Biliary Atresia and Choledochal Malformations

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Biliary Atresia

Introduction

In 1891, John Thompson, a physician from Edinburgh, described in detail the clinical features and postmortem findings of an infant with what he labelled as "congenital biliary obstruction" [1]. His drawing clearly showed an absence of a common hepatic duct and a collapsed empty gallbladder. Further reports during the early part of the twentieth-century prompted surgeons to explore the biliary tree to try and identify a blockage and perhaps a proximal bile-containing duct to anastomose to. This led to the concept that biliary atresia (BA) was either "correctable" or "uncorrectable" depending on operative findings. With increasing experience it became evident that the latter was much more common and hence survivors were exceptional. Although the use of these terms is nowadays anachronistic (because you can "correct" the uncorrectable!), it perhaps best illustrates the hopeless prognosis of these unfortunate infants.

Figure 59.1 illustrates the various types of BA and is based upon the most proximal level of obstruction. Thus, over 95% are type 3 where there is no visible bile duct in the porta hepatis (hence "uncorrectable"). It does not imply anything about causation (see later).

A more radical approach to the technique was pioneered in Sendai, Japan, during the 1950s and 1960s by Morio Kasai (1922–2008) to the problem of "uncorrectability" [2, 3]. He advocated a more radical approach to the biliary dissection and simply transected at the most proximal point in the porta hepatis. The porta, even if there were no visible ducts, was then anastomosed to a Roux loop (portoenterostomy). Transection exposes residual microscopic bile duct remnants within the fibrous tissue, which retain communication with the intrahepatic duct system (still often very abnormal). Hence bile flow actually occurs to a varying degree, but in perhaps the majority enough to lose their jaundice (see later for results and outcome), postoperative outcome significantly improved.

For the first time, KPE enabled a much larger cohort of long-term survivors, initially in Japan [3] but later from the 1970s in Europe and North America. It wasn't a cure though, and even survivors displayed many complications related to liver fibrosis and cirrhosis.

Thomas Starzl in 1963 attempted the first liver transplant in humans in a child born with BA [4]. Sadly, the child died of operative bleeding related to severe portal hypertension. This prompted a number of units around the world to set up transplantation programmes, but in the absence of effective immunosuppression, they were all terminated by the end of the 1960s. With the discovery of cyclosporine at the beginning of the 1980s, transplantation once more became a viable option, and from this the current strategy of an initial attempt to restore (some might say resurrect) bile flow with a KPE followed by liver transplantation if this fails evolved.

Variants of Biliary Atresia

BA is not a single disease; rather it should be thought of as a phenotype resulting from a number of different and entirely separate aetiologies leading to the final common phenotype of biliary inflammation, luminal obliteration and fibrosis [5].

We have been able to define clinically at least four broad groups (Fig. 59.2).

1. *Syndromic Biliary Atresia*

While BA is usually an isolated abnormality found in otherwise normal term infants, there are a group of infants

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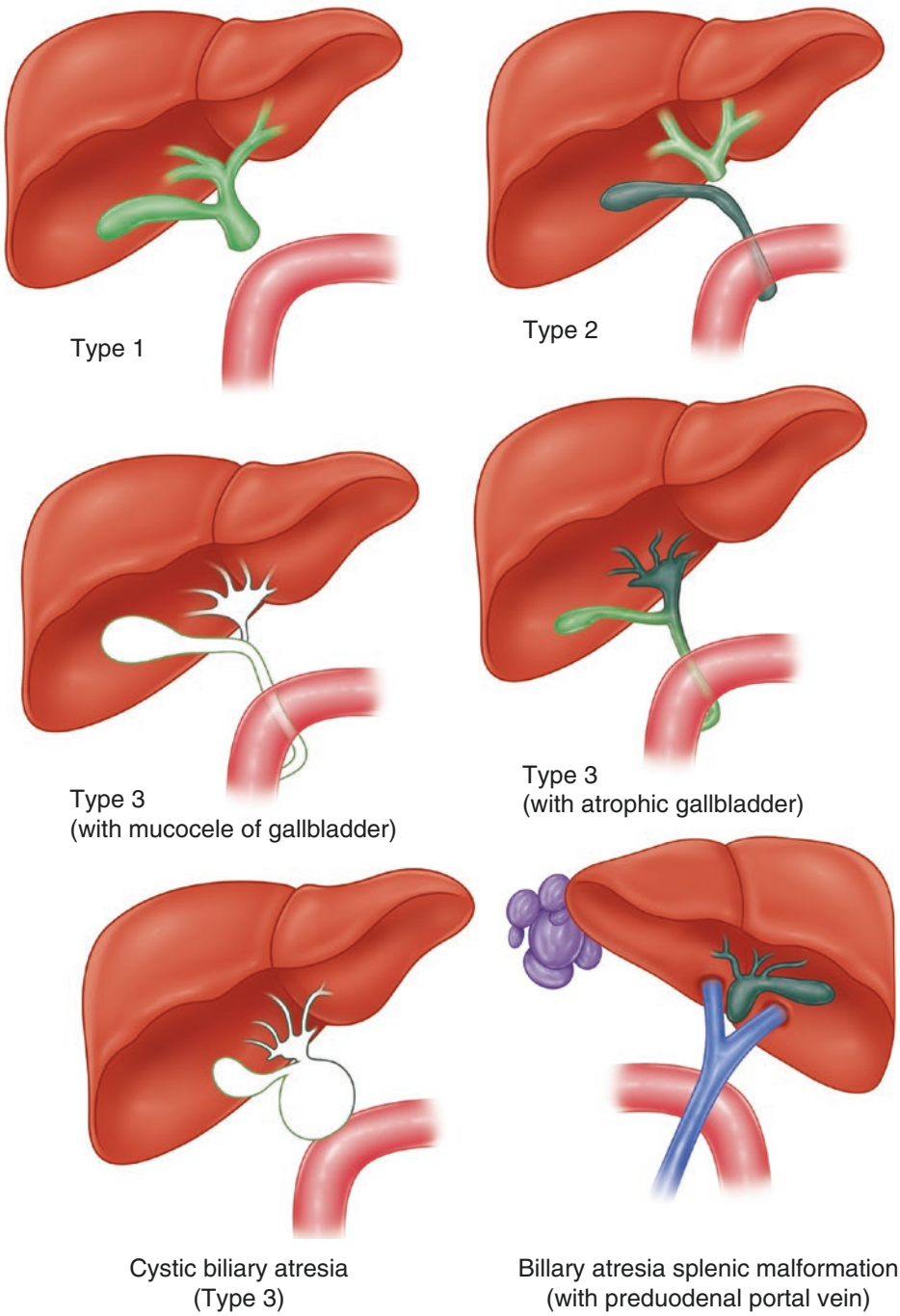

Fig. 59.1 Schematic illustration of biliary atresia. (Based on Japanese Association of Pediatric Surgeons classification)

(about 10–15% in European and North American series, but <2% in Asian series) with other non-biliary anomalies and a poorer prognosis. We have termed this specific constellation of anomalies the biliary atresia with splenic malformation (BASM) syndrome [6, 7]. All will have a splenic malformation, usually polysplenia (~80%) but occasionally asplenia or double spleens, and about half will have situs inversus and congenital heart abnormalities. Other anomalies are evident at laparotomy including preduodenal portal vein, absence of the inferior vena cava and malrotation. Most infants with this syndromic form of BA are female. It is speculated that such cases may result from some fundamental derangement of extrahepatic bile duct (and other systems) development within the embryological phase (<6 weeks of gestation). A large-scale North American study recently identified deleterious mutations in the *PKD1-L-1* gene using whole-exome sequencing in about 10% of subjects with BASM [8]. Other candidate genes have also been suggested such as *CFC-1* and

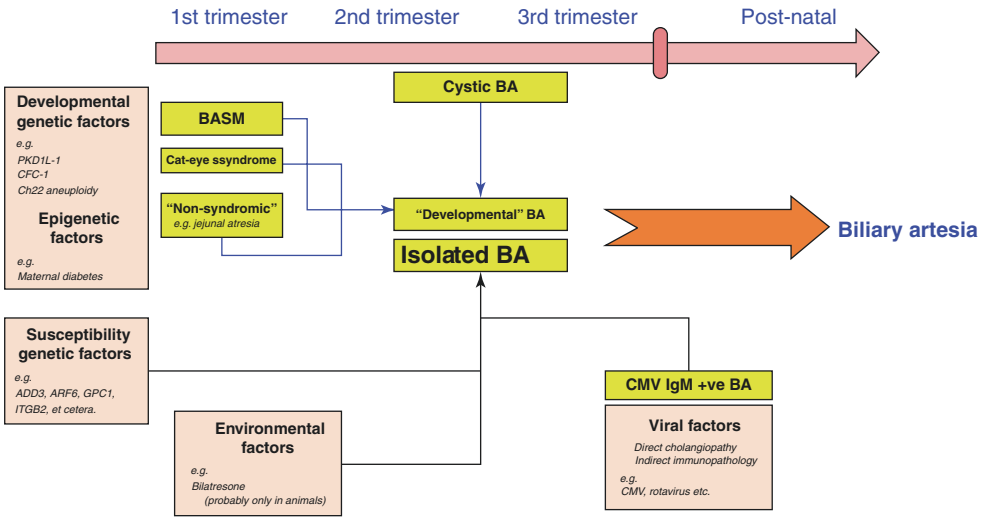

Fig. 59.2 Variants of biliary atresia. Key: Variants ; Proposed aetiological factors

FOXA2 [9]. There is also an association with an abnormal first-trimester intrauterine environment such as that found in maternal diabetes and thyrotoxicosis [7].

2. *Cystic Biliary Atresia (CBA)*

In about 5% of cases, there is an obvious cyst (sometimes containing bile) within an otherwise obliterated biliary tree. In recent years it has been possible to detect this cystic change on antenatal ultrasound scans as early as the 18th week of gestation [10, 11]. CBA should not be confused with cystic choledochal malformation, which can be indistinguishable on ultrasound and MR scans [12]. Discrimination may be made clinically as CBA will invariably have conjugated jaundice, pale stools, etc. and at laparotomy as the cholangiogram will show the abnormal and primitive intrahepatic duct structure.

3. *Isolated Biliary Atresia (IBA)*

This is the typical BA variant accounting for about 80–90% of cases [13]. They have no other significant features and usually display an obliterated biliary tree at laparotomy (usually type 3). Real evidence of what has caused BA in this group is minimal and remains open to speculation. However, some recent evidence towards a developmental pathogenesis was presented by a review of early liver biochemistry (day 1 and day 2 of life) in infants later shown to have BA. This showed that all had elevated direct/conjugated bilirubin by 24 h implying biliary obstruction at the time of birth [14] (Fig. 59.3).

4. *Cytomegalovirus (CMV) IgM+ve Biliary Atresia*

Although there is a range of possible hepatotropic cholangiopathic viruses (e.g. Reovirus type 3, rotavirus), it has been difficult to definitively ascribe clinical consequences to infection. We have recently discriminated infants with CMV IgM+ve antibodies from their IgM−ve fellows clinically, histologically and in their response to treatment [15]. These made up 10% of our clinical series and were more commonly seen in infants from a non-Caucasian ethnicity. Clinically they were older at diagnosis and came to KPE later. Biochemically, they had higher bilirubin and AST levels, with larger spleens as measured on ultrasound than comparable IgM−ve BA infants. The histological appearance within the liver was characterised with an obvious mononuclear cell infiltrate consisting of largely CD4+ Th1+ T cells [16]. These infants also appeared to have the worse response to KPE and also appeared particularly susceptible to death during early childhood [15, 17] (Fig. 59.4). Of all the clinical groups described, this is the group that appears to fulfil most of the requirements to support an immune-destructive pathogenesis following viral triggering.

Epidemiology

Population-based studies reporting incidence and outcomes of BA are scarce. There is marked variation in incidence across the globe ranging from about 1 in 5–10,000 live births in Taiwan [18, 19] and Japan [20] to about 1 in 15–20,000 in mainland Europe [21–24], England and Wales [13] and North America [25].

Furthermore, there is marked geographical variation of the specific variants mentioned above. The incidence of BASM varies widely, being rarely reported in Asian series but accounting for about 10% of European and North American series. By contrast, the incidence of CMV IgM+ve BA also varies from 10% to 20% in European series [15] to perhaps up to 50% reported in some series from China [26].

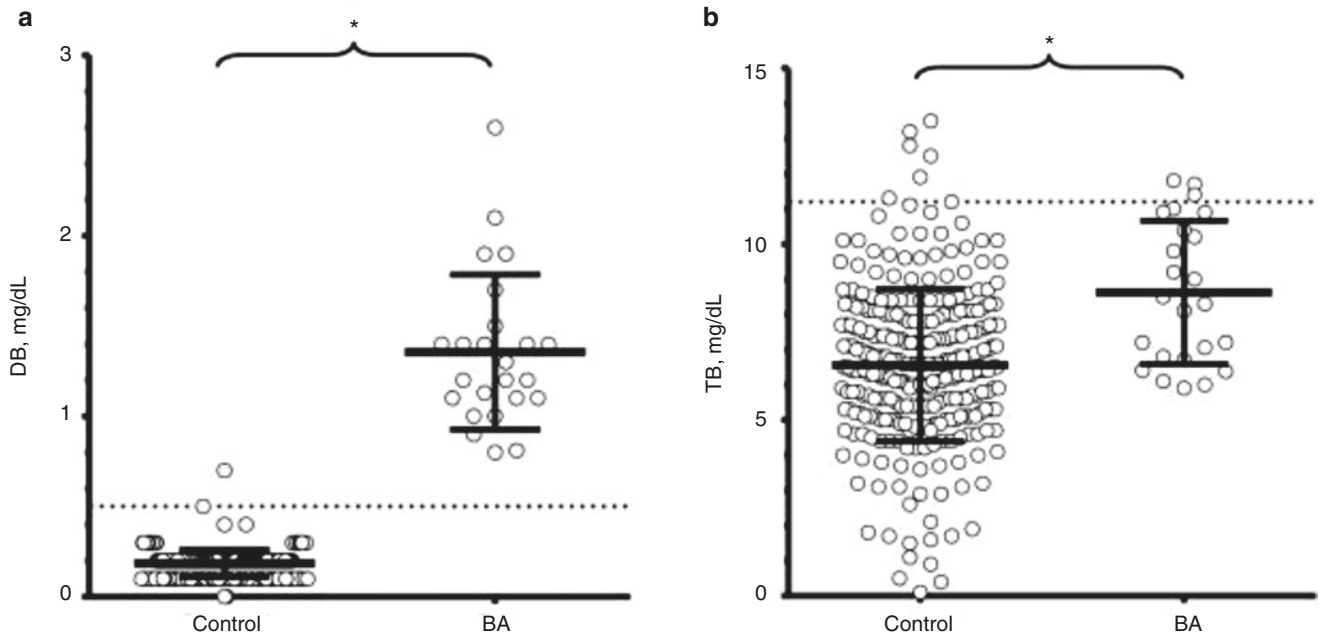

Fig. 59.3 Infants with BA have elevated direct bilirubin (DB), but not total bilirubin (TB), levels at 24–48 h of life (HoL). Shown are the mean DB (**a**) and TB (**b**) levels for controls ($n = 300$; collection time, 39 +/− 5.6 HoL) versus patients with BA ($n = 24$; collection time, 34 +/− 6.2 HoL). The dashed lines indicate the upper limits of normal (**a**, 0.5 mg/dL) or the approximate phototherapy level at 34 HoL (**b**, 11.2 mg/dL). *$P < 0.0001$

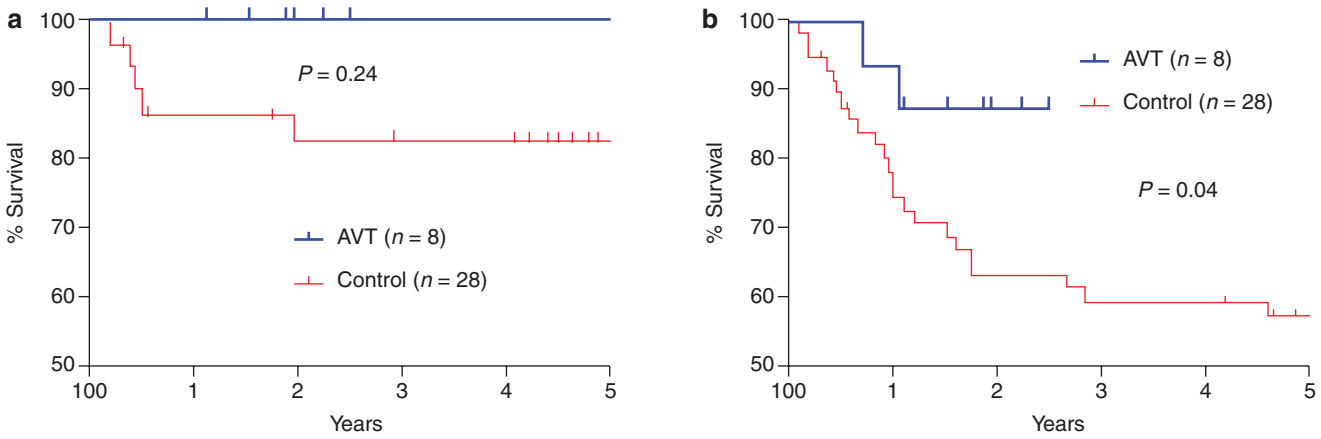

Fig. 59.4 Actuarial native liver survival (**a**) and actuarial survival (**b**) of infants with CMV IgM+ve biliary atresia. NB Both groups (controls and AVT) were treated with Kasai portoenterostomy with (AVT) or without (control) anti-viral therapy (AVT). (Reproduced with permission from Parolini et al. [17])

A number of small series suggested seasonality for BA [18, 27], though these were far from definitive and larger national series failed to observe any predilection for a particular season [13, 20, 21].

Clinical Features

The key features of BA are persistent conjugated jaundice, acholic stools and dark urine in an otherwise healthy term infant (Fig. 59.5). The latter feature is caused by excess conjugated (i.e. water-soluble) bilirubin passing into the urine causing its colour to darken. Such alternative pathways of bilirubin excretion are more developed or at least preserved in the newborn, and very high levels of bilirubin (>300 μmol/L or >17 mg/dL) are exceptional. Sometimes jaundice will be difficult to discern in infants of Asian or Afro-Caribbean origin leading to delays in diagnosis and treatment. The median time to referral was 47 days in white versus 52 days in non-white infants in one UK study [28]. Furthermore, all of those "missed" and referred beyond 100 days were non-white.

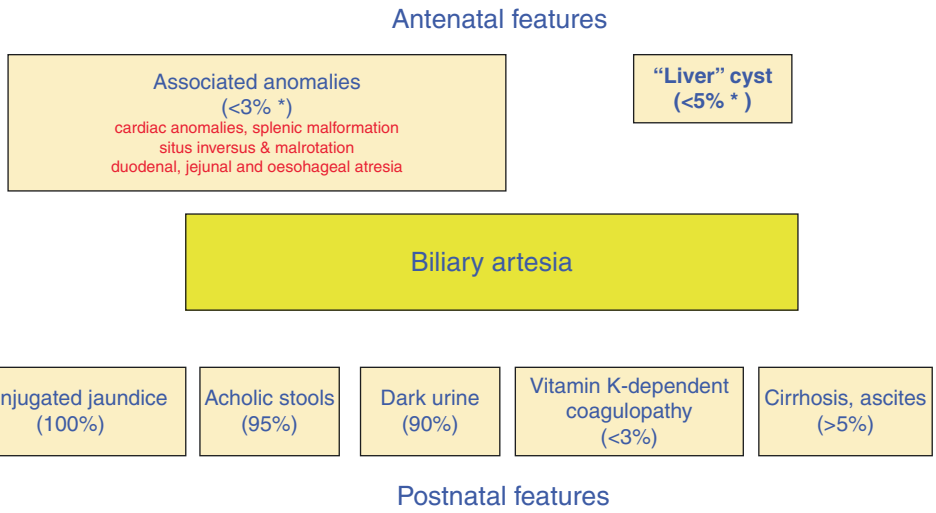

Fig. 59.5 Modes of presentation of biliary atresia. (NB the percentages reflect the mode of presentation not the actual proportion)

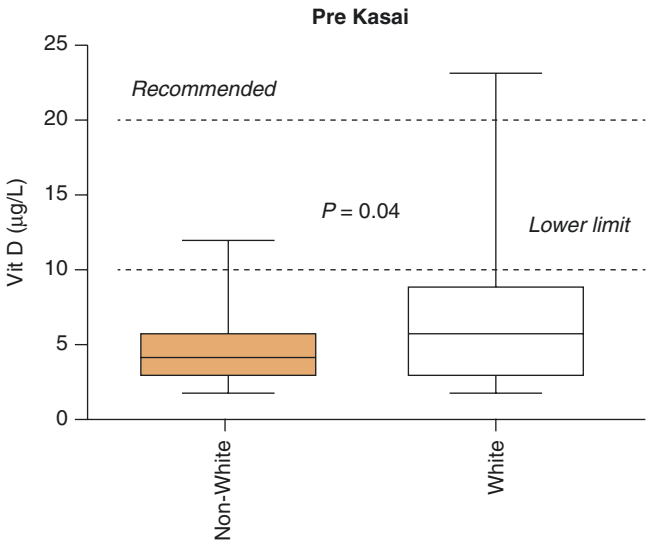

Fig. 59.6 Decreased pre-operative vitamin D levels in non-white compared to white infants with biliary atresia. (Reproduced with permission from Ng et al. [29])

Sometimes the antenatal ultrasound scan will be abnormal showing a sub-hepatic cyst, and one should then be suspicious of CBA [10]. There is no difference in gestational age or birth weight between all the BA variants with all of them presenting with failure to thrive by the time they are admitted. Fat malabsorption is the presumed mechanism, and this will also cause deficiency of the fat-soluble vitamins D, A, E and K. Low vitamin D levels are almost invariable even in those infants presenting early [29], and this is exacerbated in those of Asian family origin, presumably reflecting low maternal stores (Fig. 59.6). Vitamin K deficiency is possible, and a proportion will present with a bleeding tendency, perhaps from the umbilical stump or more catastrophically with an intracranial haemorrhage. Marked elevation of the INR or prothrombin time will be seen in those presenting late. Some syndromic cases will present early (or even antenatally) because of other abnormalities associated with BASM (e.g. cardiac anomalies, malrotation or situs inversus) [30].

Diagnosis

The diagnostic workup in our institution includes a detailed ultrasound of the liver, liver biochemistry and a percutaneous liver biopsy [12]. Using this, more than 90% will have an accurate diagnosis before laparotomy.

Ultrasonography

The ultrasound (US) examination is a key part of the diagnostic protocol as it usually excludes other surgical diagnoses (e.g. choledochal malformation, inspissated bile syndrome, etc.). All of these are being characterised by intrahepatic or common bile duct dilatation. US may be suggestive of BA as a diagnosis – by showing a shrunken, atrophic gallbladder with no evidence of filling between feeds. In about 20% of cases, a "normal gallbladder" is described – these usually turn out to have a mucocele of the gallbladder together with a relatively preserved common bile duct (CBD) and an absent common hepatic duct (CHD) (Fig. 59.1).

Laboratory Findings

Liver biochemistry will show a conjugated jaundice (typically >100 µmol/L), modestly raised transaminases (>100 µmol/L) as well as significantly raised γ-glutamyl transpeptidase (GGT > 200 IU/L). Serum protein and albumin levels should be normal. However, none of these are specific and by themselves are not diagnostic.

Percutaneous Liver Biopsy

In the authors' unit, the pre-laparotomy diagnosis of BA is usually made by percutaneous liver biopsy showing histological features characteristic of "large duct obstruction" such as bile duct proliferation, portal oedema and absence of sinusoidal fibrosis. It is less accurate the younger the infant and it does require an experienced and confident liver pathologist.

Aspartate Aminotransferase-to-Platelet Ratio Index (APRi)

The aspartate aminotransferase-to-platelet ratio index (APRi) can be used as a surrogate of liver fibrosis in many liver diseases, including BA. We have reported that this correlates significantly with age at surgery and was much higher in CMV-IgM+ve BA [31]. Macroscopic cirrhosis evident at laparotomy could also be predicted using a cut-off value of 1.2, with reasonable sensitivity (75%) and specificity (84%) in a large cohort of infants from our unit [31].

The usual differential diagnoses of conjugated jaundice include TORCH infections (e.g. toxoplasma, rubella, CMV, hepatitis, etc.), genetic conditions (e.g. α-1 antitrypsin deficiency, Alagille's syndrome (abnormal "elfin" facies, butterfly vertebrae, pulmonary stenosis), progressive familial intrahepatic cholestasis (PFIC) disorders), metabolic conditions (e.g. cystic fibrosis, galactosemia), parenteral nutrition and neonatal hepatitis.

Miscellaneous Diagnostic Techniques

Some centres rely on more functional tests *looking for* an absence of bile in the intestine such as duodenal intubation and aspiration or hepatobiliary radionuclide scans using a variety of technetium-labelled iminodiacetic acid derivatives (HIDA) [32]. The use of endoscopic retrograde cholangiopancreatography (ERCP) is possible in infants, but its use is typically confined to large specialist centres [33]. Similarly, magnetic resonance cholangiopancreatography (MRCP) is still not detailed enough to confidently diagnose BA.

The "acid test" for many remains operative visualisation (which could be laparoscopic) supplemented by on-table cholangiography where possible.

The surgical differential is less common and includes obstructed choledochal malformation, which usually shows obvious dilated intra- and extrahepatic biliary dilatation, inspissated bile syndrome which usually occurs in the preterm with a precipitating event such as dehydration or haemolysis and spontaneous perforation of the bile duct which usually shows US evidence of bile ascites and a sub-hepatic collection evident on US [12].

Screening

Some countries have adopted a population screening programme for BA [34, 35]. The most well-developed has been that of Taiwan [36, 37], where mothers are issued with colour-coded cards and asked to compare it with their infant's stool. Recognition of pale stool prompts further investigation and referral. This has certainly shortened their time to surgery – the median age at KPE is now <50 days and is currently one of the lowest nationally. The key achievement, we believe, has been the marked reduction in late-presenting infants who had already developed cirrhosis [38].

The simplest solution to early diagnosis remains education however. It is clear from so many histories that it is often the parents who recognise that persisting jaundice in their infants is not normal but then are falsely reassured by health visitors and their community doctors who fail to inquire about pale stools or dark urine (never mind looking at them) and fail to do the appropriate blood test (split bilirubin for conjugated and unconjugated fractions). The statutory community check in the UK occurs at 6 weeks of age and is far too late to make a difference in when these affected infants come to surgery.

Kasai Portoenterostomy

The aim of surgery is to excise all extrahepatic biliary remnants allowing a wide portoenterostomy onto a portal plate, denuded of all such tissue (Fig. 59.7a, b). In most cases, this will expose sufficient transected microscopic bile ductules which retain connections with the primitive intrahepatic bile ductule system to allow restoration of at least a degree of biliary drainage. This should be the object for all three types of BA.

A short right upper quadrant muscle-cutting incision (or laparoscopy) should be performed initially to confirm the suspected diagnosis or, if the gallbladder is shown to contain bile, to proceed to on-table cholangiography.

There are then two surgical strategies to expose the porta hepatis: one involving division of at least the left-sided suspensory ligaments and then eversion of the liver onto the abdominal wall. The other retains the liver in the abdominal cavity but usually requires dissection and slinging of the right and left portal veins to allow full exposure of the biliary remnants. A simple portoenterostomy using a retrocolic Roux loop (about 40 cm) completes the reconstruction (Fig. 59.8). Older techniques involving stomas in the Roux loop have been abandoned by virtually all centres.

Both the dissection and reconstruction in the open KPE can be replicated laparoscopically. However, most centres that pioneered this technique have subsequently reverted to open KPE as outcomes in terms of native liver survival rates and actuarial survival rates are unfavourable compared to conventional surgery [39, 40]. A recent study from Hong Kong confirmed the superiority of the open approach reporting 10-year native liver survival rates of

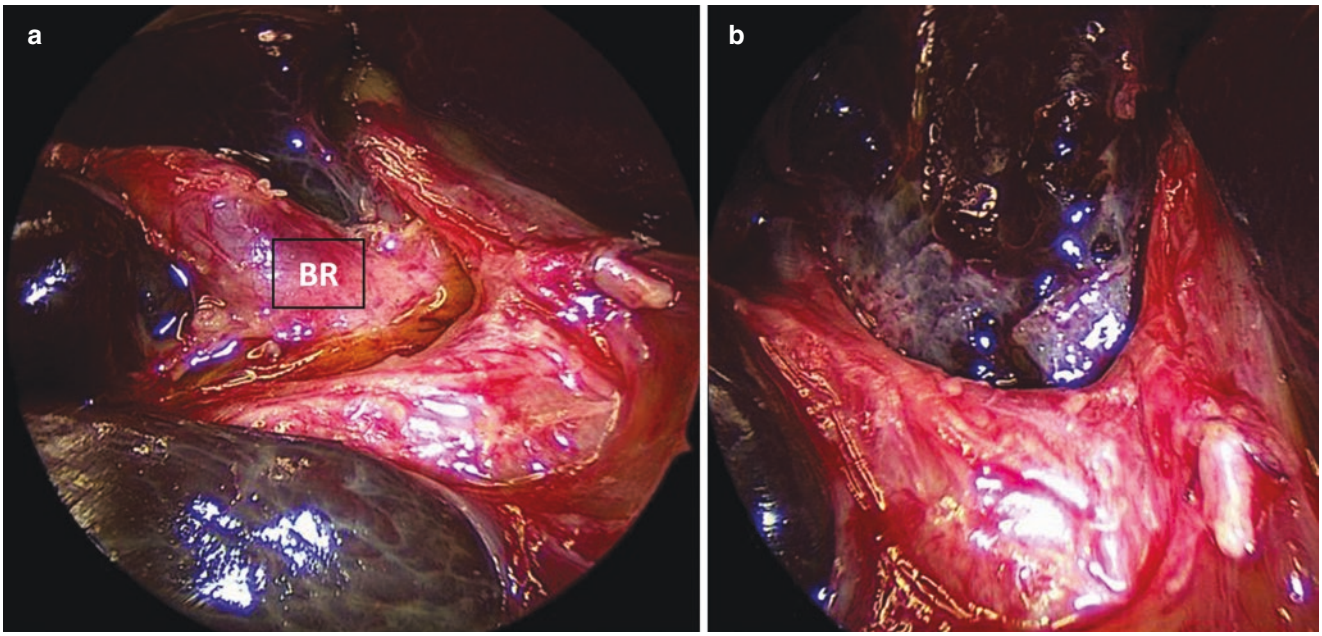

Fig. 59.7 Close-up of porta hepatis during Kasai portoenterostomy. (**a**) Hypertrophied proximal biliary remnant (BR) being separated from vascular structures of liver. (**b**) Same view following resection of BR, showing denuded portal plate

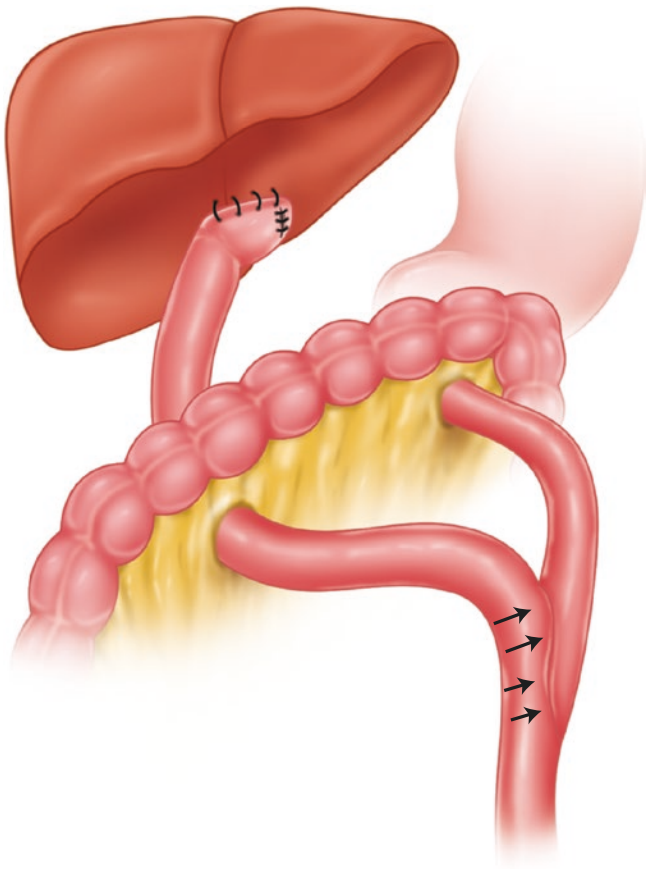

Fig. 59.8 Schematic illustration of retrocolic Roux-en-Y loop, typically measured at 40 cm from portoenterostomy to jejunojejunostomy

85% for the open and 45% for the laparoscopic KPE [41]. The portal dissection, the key to wide excisional surgery, is not improved by being performed laparoscopically, and the reconstruction remains technically challenging. There is obviously a better scar, though the infants remain in hospital for the same length of time and perhaps an adhesion-free abdominal cavity for the transplant surgeon, although even the latter has been challenged by a study from Germany [42].

Surgeons in Juntendo, Tokyo, have adopted a different approach to these issues by limiting the scale of the portal dissection and consciously limiting the transection to a basic oval shape – allowing at least some remnant to remain [43].

Postoperative Management

Intravenous fluids and nasogastric aspiration are continued until return of bowel function (about 3–4 days). Careful monitoring of blood glucose, electrolytes and INR is important in the early phase. Liver biochemistry (including bilirubin) may well worsen in the first week, but by about the fourth week, there should be a definite fall in bilirubin and consistently pigmented stools in those who will do well. Strict attention to nutritional needs is important, and all infants need regular fat-soluble vitamin supplementation. Medium-chain triglyceride (MCT)-based formula milk (e.g. Caprilon®; SHS, Liverpool, UK) is advocated to maximise calorie input and facilitate lipid absorption.

Adjuvant Therapy for Biliary Atresia

As the aetiology of BA remains ill-defined and numbers are relatively few, adjuvant treatment has been largely based on pragmatism and trial and error.

Corticosteroids

Systematic analysis (level 1A evidence) [44] of the few randomised placebo-controlled trial data [45–47] and larger single-centre cohort studies [48] have suggested that postoperative high-dose steroids do have a significant effect on clearance of jaundice with a 10–15% increase in jaundice clearance. This is particularly so in infants <70 days at KPE [49]. We have recently shown that other biochemical markers indicating more specific liver injury (i.e. AST, APRi) are also affected by high-dose steroids at least in the first 6 months post KPE, implying an actual effect on the underlying pathology of the disease process and not just perhaps on degree of restored bile flow [48].

Ursodeoxycholic Acid

The use of oral ursodeoxycholic acid (UDCA) remains popular and may be beneficial but only if surgery has already restored bile flow to a significant degree. Willot et al. from Lille in France assessed the effect of UDCA on liver function in children >1 year post-Kasai portoenterostomy and showed that it improved biochemical liver function in stable children [50]. It may also have an extra beneficial effect in BA because of its immunosuppressive properties as it has been shown to decrease proliferation of and cytokine production by mononuclear cells in vitro [51].

Anti-viral Therapy

CMV IgM+ve BA seems to have an even worse prognosis than CMV IgM−ve BA [15], and for the past few years, we have begun to treat the viral component of this variant. Admittedly this has been on an *ad hoc* basis with variation of the anti-viral agent ranging from IV ganciclovir to oral valganciclovir. However, we have noted a dramatic improvement in the outcome with increased clearance of jaundice and reduction in the medium term for liver transplantation [17] (Fig. 59.4).

Miscellaneous

The benefit of long-term prophylactic antibiotics, bile acid sequestrants (e.g. colestyramine) or probiotics remains unproven. Newer modalities such as immunoglobulin, FXR agonists (e.g. obeticholic acid) and ileal bile acid transporter (IBAT) antagonists (e.g. maralixibat) remain unproven but are now coming into consideration.

Complications

About 20–30% of infants will show no effect from KPE, their stools will remain pale and their bilirubin levels will continue to rise. These infants will inexorably develop cirrhosis and end-stage liver disease with severe failure to thrive, ascites, splenomegaly, deepening jaundice and often bleeding from varices. Such infants need expedited liver transplantation, often before their first birthday. It is important to recognise these infants early and not offer false hope that they will somehow turn a corner – they won't.

Other specific complications deserve a more detailed coverage.

Cholangitis

Re-establishment of bile drainage exposes the child to the risk of ascending cholangitis, which occurs most commonly in the year following primary surgery in about 40–50% of children. Paradoxically, it only occurs in children with some degree of bile flow, not in those with early failure as described above. The usual organisms are enteric in origin (e.g. *Escherichia coli*, *Pseudomonas*, *Klebsiella* spp.).

Clinically, an episode is characterised by fever, acholic stools and a change in biochemical liver function (rising bilirubin and AST levels). The diagnosis may uncommonly be confirmed by blood culture or rarely by percutaneous liver biopsy, but the key component is antibiotic treatment on suspicion not confirmation. Intravenous broad-spectrum antibiotics are effective against Gram-negative organisms (e.g. piperacillin and tazobactam, gentamicin). Most will respond within 24 h, and liver function is usually restored fairly quickly. Some children sustain repeated cholangitis, and they should be treated by prolonged courses of intravenous antibiotics via an indwelling vascular device. If however, it is clear that there are other features of end-stage liver disease, and then they too should be considered for transplant.

Occasionally, cholangitis occurs as a late event in otherwise normal children or adolescents, who have good liver function and have cleared their jaundice [52]. The Roux loop may be at fault here with partial obstruction leading to bile stasis. A combination of radio-isotope scans and percutaneous cholangiography may aid the diagnostic process, and operative Roux loop revision may be required. We have used an enteroscope to investigate these patients and provide radiological and endoscopic visualisation of the proximal Roux loop [53].

Portal Hypertension

Increased portal venous pressure has been shown in about 70% all infants at the time of Kasai operation [54]. However, subsequent portal hypertension depends on both the degree of established fibrosis and, most importantly, the response to surgery. There is a relationship with biochemical liver function and variceal development, and in those who fail and need early transplantation, about 30% will have had a significant variceal bleed.

Infants and children with bleeding oesophageal varices need rapid access to high-quality paediatric facilities with

the resources and expertise to manage them appropriately. Injection or banding is not a technique for the occasional paediatric endoscopist. Restoration of circulating blood volume and pharmacotherapy (e.g. 2 mL/h of 500 μg octreotide in 40 mL of saline) should precede endoscopy and achieve a measure of stabilisation. Sometimes a modified Sengstaken tube needs to be placed to achieve control of bleeding [55]. Invariably in children this can only be done under general anaesthesia but can be life-saving. The definitive treatment in older children is endoscopic variceal banding, although injection sclerotherapy retains a role in treating the varices in infants.

In common with other large centres, we therefore recommend that for each child with BA there is the opportunity to enter a programme of endoscopic surveillance to try and pre-empt variceal bleeding [56]. In this respect, there may be a role for selection based on haematological, biochemical or ultrasound variables to assign risk. One-multinational study suggested that APRi and CPR (clinical prediction rule) [57] appeared to be superior in this respect to simple univariate indices (e.g. platelets, bilirubin) or ultrasound dimensions (e.g. spleen size or resistance index).

The key variceal signs that should prompt *prophylactic* endoscopic treatment are the presence of significant red *wales* in grade II/III oesophageal varices and obvious (usually lesser curve) gastric varices [56]. Liver transplantation needs to be actively considered as definitive treatment for portal hypertension where liver function is poor and the child is already significantly jaundiced.

Ascites

This is related to portal hypertension in part, but there are other contributory factors including hypoalbuminaemia and hyponatraemia. It also predisposes to spontaneous, bacterial peritonitis. Conventional treatment includes a low-salt diet, fluid restriction and the use of diuretics particularly spironolactone. It is often seen in settings of malnutrition and end-stage liver disease, and a nutritional supplementation is important to try and increase calorie and protein intake.

Outcome Following Kasai Portoenterostomy

There are many factors, which will influence surgical outcome in BA. Some are unalterable (e.g. degree of cirrhosis at presentation, absence of, or paucity of bile ductules at the level of section), and some are subject to change (e.g. efficacy of the KPE due to surgical inexperience, poor choice of technique, complications postoperatively due to inexperienced unit, untreated cholangitis, etc.). In large centres with experienced surgeons, about 50–60% of all infants should clear their jaundice and achieve a normal (<20 μmol/L or <1.5 mg/dL) bilirubin [58]. These should do well and have a good quality of long-term survival with their native liver, though the need for transplantation is ever present and the plateau is never flat.

There is no doubt that increasing age at KPE is associated with increasing liver fibrosis and cirrhosis although the actual rates of progression differ according to underlying cause [59]. There is a marked relationship with age at surgery, for instance, with cystic BA and BASM, but it is less evident in isolated BA. So, it is not really possible to use age as a simplistic predictor in individual cases as even in those coming to surgery at >100 days may still have a response to KPE [60]. Still there may be a role for those with the signs of evident cirrhosis (e.g. ascites, heterogeneity of the liver appearance on US) for consideration of transplantation as the primary procedure. This remains an uncommon choice though in the UK and Europe, with <5% of all infants in our series, for instance [58]. By contrast, it seems to becoming a much more prevalent option in certain states in the USA (e.g. California) [61].

In England and Wales, we have adopted a policy of centralisation of surgeons and resources. So for a country of 56 million, there are only three recognised centres to treat this condition, all with surgical facilities including transplantation. This policy was adopted because previous audits of outcome had shown a significant difference depending on centre experience with the less experienced centres showing very poor outcomes [62]. Subsequent studies confirmed an improvement in overall national outcome [58, 63]. Our current outcome statistics show clearance 60–65% of infants coming to KPE at a median now of 48 days. With this at 5 years, we achieve a native liver survival of about 50% and overall survival of 93% (unpublished data; Fig. 59.9a, b). This policy has been successfully replicated by some (typically) Northern European countries [64].

Congenital Choledocal Malformation

Introduction

The German anatomist Abraham Vater recognised the ampullary nature of the junction of biliary and pancreatic ducts which since then has carried his name. Subsequently he also described what appeared to be a choledochal cyst in a pamphlet published in 1723 [65]. Further examples of this, the classical choledochal cyst, were described, but still barely 90 cases had been recorded by 1959, when Alonso-Lej et al. attempted a simple classification into three types [66]. Even as recently as 1975, Flanagan could only identify details of 955 cases from the literature [67].

Choledochal malformation (CM) (of which only some can be described as choledochal "cysts") may be characterised as, … "an abnormal dilatation of the biliary tract, in the

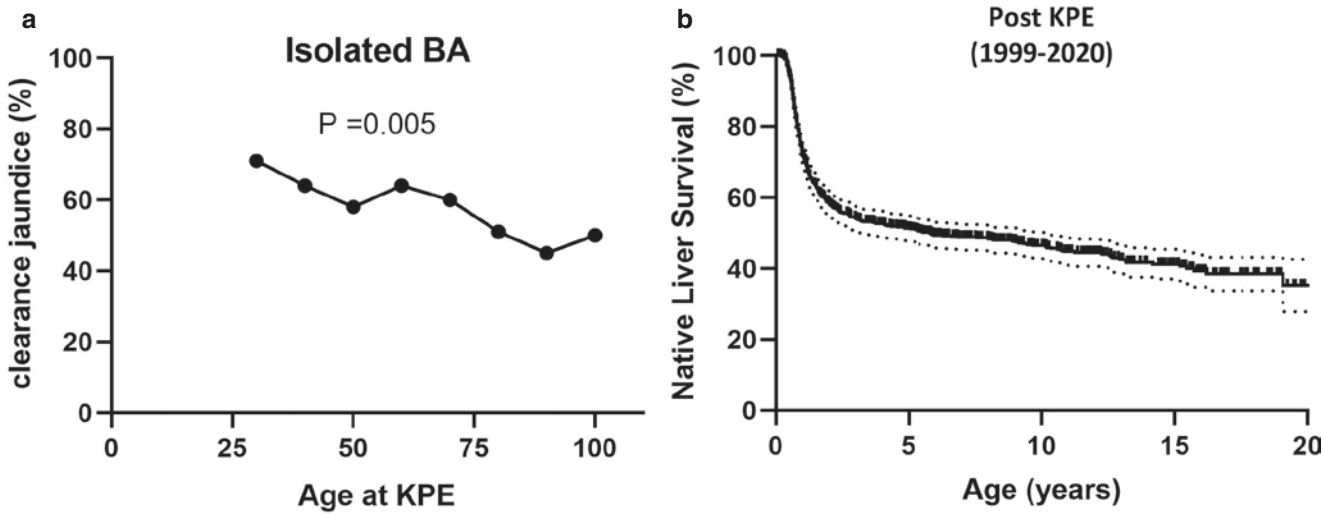

Fig. 59.9 Outcome of biliary atresia in England and Wales since centralisation (1999–2019). (**a**) Age cohort analysis: clearance of jaundice by age at Kasai portoenterostomy. Each point represents individual probability for age-defined cohort (e.g. <30d: 31–40d; 41–50d, etc.). The joining line represents overall influence of age. A "falling line" implies negative influence of clearance on increasing age. Note – NO cut-off! ($n = 613$). (Taken from England and Wales Biliary Atresia database). (**b**) Actuarial native liver survival curve (median (±95% CI)) for biliary atresia ($n = 867$)

absence of any acute obstruction". This allows us to exclude the dilated CBD secondary to choledocholithiasis and strictures secondary to chronic pancreatitis, for instance. Similarly, while many CMs present with jaundice and biliary obstruction, it is obvious that previously their function was unimpaired for much of the subject's life in the presence of clear morphological change.

Aetiology

Most CMs appear in some way to be of congenital origin though the actual mechanism itself is obscure.

There are two competing hypotheses:

1. *Pancreatic Reflux*

An intrinsic part of most examples of CM complex is an abnormal pancreatobiliary junction. Normally the pancreatic and bile ducts open separately within the wall of the duodenum at the ampulla of Vater achieving biological separation of bile and pancreatic juice. In most patients with CM, duct confluence occurs within the head of the pancreas, outside the duodenal wall resulting in a common channel that allows free intraductal mixing of both types of secretion [68, 69].

Donald Babbitt, an American radiologist, proposed that this reflux of presumably activated pancreatic juice could damage the wall of the bile duct causing weakness and then dilatation [70]. There are a number of experimental animal models which have tried to replicate the effects of pancreatic enzymes on bile ducts [71, 72], but there has been little actual documented change in the dimensions of the biliary system.

2. *Distal Bile Duct Stenosis*

Almost 25% of CMs can now be detected antenatally on the maternal US. Most of the infants are not actually jaundiced at birth – though some are and here need to be urgently discriminated from cystic biliary atresia. In all of these, the morphological type is a cystic malformation, and in these, though there might be a common channel, there is minimal amylase in bile (implying no reflux) and often a very definite abrupt change and stenotic distal bile duct segment. Furthermore, animal models involving ligation of the distal bile duct [73] produce obvious cystic change.

To try and resolve some of these questions, we performed a series of studies looking at the relationship between age at presentation, modes of clinical presentation, bile duct pressure (as measured at operation), levels of amylase in the bile (as a marker of reflux) and the histological appearance of the resected choledochus [69, 74, 75]. This showed there is a remarkable inverse relationship between pressure and amylase – the higher the pressure, the lower the amylase and that increasing histological epithelial injury and damage are found in those with higher pressures and very obviously not with high amylase levels (Fig. 59.10).

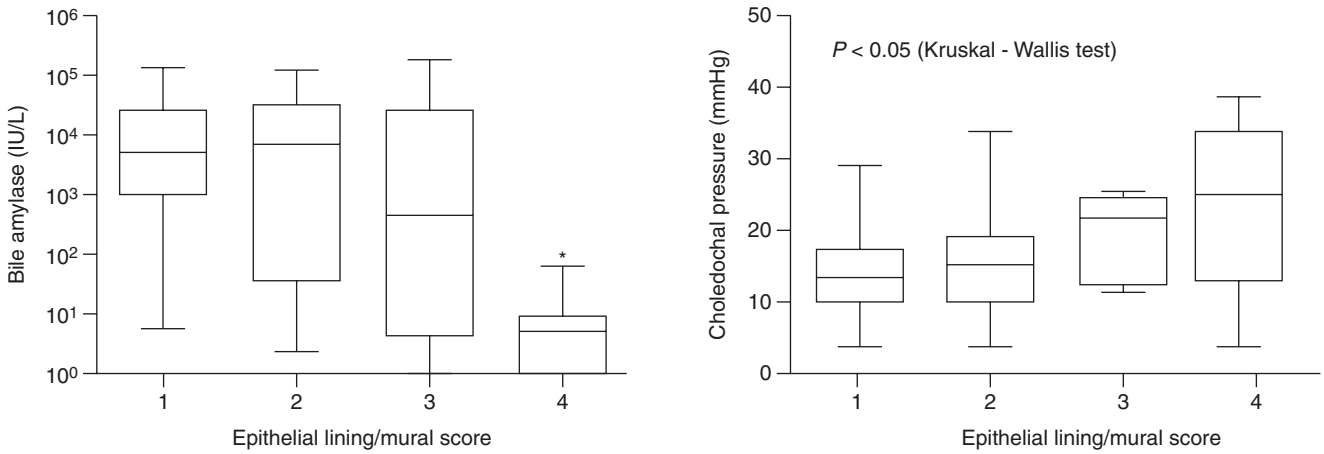

Fig. 59.10 Relationship between biliary amylase, choledochal pressure and epithelial histology. Levels of biliary amylase (**a**) (as a surrogate of pancreatic reflux) and in situ choledochal pressure (**b**) in 73 children with choledochal malformation. The Y axis (epithelial lining/mural score) uses a semiquantitative score for biliary epithelium where 0 = normal, 1 = minimal focal hyperplasia and chronic inflammation, 2 = mild chronic inflammation, 3 = pronounced hyperplasia and moderate chronic inflammation and 4 = epithelial loss, bile impregnation and biliary necrosis. (Extracted from Ref. [59])

Classification

The original Alonso-Lej classification (types 1, 2 and 3) [66] has been modified most notably by Takuji Todani, a Japanese surgeon, by adding the concept of multiple dilatation (type 4) and isolated intrahepatic dilatation (type 5) [76]. The King's College Hospital classification (Fig. 59.11), which has been in use for over 30 years, simplifies the Todani classification into types 1C and 1F (depending on the predominant appearance as cystic or fusiform) and limits type 4 to the combination of intra- and extrahepatic dilatation but again incorporating a cystic or fusiform morphology [77]. This classification has been the basis of our attempts to define pathophysiological characteristics to each type [75, 77–79]. Other workers have emulated this simpler approach.

We also prefer to use the generic term *choledochal malformation*, rather than the very specific term choledochal cyst, since not many of the described dilatations actually appear as a "cystic" (i.e. spherical or globular) entity. The principal variants of extrahepatic dilatation (type 1) making up about 80% of all cases are either *cystic CM (type 1c)* or *fusiform CM (type 1f)*. The former typically has a natural demarcation at either end (Fig. 59.12a), while the latter is much smaller in diameter but merges imperceptibly with a common channel distally or the bifurcation proximally. The only other common variant (*type 4*) is either of the foregoing extrahepatic dilatation (*4c or 4f*) together with significant intrahepatic biliary dilatation – sometimes this is because of actual obstruction with a swift return to normal calibre after surgery, but in others it may appear as an intrinsic feature of the condition (Fig. 59.12b) [79]. Of the remaining variants, *types 2 and 3* are rarely seen in children. The former can be likened to a diverticulum of the CBD, the latter a localised dilatation of the CDB as it transits the wall of the duodenum (a.k.a. choledochocele). *Type 5 CM* refers to usually solitary intrahepatic biliary cystic lesions. Most of these are detected incidentally and can be left alone.

Jacques Caroli, a French gastroenterologist and prolific author, described a number of intrahepatic biliary pathologies which carry his name [80, 81]. The term Caroli disease is usually applied to ectasia or segmental dilatation of the larger intrahepatic ducts (typically the left hepatic duct system) without any other extrahepatic manifestation and is usually sporadic. Caroli syndrome describes a condition in which there are multiple, discrete small yet saccular dilatations of the intrahepatic bile ducts with almost invariably hepatic fibrosis and usually renal disease. This is generally inherited in an autosomal recessive manner [82–84], and there is a large overlap with congenital hepatic fibrosis, polycystic kidney disease (both autosomal dominant and recessive types), etc.

Epidemiology

CMs can present at any point in the life cycle from an antenatal scan to the postmortem table, which makes the true incidence hard to define. If biliary atresia is used as a guide for a condition where the incidence is known (e.g. 1 in 17,000 in the UK) and the ratio of the two conditions presenting in infancy is taken from a specialist hepatobiliary unit, then an approximate figure of about 1 in 100,000 live births may be suggested [85]. Nevertheless, the incidence is much higher in Asian populations, and virtually all of the large series of this has been reported from Japan [86, 87] and now increasingly China [88, 89] with very few series from

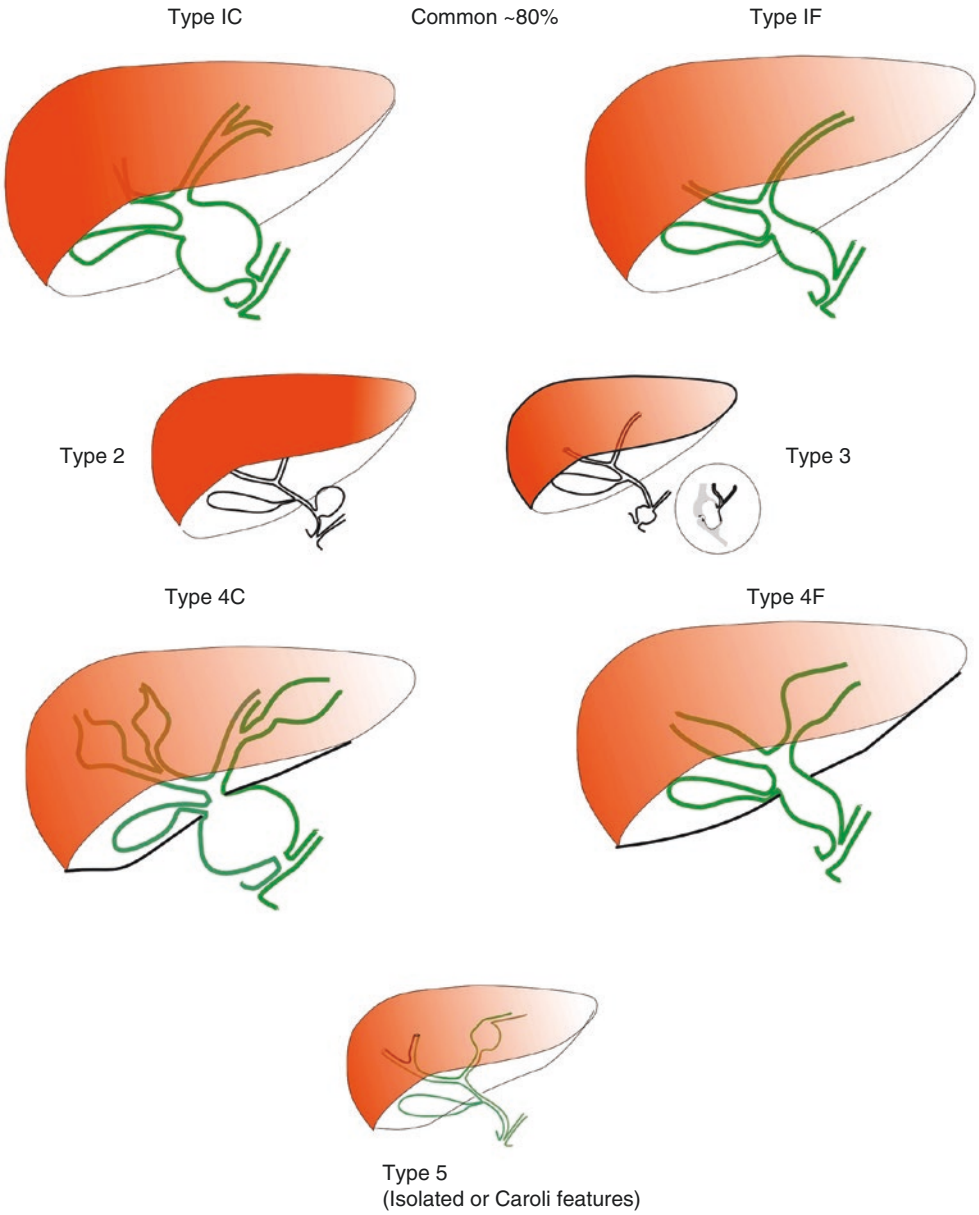

Fig. 59.11 King's College Hospital classification for choledochal malformation

North America [90, 91] or Europe [92]. There is a marked female predominance (4:1) [92], but not much in the way of an identifiable hereditary element. However, isolated examples of familial occurrence in siblings and twins have been reported [93, 94].

Clinical Features

CM can present at any age, but more than 90% will present within the first decade [92]. Clinical manifestations do differ according to the age of onset. Typical presenting symptoms in the newborn mimic biliary atresia and specifically cystic biliary atresia with obstructive jaundice, acholic stools and hepatomegaly, depending on the degree of obstruction. These sometimes have advanced liver fibrosis depending on the length of the period of obstruction. As described above, some will present with an abnormal antenatal ultrasound scan although it will quickly clear their neonatal jaundice.

Older infants and toddlers then tend to present with jaundice and may well be found to have an upper abdominal mass, and most turn out to have a type 1c CM. If obstructive features are ignored, then chronic liver disease may result, and cirrhosis is possible though seemingly not as common as in some older series [92].

Recurrent abdominal pain becomes a feature later on and may be due to an obstructed high-pressure system or actual recurrent pancreatitis. This is usually pathologically mild, oedematous and short-lived and associated with hyperamylasemia. This scenario is usually associated with the type 1f

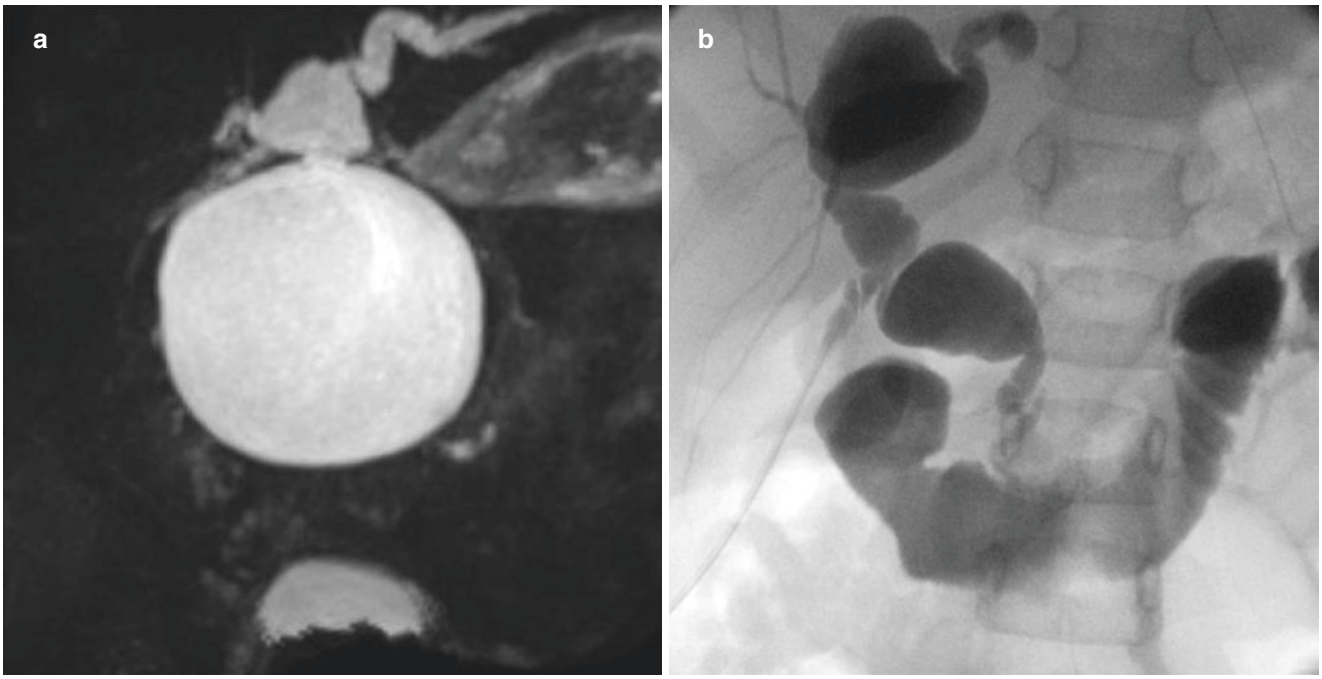

Fig. 59.12 Types of choledochal malformation. (**a**) MR scan (T2 weighted) showing "classical" type 1c choledochal malformation (CM) with a degree of left intrahepatic dilatation. Infant presented antenatally with abnormal maternal ultrasound scan. Note clear demarcation of dilatation both proximally and distally. (**b**) Operative cholangiogram of type 4 choledochal malformation with fusiform extrahepatic appearance and marked segmental dilatation of intrahepatic left hepatic duct. The distal duct gradually tapers towards a common channel (filled with debris) inserting into the third part of the duodenum. A 4-year-old child who presented with acute pancreatitis

CM. Sometimes investigation shows a common channel, presenting features of pancreatitis but not much in the way of biliary dilatation. This has been termed a *forme fruste* CM or more simply common channel syndrome (Fig. 59.13).

Perforation of a high-pressure system is perhaps surprisingly uncommon (<5%), and in these the clinical scenario may mimic spontaneous biliary perforation in infancy [95, 96] or appendicitis in the older child. Bile leakage is usually confined to the retroperitoneum and tracks down the paracolic gutter.

There is a risk of carcinomatous change in long-standing CM which will manifest later in adulthood and exceptionally rarely in adolescence. Up to 10% of adult series have established malignant change at laparotomy [78, 97, 98]. In a Japanese series of 94 patients (adults and children) with excised choledochal malformation, four later developed malignancy. The age at detection ranged from 27 to 65 years with the malignancy arising both in the liver and the head of the pancreas [97]. Similarly, Lee et al. described 80 patients with biliary malignancies from a large Korean multicentre series of 808 adults [98]. Of these most ($n = 74$) were evident at initial presentation and laparotomy while six presented 4 years after their previous choledochal excision. What is not known is what the real long-term risk is in those who have

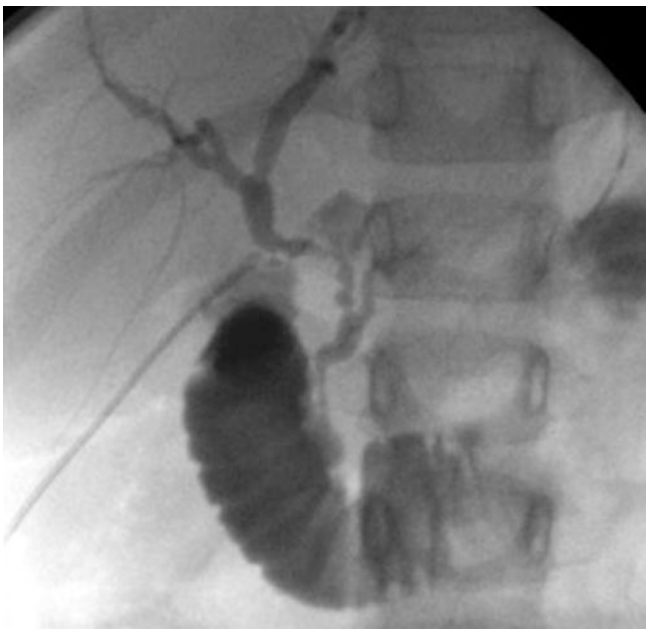

Fig. 59.13 Common channel syndrome. An 8-year-old girl with long history of recurrent acute pancreatitis requiring an ERCP to diagnose a common channel, with presumed reflux of the bile into the pancreatic duct. She was cured by disconnection of biliary and pancreatic ducts and Roux loop hepaticojejunostomy biliary reconstruction

had their definitive excisional surgery in childhood. We tried to identify these on the basis of the histological characteristics of the excised biliary tract (including Ki67 expression), levels of CA19-9 and amylase in bile but there were no consistent features [99].

Diagnosis

A choledochal cyst was first diagnosed antenatally using ultrasound by Dewbury et al. from Southampton in the UK in 1980 [100]. Since then, up to 25% of CM (in the UK at least) are diagnosed antenatally from as early as 15 weeks' gestation, and these are almost invariably types 1c or 5 CM [101]. CM may be confused with duodenal atresia, cystic biliary atresia, ovarian cyst, duplication cyst and mesenteric cyst. In this scenario, it is most important to exclude the possibility of cystic BA who requires urgent Kasai portoenterostomy [11]. If there is clinical doubt, then a dynamic radio-isotope scan (e.g. technetium^{99}-labelled iminodiacetic acid, HIDA scan) will confirm the non-obstructing CM, where surgery can be deferred to about 3–4 months.

Postnatally, US is the initial diagnostic modality of choice, allowing for precise measurements of intra-/extrahepatic duct dilatation and identification of stones/sludge. MRCP has superceded the use of CT and for the most part ERCP for pre-operative anatomical delineation of the pancreaticobiliary tract. Three-dimensional reconstruction images are easily obtained, although sedation may be required in infants and small children.

Functional assessment of CM may be shown using a dynamic radio-isotope scan which can show baseline parenchymal hepatocyte uptake together with the pattern and degree of bile excretion – important if not considering surgery. This may also be useful in diagnosing choledochal perforation. ERCP may still be required when there is diagnostic uncertainty over the nature of the pancreaticobiliary junction and common channel, particularly in those with minimal biliary dilatation and often with a presenting feature of pancreatitis.

Biochemical liver function tests may be normal or show evidence of biliary obstruction. Amylase levels may be elevated during episodes of abdominal pain suggestive of actual pancreatitis. A prolonged INR secondary to cholestasis should be corrected with intravenous vitamin K.

Surgical Management

Open surgery is still very much the standard in most centres. For the common types (type 1c, type 1f and type 4), this consists of excision of the dilated part of the extrahepatic biliary tree, clearance of debris and stones from any dilated intrahepatic ducts (best achieved with on-table cholangioscopy), clearance of any common channel debris (± transduodenal sphincteroplasty) and a reconstruction end-to-side hepaticojejunostomy using a long (40–50 cm) Roux loop. Despite often quite alarming intrahepatic dilatation in type 4 CM, the usual best course is simply excision of the extrahepatic segment with a fastidious approach to ensuring segmental drainage and cautious follow-up. Most ducts will reduce in size, particularly in children which in itself suggests the primary aetiological role of elevated intrabiliary pressure [77, 79].

The first laparoscopic cystectomy and reconstruction of a 6-year-old female with a type 1c malformation was reported by Farello et al. in 1995 from Schio, Italy [102], and has become an option in some parts of the world. The largest series are either from China or Vietnam and now number well over 200 children in each [88, 103]. The technical skills required are high, and a large throughput is important in minimising complications. The standard Roux loop reconstruction is usually carried out by extracting the small bowel through an enlarged umbilical incision though the hepaticojejunostomy is performed intracorporeally. A controversial innovation has been to discard the hepaticojejunostomy because it is difficult and perform a hepaticoduodenostomy which is easier instead [104]. This short cut may be expedient, but the long-term effects of this may be poorer. Cholangitis and biliary gastritis are both significantly more common using this so-called "physiological" alternative [105]. The other alternative, only available in certain centres of course, is robotic surgery which may facilitate the bile duct anastomosis [106], though even here the postoperative stay is no different to those treated more conventionally.

Excision of the diverticulum is probably all that is needed in the rare type 2 CM as long as normal unobstructed distal bile flow can be demonstrated radiologically [107]. Large choledochoceles (type 3 CM) can be removed transduodenally, whereas smaller choledochoceles can be treated by sphincteroplasty or endoscopic sphincterotomy, although admittedly most reported experience is in adults [108].

Most type 5 CMs are isolated, asymptomatic and picked up incidentally with US. They can probably best be treated conservatively with serial US to try and detect any complications such as stone formation [101]. In those with symptomatic or complicated Caroli-like intrahepatic dilatation, resection should be considered particularly if unilobar. The treatment of Caroli's syndrome may be complicated, and occasionally liver transplantation may be considered.

Postoperative Management

Intravenous fluids and nasogastric aspiration are continued until return of bowel function, usually on day 2 or 3 after the operation. Oral feeding is recommenced after the fluid from the nasogastric tube becomes clear.

Complications

Complications are uncommon but may include bleeding, adhesive small bowel obstruction, anastomotic leakage and leakage from the pancreatic duct. Anastomotic leakage may be treated conservatively, particularly if this has followed a difficult and challenging anastomosis. Abdominal drainage is key, and if there is no obstruction to a functioning Roux loop, then it will settle. Pancreatic leaks are less common but more challenging, particularly if the ampullary sphincter is still intact. Consideration should be given to endoscopic ERCP and stenting if a conservative trial of abdominal drainage, intravenous antibiotics, nasogastric decompression and parenteral nutrition fails.

Anastomotic stricture usually followed by recurrent cholangitis and intrahepatic stone formation are late complications [109]. Cholangitis implies a mechanical problem and should be aggressively investigated. Strictures or persistent intrahepatic dilatation can be treated by radiological intervention with surgery reserved for failure. Recurrent pancreatitis implies obstructive problems with the retained common channel. MRCP, but more likely ERCP, should be diagnostic and, in the latter's case, may be therapeutic with endoscopic channel clearing or stenting.

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