Management of biliary tract problems

Lauren Johansen
Patrick McKiernan

Abstract

Biliary disorders are relatively rare in childhood but early recognition is important and investigations need to be organized efficiently to facilitate a timely diagnosis and specific treatment. The classical clinical presentation of biliary disorders is with jaundice, particularly in the newborn period, abdominal pain and fever but incidental antenatal diagnosis is becoming an increasingly important presentation. Abdominal ultrasound remains the imaging modality of choice but magnetic resonance cholangiopancreotography and endoscopic ultrasound have an increasing role. The role of endoscopic retrograde cholangiopancreotography has evolved from a diagnostic to a therapeutic tool. Surgical treatment is necessary for many biliary disorders and while laparoscopic cholecystectomy is now the standard of care, open surgery remains the preferred method for Kasai Portoenterostomy. This review article focuses on the clinical features of biliary disorders in childhood and the diagnostic tools available. The epidemiology, clinical features and treatment of the most important biliary tract problems are then discussed.

Keywords biliary atresia; choledochal cyst; cholelithiasis; cholestasis; gallbladder dysfunction; perforation of bile duct

Introduction

Biliary disorders are individually and collectively rare. Nonetheless, a good understanding is vital for paediatricians as delay in diagnosis prolongs symptoms and leads to a poorer outcome in some cases. Investigations need to be organized efficiently to facilitate a timely diagnosis. The classical clinical presentation of biliary disorders is with jaundice, abdominal pain and fever, particularly in the newborn period. Increasing use of antenatal ultrasound has allowed the recognition of biliary cystic malformations prenatally which should lead to earlier specific treatment postnatally.

Initial investigation of suspected biliary disorders

Following an initial clinical and basic biochemical assessment, abdominal ultrasound is usually the imaging modality of choice. For cross sectional imaging, magnetic resonance cholangiopancreotography (MRCP) provides sufficient resolution to define most biliary abnormalities, although the technique may fail to clarify the anatomy of the lower biliary tree at the level of the ampulla. Endoscopic ultrasound has an increasing role in children and its excellent resolution allows accurate imaging of the lower biliary tree and can allow simultaneous biopsies to be taken if these are required. Unfortunately the size of most ultrasound endoscopes usually limits this technique to children more than 5 years old.

Hepatobiliary radio-isotope scanning is rarely necessary to confirm complete biliary obstruction but continues to have a role in evaluating the dynamics of bile flow. Finally, endoscopic retrograde cholangiopancreotography (ERCP) is now rarely used solely as a diagnostic tool but can be an effective therapeutic tool, especially for relief of biliary obstruction.

Biliary atresia

Biliary atresia (BA) is the most frequent severe liver disease in childhood and remains the commonest indication for paediatric liver transplantation. It is a progressive inflammatory cholangiopathy which leads to the destruction of intra and extra-hepatic bile ducts, and untreated is universally fatal. BA is classified according to the location of the obstruction: type 1 affects the common bile duct and proximal cystic duct, type 2 affects the common hepatic duct and type 3 affects the entire extra-hepatic biliary tree. Type 3 is by far the commonest, accounting for 90% of all cases.

There are three distinct clinical subtypes of BA; isolated, cystic and that associated with other abnormalities. Isolated BA is most common and accounts for 80–90% of cases. Cystic biliary atresia, which can be detected prenatally, accounts for approximately 10% of cases. The most common co-existent abnormality (10%) is biliary atresia splenic malformation syndrome (BASM), where infants have combinations of splenic malformation, situs inversus, absent inferior vena cava, pre-duodenal portal vein, intestinal malrotation, cardiac and pancreatic anomalies. Biliary atresia is less commonly associated with other abnormalities (in less than 5% of cases). These include oesophageal or anorectal atresia, and trisomy 18 or 21.

Epidemiology

The incidence of BA varies with geographical location. Asia has the highest incidence with frequencies of 3.7 and 1/10,000 live births in Taiwan and Japan, respectively. The incidence of BA is similar throughout Western Europe with reported frequencies of 0.50–0.58/10,000 live births. There is a significant regional variation across England and Wales, with North-West England having a lower incidence of biliary atresia in comparison to South- East England (0.38 vs. 0.78/10,000).

Racial variation has been demonstrated in several studies. In the US, biliary atresia is commoner among non-white infants compared to white infants (0.96 vs. 0.44/10,000 live births). In England and Wales there were significantly fewer cases of isolated BA in Caucasian infants vs. South Asian infants (72% vs. 89%). There is conflicting evidence on whether the incidence of BA shows seasonal variation and large European and Japanese studies could not demonstrate seasonality.

Lauren Johansen *MBBS HONS MRCPCH is Paediatric Registrar in the Liver Unit at Birmingham Children's Hospital, Birmingham, UK. Conflict of interest: none.*

Patrick McKiernan *BSc MB BCh MRCP FRCPCH is Consultant Paediatric Hepatologist in the Liver Unit at Birmingham Children's Hospital, Birmingham, UK. Conflict of interest: none.*

Familial BA is extraordinarily rare and twins rarely demonstrate concordance.

Pathogenesis

The aetiology of BA remains unknown, and probably differs between subtypes. In BASM, and where there are other malformations, the insult probably occurs at 5–6 weeks of gestation. In many cases of cystic BA the cysts can already be detected by 20 weeks gestation. In isolated BA the insult is later in gestation but it appears that most have some evidence of cholestasis at birth.

Several potential pathogenic mechanisms have been implicated including genetic causes, defects in morphogenesis or prenatal circulation, immunologic dysregulation, viral infection and maternal exposure to toxins. Viruses that have been considered potentially causative include cytomegalovirus, reovirus type 3, rotavirus, and papillomavirus. Notably though, there is a low yield of virus detection by conventional techniques in affected infants: The Hannover group recently tested liver biopsies (taken at the time of Kasai) for hepatotropic viruses and found only 42% were positive for viral RNA/DNA. It has been hypothesized that the bile duct injury may initially be triggered by a viral infection and then perpetuated by an abnormal immunological response with excessive activation of Hedgehog signalling pathways and increased expression of matrix metalloproteinases which promote hepatic fibrogenesis. Livers of affected children have shown an over expression of key pro-inflammatory genes and of genes involved in antigen presentation and T-helper type 1 (Th 1) immune polarization. This supports the hypothesis of a Th 1 inflammatory process leading to bile duct obstruction. Alternatively, Muranji et al. described increased, maternally derived, CD8+ T cells in the livers of affected infants. This supports the concept of 'maternal microchimerism' wherein immune active CD8+ and CD45+ cells cross the placenta, into the fetal liver and initiate a form of graft versus host disease.

Despite the low concordance seen in monozygotic twins genetic polymorphisms have been identified that may predispose to BA, such as a single nucleotide polymorphism in the 2q37.3 region. Mutations at the 10q24.2 locus and genetic variants in the ADDUCIN 3 gene have also been shown to increase the risk of developing BA.

Clinical presentation and investigation

Where BA is suspected it is crucial that investigations are carried out in a timely fashion so that affected children can undergo surgery as quickly as possible; while conditions which may mimic biliary atresia, for whom surgery may be harmful, are excluded. These include alpha 1 antitrypsin deficiency, hypopituitarism, cystic fibrosis and Alagille syndrome. It should take no longer than 1 week to complete these investigations. Infants with biliary atresia are typically born at term and have a normal birth weight. They present with a triad of prolonged jaundice, pale acholic stools and dark yellow urine (Figure 1). Infants may have a bleeding tendency secondary to vitamin K malabsorption. Initially infants may feed excessively to maintain growth, but later they have faltering growth. Hepatomegaly is commonly found on examination but splenomegaly and ascites are late signs suggestive of significant hepatic fibrosis and cirrhosis.

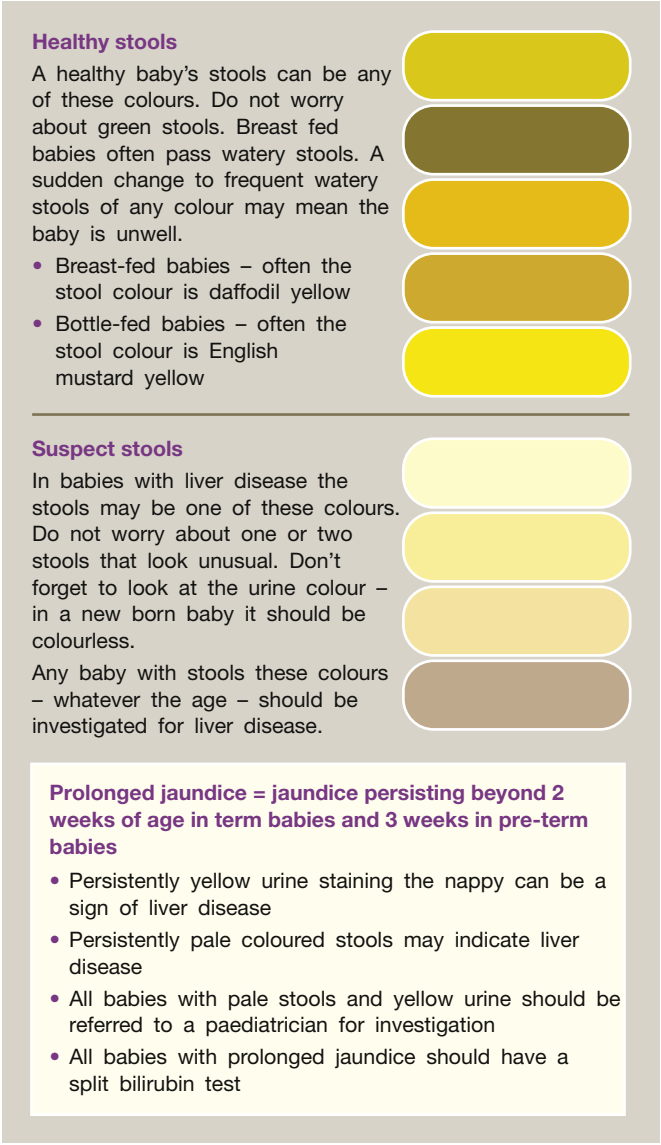

Figure 1 Stool chart.

At presentation infants with biliary atresia classically have conjugated hyperbilirubinaemia (bilirubin more than 100 μmol/l) with raised alkaline phosphatase (more than 600 IU/l) and gamma glutamyl transferase (more than 100 IU/l). Unless the infant has presented late, prothrombin time and albumin tend to be normal.

A fasting abdominal USS should be performed, which usually demonstrates an absent or contracted gallbladder, with no bile duct dilatation. The triangular cord sign (defined as more than 4 mm thickness of the echogenic anterior wall of the right portal vein) is a specific marker for biliary atresia, but sensitivity varies with operator-expertise. Infants with BASM may show additional vascular and splenic anomalies, which in this setting are diagnostic and make liver biopsy unnecessary.

Hepatobiliary isotope imaging will demonstrate hepatic uptake but no excretion of the radioisotope into the intestine at 24 hours. This test has a high sensitivity but is not specific and takes