Current management of biliary atresia

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Extra-hepatic biliary atresia occurs in approximately 1:15 000 live births leading to about 50 new cases/year in the UK. Presentation is with prolonged jaundice, usually in a term baby who develops signs of obstructive jaundice. Management has been improved by public and professional education to encourage early referral and diagnosis to facilitate initial surgery before 8 weeks of age. Surgical management is complementary and includes an attempt to restore biliary flow (the Kasai portoenterostomy) and liver transplantation if necessary. Medical management consists of antibiotics, ursodeoxycholic acid to encourage bile flow, fat soluble vitamin supplementation and nutritional support. Centralising surgery to specialised centres has improved survival of this potentially fatal disease to over 90% in the UK. Over half of infants undergoing portoenterostomy will clear the jaundice and have a greater than 80% chance of a good quality of life, reaching adolescence without transplantation. For those children developing intractable complications of cirrhosis and portal hypertension, liver transplantation provides a 90% chance of achieving normal life.

immunological dysregulation, viral infection and toxin exposure.⁴

SCREENING FOR BILIARY ATRESIA

There has been considerable interest in developing appropriate screening tests for biliary atresia because of the importance of early diagnosis and treatment. Screening of bile acids in dried blood spots has not been of value,⁵ but conjugated bilirubin measured in liquid neonatal screening bloods between 6–10 days of age proved to be a sensitive and specific marker of neonatal liver disease including biliary atresia.⁶ Further work is required to develop methods to detect conjugated bilirubin in dry blood spots for large scale neonatal screening. In some countries, public education to identify biliary obstruction using stool colour charts to detect abnormally pale stools has been of value.⁷

CLINICAL PRESENTATION AND DIAGNOSIS

Most infants with biliary atresia are full term with a normal birth weight. Such infants present with persisting jaundice from the second day of life. Other features include pale stools, dark urine, failure to thrive and hepatomegaly. Splenomegaly may be found but is a late feature and implies significant hepatic fibrosis and early cirrhosis.⁸ Occasionally infants present with bleeding from vitamin K responsive coagulopathy which is more common in breastfed infants who did not receive vitamin K perinatally. About 5% of all infants will have had an abnormal antenatal maternal ultrasound. This is due to the presence of a cyst within the otherwise obliterated biliary tree and is detectable from around 22 weeks of gestation. Interestingly, these children usually do not have syndromic features such as polysplenia (see below).⁹

The diagnosis of biliary atresia may be difficult because of confusion with physiological jaundice (due to immaturity of the infant liver) and breast milk jaundice. Physiological jaundice normally lasts 2–3 days in normal term babies, while breast milk jaundice can last for up to 4 weeks. These physiological conditions can be differentiated from liver disease because in both physiological jaundice and breast milk jaundice, the bilirubin in the blood is mainly unconjugated (indirect), whereas in liver disease most of the bilirubin in time is conjugated (direct), typically >20 µmol/l or >20% of total.⁶ Confusion often arises in breastfed infants who may have a mixture of unconjugated (indirect) bilirubin and conjugated (direct) bilirubin. In time, the level of unconjugated bilirubin falls to normal, while the level of conjugated bilirubin

Extra hepatic biliary atresia is a disease of unknown aetiology with no proven genetic basis. It is a rare disease with an incidence of approximately 1:15 000 live births.^{1 2} The disease affects both intra and extra hepatic ducts with progressive destruction leading to cholestasis, fibrosis and cirrhosis. The disease is classified according to the extent of biliary damage. Type I biliary atresia affects the common bile duct and proximal cystic biliary duct; type II biliary atresia affects the common hepatic duct; and type III biliary atresia, which is the most common, affects the entire extra hepatic biliary tree.

There appear to be two clinical phenotypes. There is a syndromic or embryonic form that accounts for 10–20% of cases and is distinguished by other congenital anomalies such as polysplenia, situs inversus, cardiac anomalies (eg, atrial and ventricular septal defects), and absence of the inferior cava, etc (biliary atresia splenic malformation syndrome³). This has been linked in some cases to extrinsic factors such as maternal diabetes. The perinatal or acquired form is more common and represents 80–90% of cases.

The underlying pathogenesis is unknown but is likely to be multifactorial based on the interaction of genetic and environmental factors. Research to date has focussed on defects in morphogenesis,

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risers. Professional teaching is based on the necessity to exclude liver disease if jaundice is prolonged beyond 14 days in a term infant or 3 weeks in a preterm infant.^{8–10}

Diagnosis is based on the clinical presentation and the development of pale stools and dark urine, and is confirmed by abnormal liver function tests. These typically demonstrate a rise in conjugated (direct) bilirubin ($>100 \mu\text{mol/l}$; normal <20), alkaline phosphatase ($>600 \text{ IU/l}$; normal $<500 \text{ IU/l}$) and gamma glutamyl transferase ($>100 \text{ IU/l}$; normal 20–40). Prothrombin time and albumin are usually normal in the early stages.

Key diagnostic investigations include abdominal ultrasound, which demonstrates an enlarged liver, and an absent or contracted gallbladder after a 4 h fast. Biliary dilatation is not seen. Hepatobiliary scanning using TEBIDA (*N*-tert-butylimino-diacetic acid) following phenobarbitone pre-treatment (5 mg/kg/day for 3–5 days) usually demonstrates good hepatic uptake but absent or reduced excretion into the intestine within 24 h.

Liver histology, obtained by percutaneous biopsy, shows portal tract fibrosis, cholestasis and proliferation of biliary ductules.⁸ It is essential to exclude other neonatal liver diseases with similar clinical presentations such as α -1-antitrypsin deficiency and other forms of neonatal hepatitis.⁸

The diagnosis is usually confirmed at laparotomy (with/without cholangiography) when the atretic biliary tree is evident. It is then usual to proceed to palliative surgery, the Kasai portoenterostomy. Some infants who present late (>100 days) and who have obvious established cirrhosis may alternatively be candidates for liver transplantation as a primary procedure. The natural history of this disease without medical or surgical management treatment is that most children die within 2 years of birth from end-stage liver failure.

MANAGEMENT OF BILIARY ATRESIA

Surgical management

Initial management is to excise the entire obliterated biliary tree, transecting it at the level of the porta hepatis in order to expose microscopic but communicating biliary channels. A Roux loop is then created from the proximal jejunum and anastomosed to the cut surface (Kasai portoenterostomy). Restoration of biliary flow is then achieved, although the degree is variable and how it has been measured is controversial.^{11–15} We have defined clearance of jaundice as normalisation of serum bilirubin within 6 months of the procedure and in a recent UK report this was achieved in 57% of cases.¹⁶

There are a number of factors which influence the success of surgery and include:

• 1) Age at surgery

Many studies have shown an improved outcome in terms of clearance of jaundice and native liver survival, the earlier the portoenterostomy is performed. This has stimulated a public and professional campaign to encourage early referral for biliary atresia and highlighted the necessity for screening.^{6–7,10} Clearly the age at operation is an important factor, and may be a proxy for the extent of liver damage. Although initial results suggested that children operated on at 40 days of age did not show a significant survival advantage,¹² recent data from Japan¹⁵ suggest a clear advantage for those infants operated on earlier than 30 days of age, no difference in outcome in those operated on between 30 and 90 days, and a significant disadvantage only for those operated on later than 90 days.

• 2) Histology

It has been suggested that the extent of histological abnormality at operation¹⁷ or the morphology of the extra hepatic biliary remnant influences both short and long term outcome, but this has not been found consistently.¹⁸ Those infants who have small (in number and cross-sectional area) residual biliary ductules in the transected remnant will have the poorest restoration of bile flow. However, this can be difficult to measure in individual cases because of difficulties with orientation and consistency of histological interpretation.

• 3) Surgical expertise

By far the most important variable is the experience of the surgeon and the surgical centre. Three studies, two in the United Kingdom and one in France, have clearly demonstrated that the short and long term outcomes for children with biliary atresia are closely related to the experience of the surgeon and the centre.^{1,19,20}

In the later British study carried out with the British Paediatric Surveillance Unit (BPSU) in 1993–1995, 93 cases of biliary atresia in the UK were confirmed. Median age at referral to a surgical centre was 40 days. Children were managed in 15 individual surgical centres. Only two centres treated more than five cases per year (group A). Primary biliary surgery was performed in 91 children at a median age of 54 days of age and was initially successful in 50 (55%). Early success of primary surgery was more likely in group A centres: odds ratio 2.02 (95% CI (confidence interval) 0.86 to 4.73) (fig 1). Survival with native liver and survival after liver transplantation were both significantly greater in group A centres: odds ratio 0.48 (95% CI 0.27 to 0.86) and 0.32 (95% CI 0.11 to 0.94), respectively. Actuarial 5-year survival without transplantation was 61% in group A centres and 14% in other centres (fig 2). The only significant factor to predict survival was the experience and case load of the centre.¹

In the French study, 472 patients were identified between 1986 and 1996. The 10-year actuarial survival with native liver was 29%. Although age at surgery and anatomical pattern of atresia were identified as prognostic factors, the experience of the centre remained the most significant factor with a twofold difference (18–36%) in survival.²⁰

These data^{1,16} led to a UK Department of Health directive for England and Wales (DOH 199/0268 30.4.99) indicating that all infants with suspected biliary atresia should be referred to one

Figure 1 Actuarial survival without liver transplantation for children with biliary atresia grouped by centre caseload (>5 cases/year; <5 cases/year). Reproduced from the *Lancet* 2000;**355**:25–29, with permission from Elsevier.

Figure 2 The British Paediatric Surveillance Unit study of biliary atresia. Actuarial overall survival for children with biliary atresia grouped by centre caseload (>5 cases/year; <5 cases/year). Reproduced from the *Lancet* 2000;**355**:25–29, with permission from Elsevier.

of three designated centres (St James Hospital in Leeds, Birmingham Children's Hospital and Kings College Hospital, London) where both the Kasai operation and, if necessary, liver transplantation could be offered.

The impact of the centralisation of biliary atresia surgery in the UK has recently been audited.¹⁶ A total of 148 infants with biliary atresia were treated between January 1999 and June 2002. Primary Kasai portoenterostomy was carried out in 142 and primary liver transplant in five (3%). Early clearance of jaundice after portoenterostomy was achieved in 57% of infants, compared to 55% in the earlier series.¹ Of 135 children who survived, 62% still had their native liver and 38% had received transplants compared to 40% in the earlier series. The overall 4-year estimated survival was 89% (95% CI 82% to 94%) compared to 85% (95% CI 77% to 92%) in the pre-centralised era, suggesting that centralisation of surgery reduced the need for liver transplantation and improved the outcome for children with biliary atresia.

Medical management

Important aspects of post-surgical management include prevention of complications and provision of nutritional and family support, requiring a multidisciplinary approach.

The role of corticosteroids in improving biliary drainage is controversial. Potential mechanisms include stimulation of bile salt independent flow,²¹ or the known anti-inflammatory and immunomodulatory effects of steroids on the development of bile duct injury and fibrosis. A number of small retrospective studies have suggested a beneficial effect with improved bile drainage and survival with native liver in children treated with post-operative steroids,^{22–23} but a recent prospective randomised placebo controlled study in 71 UK infants treated with prednisolone from day 7 to 28 (starting dose 2 mg/kg/day) found no significant effect on either native liver survival or the proportion who cleared their jaundice. However, the medication was well tolerated and a reduced bilirubin level was seen in the steroid group at 3 months (unpublished results). A large prospective placebo controlled trial is in progress in the USA through the Biliary Atresia Research Consortium.²⁴

Medical management includes prevention of cholangitis, initially with intravenous antibiotics and subsequently with prophylactic low dose oral antibiotics, which can be recycled at 8- or 12-week intervals (eg, amoxycillin 125 mg per day, cephalexin 125 mg per day, trimethoprim 120 mg per day) for 12 months as a minimum. Ursodeoxycholic acid (20 mg per kg/

day) may also be effective in encouraging bile flow and bile drainage and is used in some centres.

Nutritional support with generous oral supplements of fat soluble vitamins is essential to prevent malnutrition, overcome fat malabsorption and reduce the effect of excess catabolism.²⁵ This is best carried out by using a high calorie, high protein feed, which provides between 110% and 160% of the recommended daily amount. If the child has steatorrhoea from fat malabsorption, this can be managed by providing between 40% and 60% of the fat in the feed as medium chain triglycerides.

Fat soluble vitamin supplementation should include vitamin A 5–15 000 IU per day, vitamin D (alfacalcidol) 50 ng/kg/day, vitamin E 50–200 mg per day and vitamin K 2.5–5 mg per day.

COMPLICATIONS AND OUTCOME

Immediate complications include technical problems such as biliary leaks, exacerbation of ascites and ascending cholangitis. Longer term complications include fat malabsorption and malnutrition leading to fat soluble vitamin deficiency. Vitamin K dependent coagulopathy may occur as may vitamin D deficiency, which leads to a reduction in bone density and rickets. Clinical deficiencies of vitamin A and E are unusual with appropriate supplementation, but peripheral neuropathy secondary to vitamin E deficiency in cholestasis is well recognised.⁸

As the disease is progressive, all children will develop portal fibrosis, cirrhosis and portal hypertension to a greater or lesser extent, even if bile drainage has been established, which is more likely if there is recurrent cholangitis.²⁶ However, it is clear that 80% of children who have had a successful portoenterostomy are likely to survive more than 10 years with their native liver^{12–27} and achieve a good quality of life,^{27–28} including becoming successful parents.²⁹

LIVER TRANSPLANTATION

Modern management of biliary atresia includes consideration for liver transplantation. Currently, 76% of children under the age of 2 years who require transplantation have been born with biliary atresia (European Liver Transplant Registry 2005).

The indications for liver transplantation depend on the success of the Kasai portoenterostomy and the rate of development of complications. In those infants in whom bile drainage is not achieved, transplantation is usually indicated within the first year or life. In children with a successful Kasai portoenterostomy, liver transplantation should be considered if there is persistent or progressive cholestasis, development of cirrhosis with hepatic dysfunction or development of portal hypertension with ascites and variceal bleeding unresponsive to endoscopic management.

The outcome of liver transplantation has also improved with a greater than 95% 1-year survival rate for those children who had electively received transplants. Transplantation in infancy, which is often the most technically challenging, also has a good outcome and is associated with long term catch-up growth and nutrition and maintenance of normal development.³⁰ Furthermore, the largest North American follow-up study of children with biliary atresia who have received transplants shows that 10-year actuarial graft and patient survival is now 73% and 86%, respectively.³¹

FUTURE PROSPECTS

The future for children with biliary atresia depends on improving our understanding of the aetiology and optimising referral and surgical management. Two international initiatives should be of value. In the US, the National Institutes of Health (NIH) has established the Biliary Atresia Research Consortium

(BARC) in order to investigate the pathogenesis and to carry out therapeutic trials. In Europe, the European Federation for Biliary Atresia Research (EFBAR; www.orpha.net/nestasso/EFBAR/) plans similar studies and an application to the European Union for funding under the planned FP7 initiative. In the meantime, paediatricians in the UK should be aware of the necessity to exclude biliary atresia in infants with prolonged jaundice irrespective of whether or not they are breast fed, and refer them to one of the three national units.

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