Biliary atresia

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Biliary atresia is a rare disease of infancy, which has changed within 30 years from being fatal to being a disorder for which effective palliative surgery or curative liver transplantation, or both, are available. Good outcomes for infants depend on early referral and timely Kasai portoenterostomy, and thus a high index of suspicion is needed for investigation of infants with persistent jaundice. In centres with much experience of treating this disorder, up to 60% of children will achieve biliary drainage after Kasai portoenterostomy and will have serum bilirubin within the normal range within 6 months. 80% of children who attain satisfactory biliary drainage will reach adolescence with a good quality of life without undergoing liver transplantation. Although much is known about management of biliary atresia, many aspects are poorly understood, including its pathogenesis. Several hypotheses exist, implicating genetic predisposition and dysregulation of immunity, but the cause is probably multifactorial, with obliterative extrahepatic cholangiopathy as the common endpoint. Researchers are focused on identification of relevant genetic and immune factors and understanding serum and hepatic factors that drive liver fibrosis after Kasai portoenterostomy. These factors might become therapeutic targets to halt the inevitable development of cirrhosis and need for liver transplantation.

Introduction

Biliary atresia is a destructive inflammatory obliterative cholangiopathy of neonates that affects varying lengths of both intrahepatic and extrahepatic bile ducts. No analogous pathological process exists in older children or adults. If untreated, progressive liver cirrhosis leads to death by age 2 years. The disease is classified according to the level of most proximal biliary obstruction. Thus, biliary atresia type 1 (about 5% of cases) has luminal patency down to the common bile duct (often associated with a proximal cystic element) and proximal cystic biliary duct, type 2 (about 2%) has patency to the level of the common hepatic duct, and type 3 (>90%) is where the most proximal part of the extrahepatic biliary tract within the porta hepatis is entirely solid (figure 1).

Nonetheless, even in these type 3 cases, residual but microscopic biliary ductules (of varying size and number) retain continuity with the intrahepatic biliary system. A Kasai portoenterostomy is a palliative surgical procedure done to establish bile drainage by uncovering these ductules and re-establishing some bile flow. Liver transplantation is indicated for failure to establish bile flow, and biliary atresia remains the most common indication for liver transplantation in children, accounting for about 75% of transplantations in those younger than 2 years (European Liver Transplant Registry 2005).

For the **European Liver Transplant Registry** see http://www.eltr.org

Screening and epidemiology

Researchers are interested in development of screening tests for biliary atresia because of the importance of early diagnosis and treatment. Dry blood spots on the universal Guthrie screening card have been tested for concentration of bile salts but did not have specificity,[1] whereas conjugated bilirubin measured in liquid screening bloods of neonates between age 6–10 days is a sensitive and specific marker of neonatal liver disease, including biliary atresia.[2] Unfortunately, development of methods to detect conjugated bilirubin in dry blood spots for large-scale neonatal screening has not yet been achieved. In some countries (eg, Taiwan and Japan) the distribution of stool colour charts to help parents to identify when stools are abnormally pale (as a consequence of biliary obstruction) and speed up earlier referral has reduced time to Kasai portoenterostomy.[3]

Biliary atresia is a rare disorder, with the most accurate estimates of national prevalence from the UK and France ranging from 1 in 17 000–19 000 livebirths.[4,5] It is most common in east Asian countries, with a reported frequency in Taiwan of about 1 in 5000.[3] Other estimates are 1 in 15 000 in the southeast region of the USA[6] and 1 in 19 000 in the Netherlands.[7] Evidence of a classic genetic inheritance is scarce. Thus, the disorder rarely arises within families, and in twins it is rarely concordant.[8] Exceptional cases have been reported, such as a Native American family with affected dizygotic twins and another sibling,[9] and apparent vertical inheritance in which a mother with corrected type 3 biliary atresia gave birth to a baby with type 1 disease.[10]

Although a seasonal variation might affect development, results of a large study[11] of 119 Japanese infants did not show evidence of seasonal clustering. Biliary atresia is reported in all racial groups but some seem more susceptible than are others. In one US study,[12] black mothers were 2·5 times more likely to give birth to an affected child than were white mothers. No association was identified between the disorder and smoking,

Search strategy and selection criteria

We searched Medline for reports published in English from January, 1948, to January, 2008, with emphasis on those published from January, 2003, to January, 2008. Search terms used were "biliary atresia", "Kasai portoenterostomy", and "liver transplant". Publications were largely selected from the past 5 years but also included important older reports. Book chapters are cited to provide readers with more details than provided in this Seminar. Publications from reference lists of reports identified in the search were selected when appropriate.

maternal age, education, alcohol use, folic acid intake, gravidity, parity, parental income, infant sex, preterm birth, infant birthweight, or plurality.

Up to 20% of all cases are associated with other congenital anatomical abnormalities. The most common is biliary atresia splenic malformation syndrome, reported in about 10% of European and US series, including polysplenia (90%), situs inversus (50%), and unusual vascular anomalies such as absence of an inferior vena cava and a preduodenal portal vein. Table 1 lists other associated features.[13] An association might exist between maternal diabetes and this syndrome, although whether this relation is attributable to exposure of the developing embryo to a hyperglycaemic or hypoglycaemic environment is unknown.[13] Biliary atresia has also been described with several other genetic abnormal findings, such as trisomy 18 and 21 (webappendix p 1).

This disorder seems to be an isolated finding in the remaining 80–90% of neonates. The theory is that in these newborn babies the pathological obliterative process begins later (perhaps in the perinatal period) than it does in those of syndromic origin (beings in the embryonic phase). Some cases of isolated biliary atresia are associated with cystic change within the obliterated biliary tree—termed cystic biliary atresia. At least half of these cases are detectable on antenatal ultrasound scan (from 20 weeks' gestation), showing that even in isolated non-syndromic cases the biliary tree has abnormal changes well before birth.[14]

Pathophysiology

Although the cause of biliary atresia is largely unknown, it can be multifactorial in nature and has a common endpoint of an obliterative cholangiopathy. Some factors that might contribute to development are genetic, infective, inflammatory, and even toxic insult (figure 2). The consistency of the group of anatomical abnormalities forming the biliary atresia splenic malformation syndrome implies that a crucial event takes place in the genetically controlled developmental pathway at a specific stage of embryogenesis. The *inv* mouse was first described in 1993 with situs inversus and biliary atresia with pathological changes in the ductal plate.[15] This finding suggested a direct genetic role in development of this disorder.[16] However, human mutations in the *INVS* gene result in situs abnormal changes but not development of biliary atresia, whereas infants with biliary atresia splenic malformation do not have mutations in *INV*.

However, genetic polymorphisms might exist that lead to susceptibility to development of inflammation and fibrosis in the affected liver. Genes associated with different parts of the inflammatory pathway have variable polymorphism frequency in patients with biliary atresia. Such genes include *CFC1*, *ICAM1*, macrophage migration inhibitory factor gene, *CD14* endotoxin receptor gene, and hepcidin antimicrobial peptide gene. Study of the role of these genes might provide therapeutic targets to modify progression of fibrosis in the disorder.[17–21]

Animal studies have explored viral causes for non-syndromic biliary atresia. When mice of age 2 days were inoculated with rotavirus strains RRV and SA11-FM they developed jaundice with intrahepatic histology similar to that of biliary atresia.[22,23] Similar findings have been reported with reovirus and cytomegalovirus in mice.[24,25] Results of some serological studies[26] have suggested an increased frequency of reovirus in patients with biliary atresia but PCR techniques with liver tissue have not confirmed this finding.[27]

Rauschenfels and co-workers[28] investigated evidence of viral infection in human biliary atresia. They tested wedge liver biopsy samples obtained from 74 infants at Kasai portoenterostomy for a panel of DNA and RNA hepatotropic viruses, investigated along with Mx protein, which is a marker of inflammation that can be secondary to viruses. One or more viruses were detected in about a third of infants and the detection rate

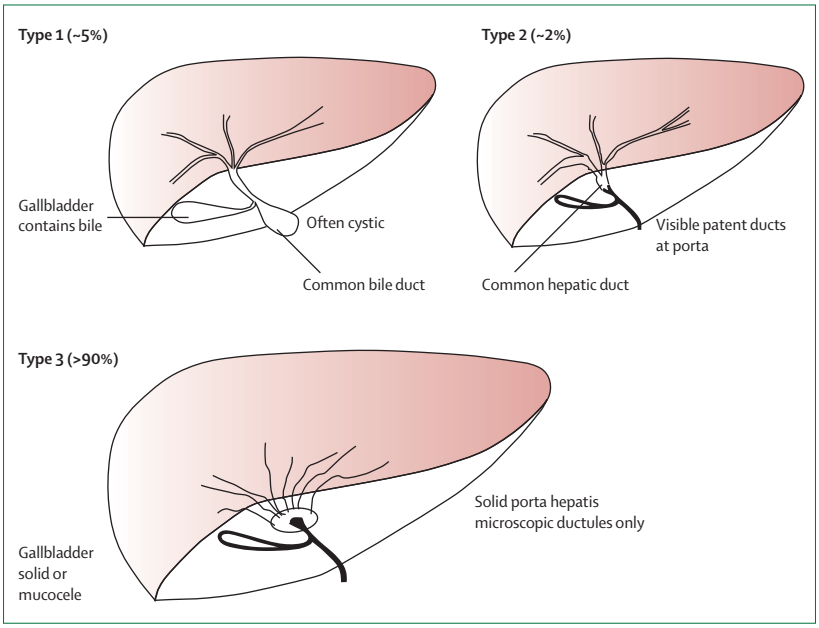

Figure 1: **Schematic illustration of classification of biliary atresia types 1–3**

	Estimated frequency
Splenic malformation (eg, polysplenia, asplenia, double spleen)	100%
Situs inversus	37%
Preduodenal portal vein	40%
Intestinal malrotation	60%
Absent inferior vena cava	70%
Cardiac anomalies (eg, ventricular septal defect, atrial septal defect, hypoplastic left heart)	45%
Pancreatic anomalies (eg, annular pancreas)	11%

Table 1: **Clinical features in biliary atresia splenic malformation syndrome**

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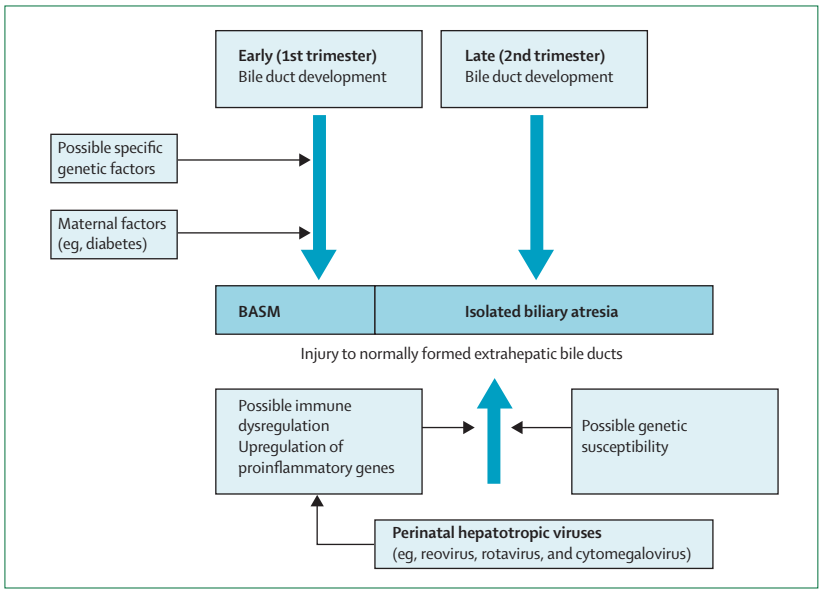

Figure 2: **Possible causal relations in biliary atresia**
BASM=biliary atresia splenic malformation syndrome.

increased with age, implying viral infection was a secondary finding and unlikely to be the specific cause. Further, despite the low yield of virus detection, more than 90% of infants expressed Mx protein, suggesting that this protein might be an indicator of continued inflammation secondary to an immune response—ie, similar to that mounted by a viral infection.[28]

A direct viral cause in the pathogenesis of biliary atresia is unlikely because viral particles in the liver or biliary tract of affected infants have not been identified, although possibly all direct traces are cleared while the inflammatory reaction continues. This mechanism might be similar to that by which double-stranded DNA viruses such as reovirus induce expression of tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) in human biliary epithelial cells. This innate immune response is activated by the double-stranded virus and leads to cell apoptosis and death.[29] Clinically, cytomegalovirus infection in infants with biliary atresis seems to have a severe clinical course, with low rates of jaundice clearance and raised rates of cholangitis and liver fibrosis. Although this severity might implicate cytomegalovirus in the primary pathogenesis, more likely is that the infection is a second injury to a liver already susceptible to damage through genetic or immunological dysregulation.[30]

A pronounced inflammatory response happens both within the liver and circulation. In the liver this response is a periductal infiltrate of mononuclear cells and amplified expression of HLA-DR on vascular and biliary epithelium, with expression of various intracellular adhesion molecules (eg, ICAM1 and E selectin).[31] In the circulation raised numbers of soluble inflammatory adhesion molecules and cytokines are detected[32] (such as interleukin 2, interleukin 18, and TNFα), which persist despite apparently successful Kasai portoenterostomy. Lymphocyte-mediated biliary inflammation seems to be the most likely mechanism by which bile duct damage takes place, although the trigger for this response remains unknown.

Gene expression microarrays of RNA from extrahepatic biliary tissue and gallbladders from rotavirus-induced murine models of biliary atresia have shown upregulation of many genes regulating immunity.[33] Specifically, interferon inducer genes IRF7 and IRF9 were prominent in early stages of disease, with enhanced expression of interferon-γ and interferon-γ activated genes at the time of bile duct obstruction. Thus, upregulation of proinflammatory genes might have a regulatory role in pathogenesis.[33] Microarray gene-expression analysis of human biliary atresia samples has also shown[34] overexpression of immune regulatory genes, many of which seem to share regulatory binding sites for the nuclear factor κ B and REL family of transcription factors.

Additionally, apoptosis might play a large part in the cause of damage to the bile duct through the synergistic role of IFN-γ and TNFα.[35] Inflammatory cytokines such as interleukin 2, interleukin 12, IFN-γ, and TNFα are upregulated in patients with biliary atresia,[36] as are Kupffer cells, natural killer cells, CD3+ and CD8+ T cells, and the lymphocyte chemokine receptor CXCR3+ cells.[37] Oligoclonal expansion of CD4+ and CD8+ T cells within the liver and extrahepatic bile ducts is suggestive of a response to specific antigenic stimulation.[36]

In mouse studies the development of biliary atresia after inoculation with rotavirus greatly increased when type I interferon receptor was inactivated.[38] Murine rotavirus also triggers interferon-γ-induced tissue specific hepatobiliary inflammation and features of biliary atresia. Jaundice develops with inhibition of interferon-γ, but inflammatory and fibrosing obstruction of the extrahepatic bile ducts do not.[39] This finding implies that immune dysregulation might play a part in pathogenesis.

Researchers investigating maternal microchimerism have proposed that an alloimmune response similar to graft-versus-host-disease might take place. Furthermore, an increased number of maternal chimeric CD8+ T cells in biliary atresia liver cells suggests that a maternal immunological insult might have a role in pathogenesis.[40,41] An outbreak of biliary atresia in lambs in New South Wales, Australia, was attributed to exposure of pregnant ewes to phytotoxin during a drought season. No human cases were identified.[42] Investigation of genetic susceptibility and the immune response in the pathogenesis to biliary atresia are essential for identification of potential targets for therapeutic intervention.

***Panel:* Clinical findings of biliary atresia at presentation**

Jaundice
Presenting sign.

Pale stool
Variable colour from white to beige.

Dark urine
Caused by excretion of water-soluble bilirubin conjugates; urine might stain the nappy and coat the stool, leading to false identification of coloured stool.

Coagulopathy (responsive to intravenous vitamin K)
Common in infants who are breastfed and those who have received oral vitamin K or no vitamin K in the postnatal period.[43]

Failure to thrive
Results from poor absorption of long-chain fats and the catabolic state;[44] excessive feeding is a characteristic clinical sign of failure to thrive.

Hepatosplenomegaly and ascites
Late (>3 months of age) signs suggestive of cirrhosis.

	Typical concentration at presentation	Normal range
Bilirubin (μmol/L)	>100	<20
Alkaline phosphatase (IU/L)	>600	<500
γ-glutamyl transferase (IU/L)	>100 IU/L	20–40
Aspartate aminotransferase (U/L)	80–200	15–40
Alanine aminotransferase (U/L)	80–200	10–55
Albumin (g/L)	Normal at presentation	37–56
Prothrombin time (s)	Normal at presentation	9–13

Bilirubin, alkaline phosphatase, and γ-glutamyl transferase are raised, indicating cholestasis, but hepatic synthetic function is usually normal.

***Table 2:* Biochemical variables in biliary atresia**

Diagnosis

Typically, biliary atresia presents shortly after birth with persistent jaundice, pale stools, and dark urine in term infants with normal birthweights (panel). All term infants who remain jaundiced after 14 days (and preterm infants after 21 days) should be investigated for liver disease—initially with simple measurement of the conjugated fraction of bilirubin. Those with physiological or breast-milk jaundice have increased serum concentrations of unconjugated bilirubin, whereas conjugated bilirubin is raised in jaundice secondary to most forms of liver disease. Splenomegaly is not usually a feature unless presentation is late and it is thus a sign of portal hypertension. An antenatal maternal ultrasound with abnormal findings showing a cyst related to the porta hepatis, bile duct, or liver is seen in about 5% of all infants with biliary atresia (cystic biliary atresia). Although this finding is non-specific and is often indicative of a cystic choledochal malformation or parenchymal liver cyst, it warrants thorough postnatal assessment.

Early diagnosis is essential, and thus investigation of infants with conjugated hyperbilirubinaemia is designed to identify biliary atresia and to exclude other causes. Laboratory studies typically identify cholestatic liver function tests (table 2). Serum gamma-glutamyltransferase (GGT) is usually higher in biliary atresia than in other causes of neonatal cholestasis—especially when correlated with age.[45] Serum cholesterol might be raised but triglycerides are within the normal range.

Figure 3 shows a suggested protocol for investigation of a child with long-term conjugated jaundice and suspected biliary atresia or other surgical pathological changes. An abdominal ultrasound[46] can also be done, which shows an enlarged liver, absence of biliary dilation, and typically an absent or contracted gallbladder after a 4 h fast (although 20% of cases might have a normal gallbladder). Identification of hyperechogenic liver hilum, known as the triangular cord sign, is a specific finding in almost all cases, but is operator-dependent and can be difficult to do, with reported sensitivities varying from 49% to 73%.[47]

Radioisotope excretion studies—eg, with a N-tert-butyliminodiacetic acid (TEBIDA) scan after pretreatment with phenobarbital 5 mg/kg per day for 3–5 days—typically show good hepatic uptake but absent or reduced excretion into the intestine within 24 h. Unfortunately this result is not specific for biliary atresia and is reported in children with severe intrahepatic cholestasis such as Alagille's syndrome.[48] The duodenal tube test, often done in Japanese and Chinese centres, uses a nasoduodenal tube that is passed into the third part of the duodenum to enable continuous aspiration to identify bile. Simple identification of bile avoids the need for surgery, whereas clear and non-bile stained intestinal secretions over 24 h is strongly suggestive of biliary atresia.[49]

Liver histology (obtained by percutaneous biopsy) is the usual diagnostic method of choice in the UK and typically provides evidence of extrahepatic biliary obstruction by varying degrees of portal tract fibrosis, oedema, ductular proliferation, and cholestasis with the appearance of bile plugs. Evidence of giant cell transformation might be present, making differentiation from other causes of neonatal hepatitis difficult.[50] Liver biopsy samples taken early in development of biliary atresia (before 6 weeks of age) might not have typical histological features, and serial biopsy samples might be necessary for diagnosis.[51]

Endoscopic retrograde cholangiopancreatography to visualise the biliary tract is occasionally needed when the diagnosis is unclear, but it is technically difficult in infants and use is confined to large centres. Magnetic resonance retrograde cholangiopancreatography has a small role at present because of technical constraints in

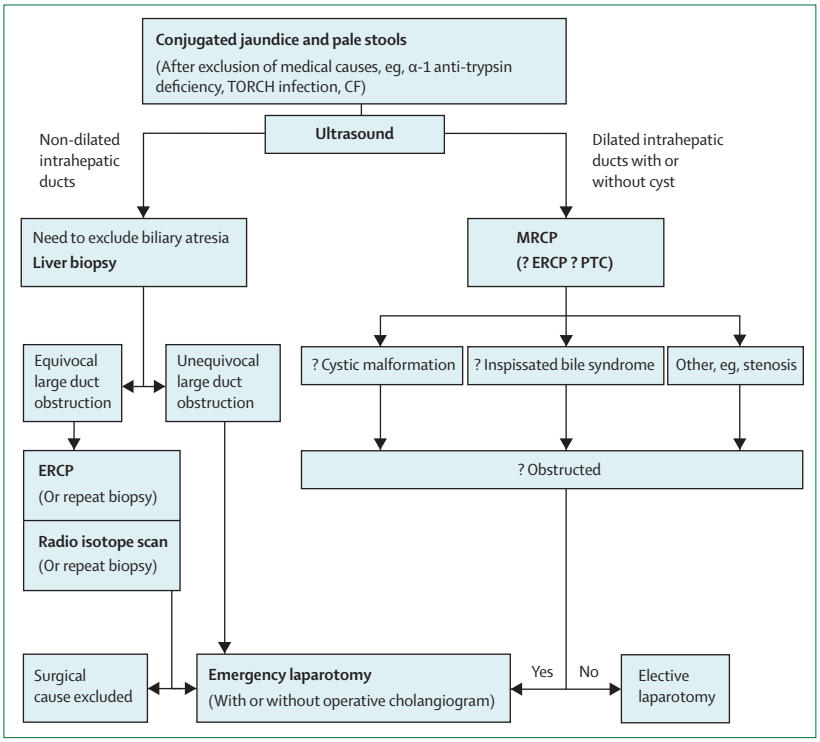

Figure 3: **Suggested algorithm for investigation of infants**
Algorithm for infants with long-term conjugated jaundice and a suspected surgical cause. TORCH=toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex. CF=cystic fibrosis. MRCP=MR retrograde cholangiopancreatography. ERCP=endoscopic retrograde cholangiopancreatography. PTC=percutaneous transhepatic cholangiography.

identification of luminal patency of the infantile bile duct—often only 1 mm in diameter or less—but is increasingly important when other surgical pathological changes are likely.[52,53] Although most infants in the UK come to definitive surgery with a secure preoperative diagnosis, operative cholangiography (which can be undertaken laparoscopically) is done when doubt exists before Kasai portoenterostomy, and is regarded as the gold standard and definitive investigation in diagnosis of biliary atresia.

Management

Surgery

Portoenterostomy (first described by the Japanese surgeon Morio Kasai in the 1950s) and liver transplantation remain the cornerstones of treatment of children with biliary atresia. Kasai portoenterostomy can achieve complete clearance of jaundice, restore excretory and synthetic liver function, and enable healthy growth and development, although this outcome is neither certain nor predictable from the outset. In this procedure the entire extrahepatic biliary tree is excised so that the porta hepatis is transected at the level of the liver capsule and the ductules that remain (typically microscopic) are exposed (figure 4). A jejunal Roux loop is anastomosed to the cut surface, thus completing the reconstruction.

The role of minimally invasive techniques is controversial. The first laparoscopic Kasai procedures were reported in 2002 by surgeons from Brazil.[54] Whether this laparoscopic technique provides benefits other than cosmetic benefits and a short postoperative recovery is unclear. The portal dissection, proximal biliary resection, and high clean portal-plate transection with exposure of the maximum possible number of biliary ductules to drain into the Roux loop is difficult to do laparoscopically (despite magnification and robotic technology), and outcomes[55] are only occasionally similar. Success of the Kasai procedure is measured by clearance of jaundice and is defined as achievement of a normal bilirubin concentration within 6 months of the procedure. Several factors affect the success of this surgery including age at surgery, extent of liver damage, and experience of the centre in which the surgery is done.

Liver damage and transformation to cirrhotic change worsens with long-term liver obstruction. This principle has stimulated a public and professional campaign to encourage early referral for biliary atresia, and draws attention to the need for screening.[2,3] However, biliary atresia might only be a final common phenotype for several pathogenetic processes—actual time of biliary occlusive onset might vary between prenatal and postnatal cases. Evidence from a large series[56] (with only two surgeons and a standardised technique) did not substantiate the notion of a cut-off (eg, 60 days, 80 days) beyond which Kasai portoenterostomy is likely to be unsuccessful, particularly in children with isolated biliary atresia. By contrast, evidence of a pronounced effect of age was reported in those with the less common subgroups of biliary atresia splenic malformation syndrome or cystic biliary atresia. Undertaking of this procedure in infants older than 100 days has been controversial, with some centres opting for primary liver transplantation. However, even in such cases a survival rate of 45% at 5 years with native liver can be achieved.[57]

Extent of histological abnormal changes at operation might affect both short-term and long-term outcomes,[58] although this finding has not been consistent.[59] Infants who have small (in number and cross-sectional area) residual biliary ductules in the transected remnant have little restoration of bile flow. However, because of difficulties with orientation and consistency of histological interpretation, this result can be difficult to estimate in individual cases. Relief of mechanical obstruction is only one factor that contributes to a successful outcome because intrahepatic inflammatory processes continue for at least 6 months after Kasai portoenterostomy.[30] This process might explain why some infants who have initial restoration of bile flow subsequently develop progressive fibrosis and cirrhosis.[32,36]

A relation exists between outcome and experience of the surgical centre. In the UK, a prospective study in 1993–95 identified 93 cases with biliary atresia, and showed that of 15 UK centres only two operated on five

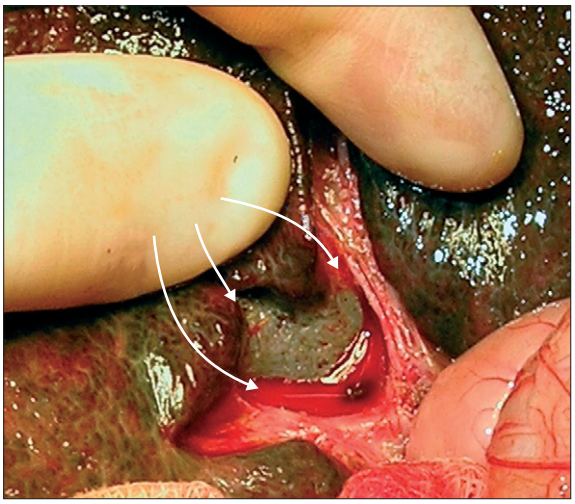

Figure 4: **View of porta hepatis after transection**
Gallbladder and all solid extrahepatic remnants removed from patient with type 3 biliary atresia. Several scattered ductules visible on the portal plate. Arrows show portal plate.

or more cases per year. This variation resulted in statistically significant differences in 5-year native liver survival (61% in centres that did five or more cases *vs* 14% in others)[4] and overall survival, leading the UK Department of Health to centralise services for biliary atresia. The effect of this centralisation has since been audited[60] in 142 infants. This audit showed clearance of jaundice was achieved in 57% after Kasai porto-enterostomy, with a 4-year survival with native liver of 51% and an overall survival of 89%. The advantage of surgical experience was re-confirmed in a French national study[61,62] in which a collaborative policy between several centres was used rather than centralisation to very few centres. This strategy resulted in a lower 4-year native liver survival (42%) than in the UK, but little change in overall survival (87%) compared with the UK over a similar period.

Adjuvant therapy

Effective postsurgical management includes prevention and treatment of complications such as cholangitis, and provision of effective nutritional and family support. Thus, an integrated multidisciplinary approach with good communication between the specialist centre and local services is needed. All infants should have supplementation of nutrition and fat-soluble vitamins to prevent malnutrition, overcome fat malabsorption, and reduce the effects of excess catabolism.[44] Supplementation is best achieved with a high-energy, high-protein feed that provides between 110–160% of the recommended daily amount. Steatorrhoea from fat malabsorption can be managed by provision of between 40% and 60% of fat in the feed as medium-chain triglycerides.[63] Fat-soluble vitamins can be poorly absorbed, and thus supplementation should include vitamins A, D, E, and K. High-dose oral vitamins should meet nutrition requirements and serum concentrations should be monitored. In refractory cases parenteral vitamins might be needed.[64]

The role of corticosteroids in improvement of biliary drainage is controversial. Potential mechanisms of action are stimulation of bile flow independent of bile salts[65] or the known anti-inflammatory and immunomodulatory effects of steroids on development of injury to the bile ducts and fibrosis. Researchers of a few small retrospective studies[66,67] have suggested a beneficial effect, with improved bile drainage and survival with native liver in children given postoperative steroids . In a prospective randomised placebo–control study[68] of 71 infants from the UK given prednisolone from day 7 to day 28 (starting dose 2 mg/kg per day), researchers reported little effect on either survival of native liver or the proportion of infants who cleared their jaundice, although the steroid group had a significantly reduced concentration of bilirubin at 1 month ($p=0·01$). A systematic review[69] (20 studies) of 1175 infants who received steroids and 645 who had no steroid treatment after Kasai portoenterostomy showed an improvement in clearance of jaundice and survival with use of steroids. A large prospective placebo–control trial is recruiting in the USA through the Biliary Atresia Research Consortium[70] and might provide a definitive recommendation.

Complications

Direct communication of the intestine with the intrahepatic bile ducts and poor bile flow might lead to ascending cholangitis. Most likely to develop in the first few months after surgery, ascending cholangitis can present with recurrence of jaundice, acholic stool, and abdominal pain, and in some cases severe sepsis needing resuscitation and intensive care. Diagnosis is confirmed by blood cultures or culture of a liver biopsy specimen, and treatment is with intravenous antibiotics. Identification of an effective prophylactic regimen has proved difficult. Some centres have used a low-dose regimen of oral antibiotics of amoxicillin, cefalexin, and trimethoprim for the first year. Ursodeoxycholic acid 20 mg/kg per day might also effectively encourage bile flow and bile drainage, and is used in some centres.

Recurrent or late cholangitis might suggest an obstruction of the Roux loop as it passes through the mesocolon. A radioisotope excretion scan should identify proximal bile stasis and need for surgical revision.[71] In some cases Roux loop drainage seems satisfactory, and intensive continuous (possibly intravenous) antibiotic prophylaxis should be started. Bile lakes can develop in the liver at any time after surgery and could be a source of recurrent infection.

Even children with an apparently successful Kasai portoenterostomy will have some hepatic fibrosis or cirrhosis.[72] Portal hypertension is present in most cases and needs treatment when complications such as ascites or bleeding from oesophageal varices develop.

Hepatopulmonary syndrome is a poorly understood complication in which incompletely metabolised vasoactive substances cause abnormal shunting in the pulmonary vascular bed, leading to hypoxia. It might have an increased frequency in infants with the variant for biliary atresia splenic malformation syndrome, even when jaundice has been cleared.[59] Long-term survival with a cirrhotic liver is a risk factor for development of malignancy (hepatoblastoma, hepatocellular carcinoma, and cholangiocarcinoma) in the native liver,[73,76] although the risk and prevalence are unknown. Accordingly, regular screening with ultrasound scans and serial α-feto-protein (probably yearly) should be part of long-term review—even in stable patients.

Outcomes

Kasai portoenterostomy is a palliative procedure and does not cure biliary atresia. The disease progresses in 70% of children in whom bile drainage is established, with development of fibrosis, portal hypertension, and cirrhosis. The rate of progression varies, but progression is most likely when cholangitis is recurrent.[77] Despite this fact, more than 80% of those who have had a successful procedure survive longer than 10 years with their native liver with good quality of life.[78] After a successful operation nutrition improves and growth and insulin-like growth factor-1 return to normal concentrations.[79] A quality-of-life assessment of 55 long-term survivors (from England and Japan) showed no difference in normative quality-of-life indices in the English group and only minor changes within some subindices (eg, general health and vitality) in the Japanese group compared with the general population.[80]

Hepatic and serum factors that affect progression of fibrosis after a successful procedure are potential targets for therapeutic intervention. Osteopontin expression and its downstream regulating factors are increased in the livers of children with biliary atresia compared with controls. A positive association with fibrosis suggests that osteopontin might have a role in generation of fibrosis.[81] Basic fibroblast growth factor and hepatocyte growth factor are also increased in biliary atresia with progressive fibrosis,[82,83] whereas raised concentrations of serum transforming growth factor-β and epidermal growth factor are associated with a good outcome.[84]

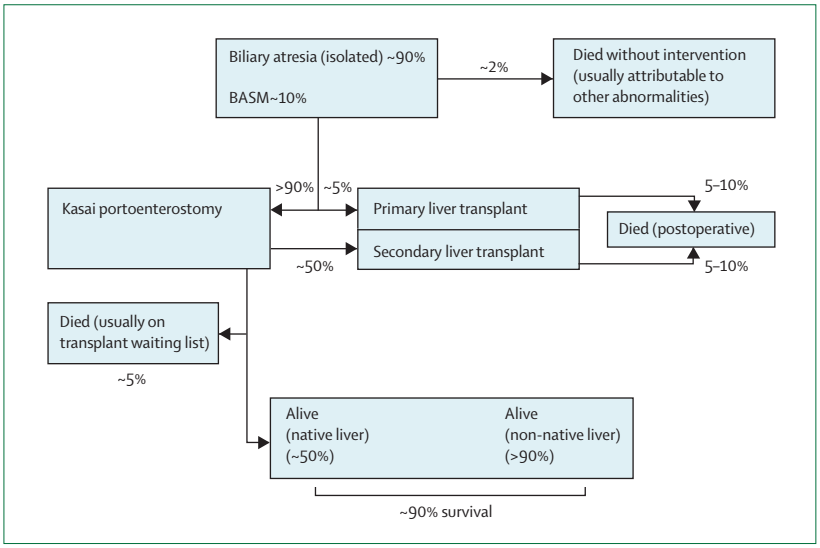

Figure 5: **Outcomes of patients with biliary atresia**
Previously unpublished data, based on UK Biliary Atresia Registry (1999–2008).[93] BASM=biliary atresia splenic malformation syndrome.

Liver transplantation

Indications for liver transplantation depend on the success of Kasai portoenterostomy and the rate of development of complications. In infants in whom bile drainage is not achieved, transplantation is usually indicated within 6 months to 2 years of age. In those who have had a successful procedure, liver transplantation should be considered in the presence of persistent or progressive cholestasis, development of cirrhosis with hepatic dysfunction, or development of portal hypertension with ascites and variceal bleeding unresponsive to endoscopic management. Investigation of factors that predict the need for transplantation help with planning and counselling of families. Such factors are the concentration of bilirubin at 30 days after surgery[85] and a paediatric end-stage liver disease score approaching 10.[86]

In children with the syndromic variants of biliary atresia, associated anomalies, especially congenital cardiac malformations, increase the risk of both early mortality and morbidity. In such children the need for liver transplantation is great. When transplantation is considered in these patients vascular imaging of anatomical anomalies should be thorough, because technical modifications are needed during surgery. Nevertheless, results[87] that are similiar to those in children with isolated biliary atresia can be achieved.

Living-related liver transplantation programmes have been very successful in countries (eg, Taiwan and Japan) where, for cultural or religious reasons, cadaveric donations are not allowed, and are increasingly being used in other high-income countries. These programmes allow for a planned and timely liver transplantation with excellent reported outcomes (98% recipient 5-year survival).[88] Outcomes after liver transplantation have improved with early (1–3 year) survival rates from 85 to 94%.[89–91] Transplantation in infants, which is often the most technically challenging, also has a good outcome and is associated with long-term catch-up growth, improved nutrition, and maintenance of healthy development.[92] Data from the largest US follow-up study[89] of 1976 transplanted children with biliary atresia show that 10-year actuarial graft survival is 73% and patient survival is 86%. Figure 5 depicts the present expected outcome for an infant born with biliary atresia in the UK.

Future perspectives

Management of children with biliary atresia has improved greatly but areas of controversy and management dilemmas remain, needing further exploration. Development of a universal screening method measuring the conjugated amount of bilirubin in the dried blood spot from the present neonatal screening heel prick would help with early diagnosis of biliary atresia. Further knowledge of the pathogenesis of biliary atresia will enable an improved understanding of the disease process and show potential targets for therapeutic intervention.

Research into the serum and hepatic factors that affect development of fibrosis and cirrhosis in the post-Kasai liver will provide targets for future therapies, thereby reducing the need for liver transplantation. Results are awaited from a multicentre, prospective, placebo–control study for use of steroids after Kasai portoenterostomy. The rarity of biliary atresia hinders large definitive studies from single centres. Thus, development of disease registries and consortia throughout countries and continents will enable large amounts of data to be collected, improving knowledge of epidemiology, natural history, pathogenesis, and outcome. The Biliary Atresia Research Consortium[94] in the USA and the European Biliary Atresia Registry[95] in Europe have been formed to help with data collection and provide a platform for large research studies.

Contributors

All authors contributed equally to the writing of this article.

Conflicts of interest

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