliary atresia, choledochal cyst or spontaneous perforation of the bile ducts.

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Causes of infantile cholestasis

Infections

Viral

- Toxoplasma
- Rubella
- Cytomegalovirus
- Herpes simplex virus
- Human herpesvirus-6
- Varicella zoster
- Hepatitis A–C
- Non-A–C hepatitis
- Echo, adeno, coxsackie viruses
- HIV
- Reovirus type III
- Epstein–Barr virus
- Parvovirus B19

Bacterial

- Syphilis
- Listeria
- Malaria
- Tuberculosis

Endocrine

- Hypopituitarism
- Diabetes insipidus
- Hypoadrenalism
- Hypothyroidism
- Hypoparathyroidism

Chromosomal disorders

- Trisomy 18, 21

Toxic

- Copper
- Parenteral nutrition

Bile duct abnormalities

- Biliary atresia
- Choledochal cyst
- Spontaneous perforation of bile ducts
- Gallstones
- Inspissated bile syndrome
- Neonatal sclerosing cholangitis
- Caroli syndrome and disease
- Non-syndromic bile duct paucity

Metabolic

- Alagille's syndrome
- α_1-antitrypsin deficiency
- Galactosaemia
- Tyrosinaemia
- Fructosaemia
- Progressive familial intra-hepatic cholestases
- Cystic fibrosis
- Niemann-Pick type A, type C
- Gaucher disease
- Wolman disease
- Zellweger syndrome
- Carbohydrate glycoprotein deficiency
- Neonatal haemochromatosis
- Primary disorders of bile acid synthesis
- Mitochondrial cytopathy

Miscellaneous

- Haemophagocytic lymphohistiocytosis
- ARC syndrome (arthrogryposis, renal tubular dysfunction and cholestasis)

Table 1

Investigations for infantile cholestasis

Urgent investigations

- Bacterial culture of blood and urine
- Urine microscopy and analysis for reducing substances
- Prothrombin time/INR
- Full blood count and reticulocyte count
- Blood sugar, urea and creatinine
- Serum electrolytes
- Blood group and cross-match

Standard investigations

- Liver function tests including split bilirubin and γ-glutamyl transpeptidase
- Torches screen, HIV, hepatitis A, hepatitis C, hepatitis B
- α_1-antitrypsin phenotype/genotype
- T4, thyroid-stimulating hormone, cortisol (for endocrinological problems)
- Lactate, pyruvate, ammonia
- Galactose-1-phosphate uridyltransferase (red blood cells)
- Immunoreactive tryspin/sweat electrolytes (for cystic fibrosis)
- Amino acids (serum and urine)
- Succinyl acetone, organic acids (urine) (for tyrosinaemia)
- Bile acids mass spectrometry (urine) (for bile acid synthesis disorders)
- Direct Coombs' test (if appropriate)
- Ferritin
- Cholesterol, triglycerides

Specialized investigations (tertiary centre)

- Ultrasound scan of liver
- Chest X-ray/echocardiogram
- Liver biopsy
- Cholangiography (selected cases) (magnetic resonance, endoscopic, percutaneous)
- Radionuclide hepatobiliary scanning following phenobarbital (limited value)

Second-line investigations (tertiary centre)

- Blood tests for rare metabolic disorders (white cell enzymology, transferrin electrophoresis, etc.)
- Bone marrow aspirate for storage disorders
- Skin biopsy for fibroblast culture and enzyme analysis
- Muscle biopsy (mitochondrial respiratory chain defect)

Table 2

Observation of the stool colour is a helpful diagnostic tool since white or brown, but not green or yellow, stools suggest bile duct obstruction (Figure 1). Other investigations include imaging of the liver and bile ducts by ultrasound scan and liver biopsy, both of which should be interpreted by experienced observers. Radionuclide scans are valuable only where excretion of radioisotope in the gut excludes complete bile duct obstruction; they do not help in differentiating between parenchymal or bile duct disease when no bowel excretion is observed. Phenobarbital (5 mg/kg/day) should be started 48 hours before the test to optimize biliary excretion.

Third-line investigations involve blood tests aimed at identifying rare metabolic disorders, suspected on the basis of specific clinical findings or because no other aetiology is recognized. These include white cell enzymology and/or bone marrow aspirate for metabolic disorders, transferrin electrophoresis for a congenital defect of glycosylation, and skin and muscle biopsy for mitochondrial respiratory chain defects.

Biliary atresia (BA)

BA is the end result of a destructive, idiopathic, inflammatory process affecting both intra- and extra-hepatic bile ducts, leading

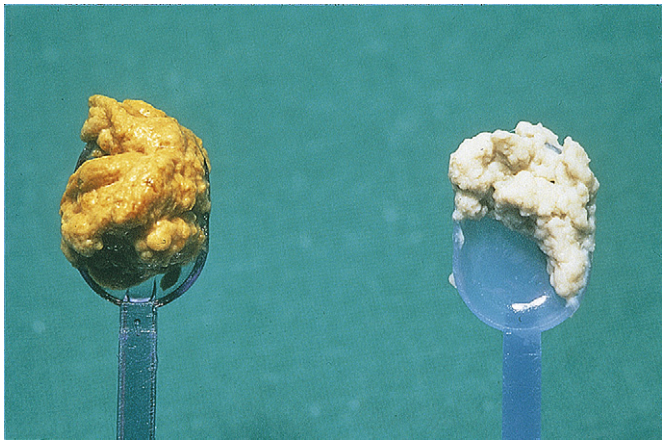

Figure 1 Stool samples from two children with biliary atresia. Neither sample is green or yellow, as normal infant stools should be, suggesting complete bile duct obstruction.

to fibrosis and obliteration of the biliary tract and eventually biliary cirrhosis.[3] It is the most common surgically correctable liver disorder in infancy and affects 1/5000–19,000 live births worldwide; it is also the most frequent cause for liver transplantation in children. The cause of BA remains unknown but is thought to be multifactorial, the bile duct damage resulting from several possible contributing factors (genetic, infective, inflammatory and/or toxic).[4] BA is a progressive disorder and in some cases the stools are pigmented during the first week of life, becoming acholic only later. This fact not uncommonly leads inexperienced health professionals to reassure parents that complete bile duct obstruction is unlikely. All infants with pale or acholic stools at whatever age should be referred promptly to specialized centres, because early surgical treatment of BA is essential for a good outcome.[5,6]

Biochemical findings are usually not helpful. An ultrasound scan revealing an absent or abnormal gallbladder with an irregular wall, or, in older infants, the triangular cord sign, are suggestive of BA. However, a normal gallbladder or absence of the triangular cord sign does not exclude BA. Histological examination of the liver by an experienced histopathologist leads to the correct diagnosis of BA in over 90% of the cases. In up to 20% of cases of BA, other congenital anatomical abnormalities, including polysplenia, situs inversus and unusual vascular abnormalities such as absence of the inferior vena cava and a preduodenal portal vein can be seen. Cystic BA, a form of BA associated with a cystic change of the biliary tree, can be detected on antenatal ultrasound scan and requires early referral to a specialized centre for appropriate management.

After the diagnosis of BA has been confirmed, surgical treatment consists of a Kasai portoenterostomy, where the fibrous tissue at the porta hepatitis, replacing the atretic biliary structures, is transected and a Roux-en-Y loop of jejunum is anastomosed to the liver. The success of the operation is judged by the appearance of pigment in the stools and clearance of jaundice. The overall 4-year survival of 148 children with BA treated between 1999 and 2002 in the UK was 89% and the 4-year survival with native liver 51%.[7]

The most common postoperative complication is cholangitis with a reported incidence of about 30–40% at 5 years, the majority of children having one single episode. Portal hypertension is already present in the majority of patients at the time of initial surgery, but only approximately 15% will develop upper gastrointestinal bleeding secondary to varices in childhood. These can usually be managed with banding or sclerotherapy.

For children with an unsuccessful Kasai portoenterostomy, or who develop progressive liver disease despite successful surgery, liver transplantation is the only therapeutic option.

α_1-antitrypsin deficiency (A1ATD)

A1ATD is the most common inherited cause of infantile liver disease. A1AT is a glycoprotein that acts as a protease inhibitor, thereby inhibiting inflammatory processes. It is synthesized by hepatocytes and alveolar macrophages.

More than 90 alleles, controlled by the protease inhibitor (Pi) gene on chromosome 14q31-32.2 have been isolated and identified, the most common being PiM. Inheritance is autosomal codominant. A1ATD, a single gene defect leading to significantly reduced or absent serum A1AT, is associated to the PiZZ, PiNulNul and PiZNul variants.[8] The prevalence of the PiZ allele in the European population is between 0.5% and 2%. PiZZ A1ATD causes chronic liver disease in 10–20% of affected children. The cause of liver disease is unknown and genetic, environmental and physical factors are likely to be involved. Clinical features of A1ATD are variable, some patients being asymptomatic, about 20% developing liver disease of variable severity and about 60% developing emphysema during adulthood. A1ATD should be suspected in all cases of infantile cholestasis and in unexplained liver disease in childhood. More than 50% of children with PiZZ phenotype have abnormal liver function tests, but only 10–15% develop overt liver disease, most commonly during the first 4 months of life. Clinical presentation can mimic BA, though children with A1ATD are more likely to fail to thrive. In about 10%, serious bleeding diathesis is the presenting symptom. One to two percent of PiZZ patients present with cirrhosis in childhood or adult life, despite having no history of infantile liver disease.

The diagnosis is made by determining the A1AT phenotype by isoelectric focussing or agarose electrophoresis. Serum A1AT can be misleading since A1AT is an acute phase reactant and the concentration may be within the normal range during the early hepatitic stage of the disease. Biliary features may be prominent on histology and similar to those seen in BA. The distinctive periodic acid-Schiff (PAS)-positive diastase-resistant A1AT globules in periportal hepatocytes are detectable only after 12 weeks of life. A diagnosis of A1ATD should be excluded by determining the phenotype in all children with suspected BA before surgical intervention.

There is no specific treatment for A1ATD. Supportive management with fat- and water-soluble vitamin supplements and dietary management are indicated. If decompensation occurs, liver transplantation is the only therapeutic option, A1ATD being the most common indication for liver transplant among metabolic disorders.[9] The prognosis of liver disease in PiZZ A1ATD is related to the presence of fibrosis and the severity and duration of the acute hepatitis in infancy. Antenatal diagnosis is available but genetic counselling is difficult because of the varying severity of the clinical phenotype and the difficulties in predicting the outcome.

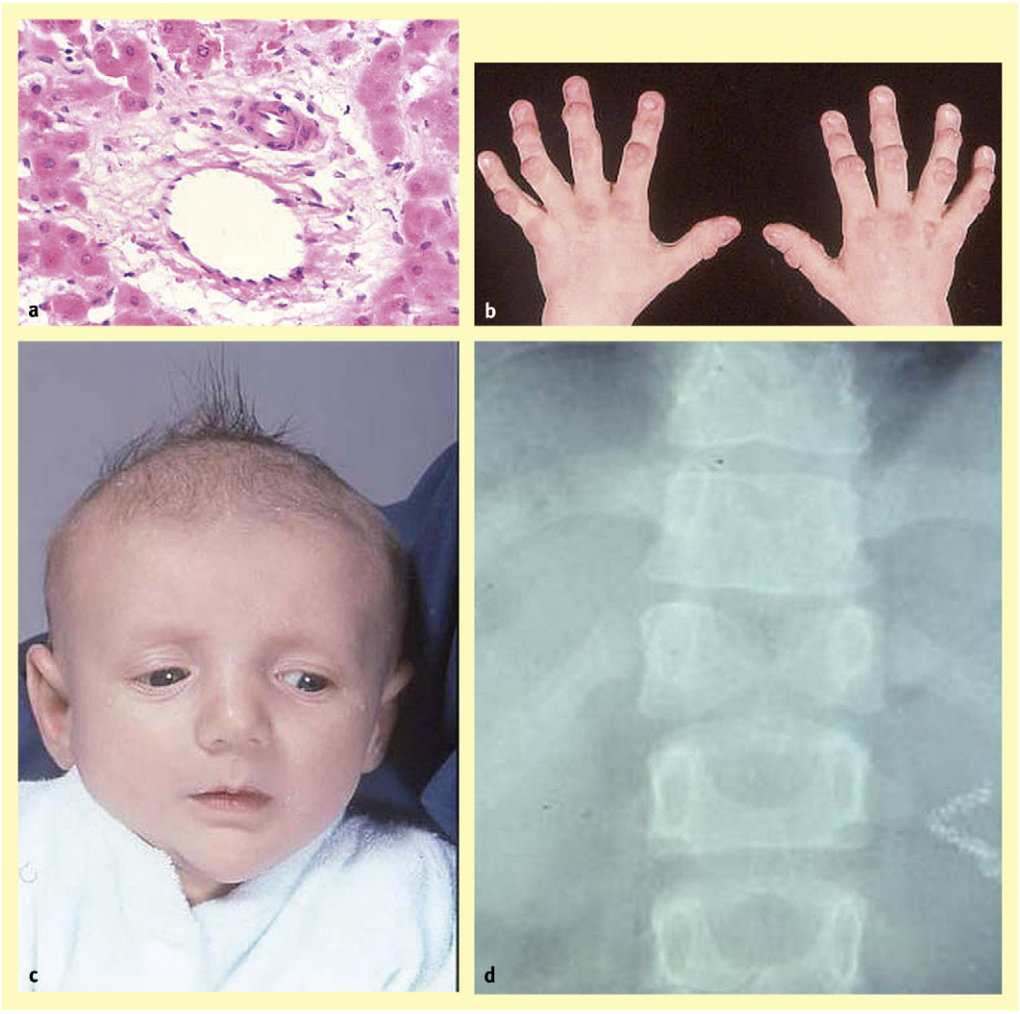

Figure 2 Alagille's syndrome – (**a**) liver biopsy showing lack of bile duct in the portal tract, (**b**) large hand xanthomas, (**c**) classical facial appearance of Alagille syndrome (deep-set eyes, mild hypertelorism, overhanging forehead, small pointed chin). This facial appearance may be difficult to detect in very young infants. (**d**) Typical appearance of a 'butterfly' vertebra.

Hereditary cholestasis

Severe forms of intra-hepatic cholestasis with progressive hepatocellular damage occur sporadically or on a familial basis.[10]

FIC1 (familial intra-hepatic cholestasis type1) and BSEP (bile salt export pump) deficiency

FIC1 and BSEP deficiency are characterized by low serum γ-glutamyltransferase (GGT). *ATP8B1* encodes FIC1, a widely expressed membrane P-type ATP-ase, and *ABCB11*, expressed only in the liver, encodes BSEP. The FIC1 protein is widely expressed, its expression being high in the small intestine and pancreas and low on the hepatocyte canalicular membranes. Infants with FIC1 present within the first 6 months of life with cholestasis, which is of variable severity and at times episodic. Other characteristics are diarrhoea, fat-soluble vitamin deficiency, hearing loss and recurrent pancreatitis. Pruritus is a dominant feature after infancy.

BSEP is a canalicular bile acid transporter expressed only in the liver. Most children present during the first few months of life with an isolated mild neonatal hepatitis. Pruritus is also a characteristic feature.

In both FIC1 and BSEP deficiency, failure of bile acid excretion at canalicular level is the reason for low serum GGT and normal serum cholesterol.

Both are usually progressive diseases.[11] Management consists of supportive medical treatment for the complications of cholestasis – fat-soluble vitamin deficiency and pruritus. Ursodeoxycholic acid (UDCA) may have a beneficial effect by increasing the hepatocyte excretion of endogenous bile acids and inhibiting their intestinal reabsorption, thereby limiting their return to the liver. Surgical partial external biliary diversion or ileal exclusion has been reported to arrest disease progression and relieve pruritus, but the results are not consistent. BSEP deficiency confers a high risk of hepatobiliary malignancy, particularly in those patients carrying two null mutations.[12] Liver transplantation is indicated in patients with decompensated cirrhosis or failed diversion and severe pruritus. Although the survival rate is excellent after transplantation, failure to thrive, pancreatitis and chronic diarrhoea usually persist in FIC1, whereas in BSEP deficiency recurrence of low GGT cholestasis after transplantation has been reported, due to the production in the recipient of anti-BSEP antibodies against the BSEP protein present in the donor liver.

PFIC-3 (MDR3 deficiency)

A third type of PFIC, characterized, in contrast to type 1 and 2, by high serum GGT, is associated with multidrug resistance gene-3 (MDR3) deficiency due to mutations of the *ABCB4* gene.

Multifactorial cholestasis in premature infants

Compared to older infants, very-low-birth-weight neonates have a higher risk of developing cholestasis because of more pronounced immaturity of bile metabolism. Additional factors are a diminished immune response to sepsis, an increased incidence of necrotizing enterocolitis and consequent short bowel syndrome with bacterial overgrowth, the use of parenteral nutrition, drug toxicity and hypoxia.[13] Often a liver biopsy is not possible because of the small weight and serious clinical condition of the child, so initial investigations should concentrate on excluding metabolic disorders and other factors contributing to cholestasis. Though BA should be suspected, it is a less common cause of infant cholestasis in premature babies. Blood tests, urine and ultrasound scan are the first line of investigation (Table 2). UDCA (20 mg/kg/day in two or three divided doses) is usually given until the jaundice has resolved. If possible, parenteral nutrition should be decreased or stopped and replaced by enteral feeding, which promotes enterohepatic circulation of bile acids and a better control of intestinal bacterial overgrowth. Where prolonged use of parenteral nutrition is required, there is evidence that lipid emulsions containing fish oils may prevent/improve parenteral nutrition-associated cholestasis,[14] but large controlled trials are required to confirm this observation. A lactose-free formula is recommended until galactosaemia has been excluded; MCT-based formulae should be used in the presence of marked cholestasis. Fat- and water-soluble vitamin supplements should be prescribed. In the presence of persistent cholestasis and acholic stools, further investigations are required, as described above.

Alagille's syndrome

In 1969 Alagille and colleagues described a syndrome of idiopathic bile duct paucity associated with cardiovascular, skeletal and ocular anomalies. Alagille's syndrome (AGS) ('syndromic paucity of intra-hepatic bile ducts', 'arteriohepatic dysplasia') has an estimated incidence of 1/50,000 individuals and is inherited in an autosomal dominant fashion with variable expression. Mutations in the human *JAG-1* gene on chromosome 20p12 are associated with the syndrome.[15] Mutations, however, are also found in asymptomatic individuals and other liver conditions, including BA. Besides the paucity of intra-hepatic bile ducts (Figure 2a), five major clinical features characterize the syndrome: (1) chronic cholestasis, causing jaundice, pruritus, hypercholesterolaemia and xanthomas (Figure 2b); (2) facial features with deep-set eyes, small pointed chin, mild hypertelorism, overhanging forehead an a straight nose, which is on the same plane as the forehead in profile (Figure 2c); (3) vertebral arch defects on spinal radiographs (Figure 2d); (4) cardiac abnormalities, most commonly peripheral pulmonary artery stenosis; and (5) ocular abnormalities such as posterior embryotoxon. Other common features are renal abnormalities, growth retardation, developmental delay, cerebrovascular abnormalities and pancreatic insufficiency. Facial features may be difficult to recognize during the neonatal period. The hepatic involvement in AGS is variable, ranging from asymptomatic elevations of hepatic transaminases to end-stage liver disease, which occurs in approximately 20–30% of cases.[16,17]

Management consists of vitamin supplements, nutritional support and control of pruritus. Long-term prognosis is uncertain. Liver transplantation can be an option in cases of ongoing severe cholestasis and pruritus, but careful assessment of the cardiac status is required before surgery can be considered. ◆

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Practice points

- Liver disease infancy has various causes, the prognosis of many of which is radically modified by early treatment; the first sign is jaundice, which is often ignored because unconjugated hyperbilirubinaemia (physiological jaundice) is common in neonates
- Liver disease should be suspected in all jaundiced babies, particularly if jaundice is present at birth or lasts for >2 weeks; if the stools are not green or yellow and the urine is frankly yellow and stains the nappy, the infant has liver disease and must be referred promptly to specialized centres for further investigation
- Biliary atresia is the most common cause of severe liver disease in infancy, but at the time surgery is most effective (before 60 days) babies often have no signs of ill health apart from persistent jaundice
- Cholestatic babies must be treated promptly with fat-soluble vitamins (A, D, E and K) to avoid serious complications, particularly intracranial bleeding caused by vitamin K deficiency