Biliary Atresia and Other Congenital Disorders of the Extrahepatic Biliary Tree

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Key Points

- Biliary atresia, congenital choledochal malformations and spontaneous bile duct perforations are the usual surgical causes of obstructive jaundice in infancy.
- Novel mechanisms (immune dysregulation, genetic aspects, viral infections) have been considered in the pathophysiology of biliary atresia.
- The diagnosis of biliary atresia is made with imaging, laboratory tests and (usually) liver biopsy. Infants should be evaluated as soon as possible because the success rate of Kasai operation diminishes with an older age at surgery.
- The treatment of biliary atresia and congenital choledochal malformations always involves surgical correction.
- Biliary atresia is a rare disease, but it is responsible for the highest proportion of liver transplantations performed in children and young persons.

Research Required in the Field

- National databases with rigorous follow-up on cases of biliary atresia to assess national outcomes with this disease and facilitate collaborative multicentre studies and frame future research initiatives.
- Utilization of next-generation screening of genome of syndromic forms of biliary atresia.
- Evaluation of effectiveness and safety of corticosteroids after Kasai operation.
- Exploration of new therapeutic strategies (e.g. antiviral therapy, anti-fibrotic therapy, stem cell therapy).

7.1 Part I: Biliary atresia

7.1.1 Introduction

The most frequent cause of surgical jaundice in infants is biliary atresia (BA) and dates from the time of birth in the vast majority of cases with presentation in the first few weeks of life. It is the end result of a destructive sometimes inflammatory process with unclear origins affecting intra- and extrahepatic bile ducts.

The earliest reference to what was probably an infant with BA was reported in 1817 by Dr. John Burns as an "incurable state of the biliary apparatus" [1]. Towards the end of the nineteenth century, John Thompson in 1892 made the first accurate description of the clinical features and post-mortem findings in an infant who appeared to have no common hepatic duct [2].

Treatment is entirely surgical being an attempt to restore bile flow from the native liver in the first instance and is known as a Kasai portoenterostomy (KPE), reserving liver transplantation for those where this approach is unsuccessful. The first surgical successes were probably described by the Boston surgeon William E. Ladd in 1935 in a series of patients with con-

M.D. dedicates this work as always to Georgina.
P.B. dedicates this work to Valentina, Paolo and Bianca.

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genital biliary obstruction [3]. Typically he anastomosed dilated proximal parts of the obstructed biliary tree with the intestines so restoring some kind of continuity [3]. It, however, became clear that in most infants recognized to have BA, there was no proximal dilated remnant to find irrespective of how high one dissected into the porta hepatis. These were described as having "uncorrectable" BA. This dire situation really did not change until the work of Morio Kasai became more widely appreciated outside of Japan [4, 5]. In the late 1950s, Morio Kasai first began simply to transect high in the porta hepatis and join this up to a mobilized Roux loop even if there were no visible ducts present. In a proportion this enabled restoration of bile flow and clearance of jaundice.

7.1.2 Epidemiology

There is a marked variation in geographical incidence of BA ranging from about 1 in 5–10,000 live births in Japan, China and Taiwan [6] to about 1 in 15–20,000 in Europe [7], England and Wales [8] and North America [9]. There is a female preponderance in those considered to have a "developmental" origin but is near to equality in the majority with isolated BA [10, 11]. The incidence of biliary atresia splenic malformation syndrome (BASM) is rarely reported in Asian series but accounts for about 10% of European and North American series [12–14].

7.1.3 Aetiology and Pathogenesis

BA should be thought of as a number of diseases with a similar appearance by the time of presentation (Fig. 7.1). There appears to be a number of different aetiological mechanisms and phenotypes, and at least four different variants of BA can be distinguished based on clinical or laboratory features [15, 16].

1. Associated with other congenital anomalies and typically **BASM.**
2. **Cystic BA**, i.e. extrahepatic cyst development within an otherwise obliterated biliary tree.
3. Viral-associated BA—Particularly **CMV-associated (IgM-positive) BA.**
4. **Isolated BA,** i.e. no features of the above.

It is highly likely that BA with other congenital anomalies and cystic BA have in utero origins and can be regarded as "developmental" variants. BASM is associated with extrahepatic abnormalities such as polysplenia or asplenia; cardiovascular anomalies; situs inversus, malrotation or non-rotation; pre-duodenal portal vein; and absence of the inferior vena cava with azygous continuation. About 1/3 have situs inversus and have been quoted as examples of "laterality defects", strongly suggesting their origin within the early embryonic phase of development.

Given this it also seems probable that there is a genetic or epigenetic aetiology [10, 11, 17]. Genetic mouse models exist with defects of laterality and failure to form normal bile ducts, though as yet the putative gene defects themselves (*CFC-1, INV* et al.) have yet to be identified in humans. Our own series identified maternal diabetes as a key clinical association possibly acting in an epigenetic manner. Other variants include an association with other major congenital malformations such as oesophageal or jejunal atresia but without any sign of laterality defects (<2% overall) [18].

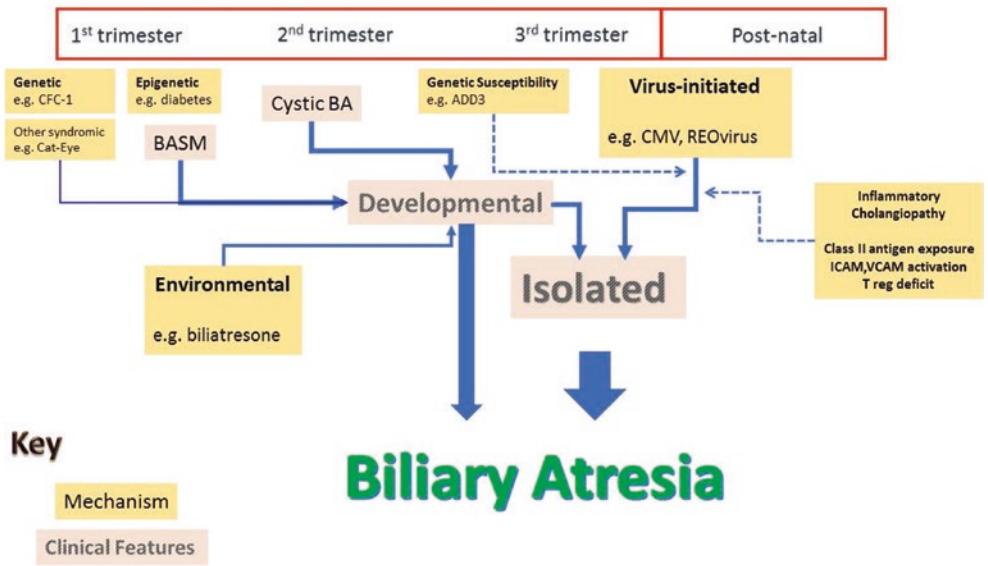

Fig. 7.1 Schematic illustration of possible pathophysiology of biliary atresia

Cystic biliary atresia (Fig. 7.2) is seen in about 5–10% of most large series, whatever the geographic origins. The cyst may contain bile or mucus implying in the former case onset after establishment of continuity between intra- and extrahepatic bile ducts [16]. Redkar et al. [19] showed that many examples of cystic BA can be detected by ultrasound during prenatal scanning and that they have a good prognosis post-surgery.

Most infants with BA will simply appear as isolated anomalies with a negative serological profile for common hepatotropic viruses for which we have no evidence of a specific cause. It is controversial whether infants born with a normal biliary tree can be damaged secondarily after birth, although much experimental research with animal models is based on this assumption. Harpavat et al. from Texas, USA, retrospectively analysed blood obtained from their BA series on day 1 or 2 of life and showed that all had elevated levels of conjugated bilirubin at this point implying that all had biliary obstruction at the time of birth [20].

Still, there have been many theories regarding pathogenesis of isolated BA. The viral-induced, immune or autoimmune-mediated inflammatory obstruction of the biliary tree has been the most commonly accepted theory but is most entirely based on experimental laboratory observations in mice. We have described infants with a different clinical and laboratory phenotype (later presentation, an inflammatory appearance in liver histology and a Th1-dominant T cell infiltrate) in our clinical series associated with CMV-associated (IgM-positive) serology [14–21], but that doesn't automatically mean cause and effect.

BA is as an occlusive pan-ductular cholangiopathy affecting both intra- and extrahepatic bile ducts. The most common pathological classification divides biliary atresia into three types based on the most proximal level of occlusion of the extrahepatic biliary tree (Fig. 7.3).

In Type 1, a biliary lumen exists from the liver to the common bile duct which is atretic, and many are associated with cystic change; in Type 2, the biliary lumen extends to the common hepatic duct which is atretic. In both types there is a degree of preservation of structure in the intrahepatic bile ducts, but they are still irregular although not dilated (a key distinction from congenital choledochal malformation). Type 3 is the most common (>95% of all cases) in which there is no apparent connection and a "solid" proximal bile duct remnant at the level of the porta hepatis. Type 3 intrahepatic bile ducts are inevitably grossly abnormal with myriad small ductules coalescing at the porta hepatis, which can be accessed at KPE. Sometimes this can be visualized radiographically as a "cloud".

Extrahepatic cyst formation may also be evident containing clear mucus or bile and therefore may be described as Type 3 or 1 (CBA), respectively.

Liver histology shows features suggestive of "large duct obstruction" with oedematous expansion of the portal areas, ductular proliferation and the appearance of bile plugs. There is in some a marked inflammatory aspect with infiltration of activated mononuclear cells, such as CD4+ T cells and NK cells. As the disease progresses, monocytes/macrophages also appear prominent with progressive bridging fibrosis between portal areas. The extrahepatic remnant in Type 3 BA is characterized by a multiplicity of microscopic bile ductules embedded within a fibro-inflammatory stroma—most evident at the level of the porta hepatis. Even in these the gallbladder and distal common bile duct may look completely normal, though the former contains clear "mucus".

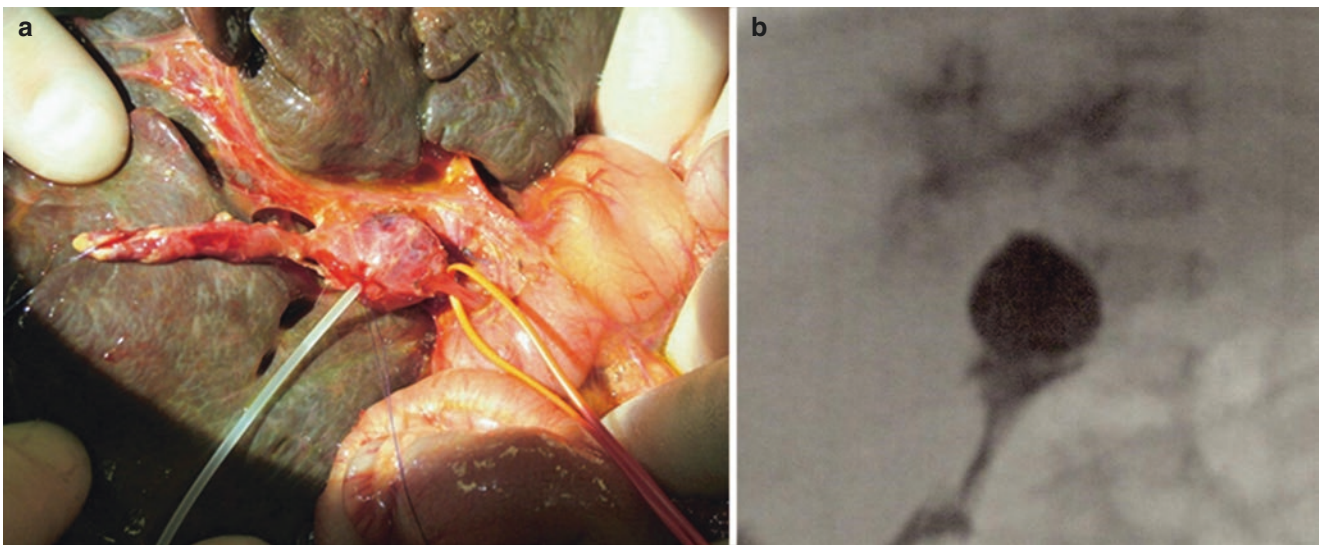

Fig. 7.2 Cystic biliary atresia: 10-mm-diameter bile-containing antenatally detected cyst and cholangiogram showing presence of and communication with primitive, disorganized ("cloud-like") intrahepatic duct system

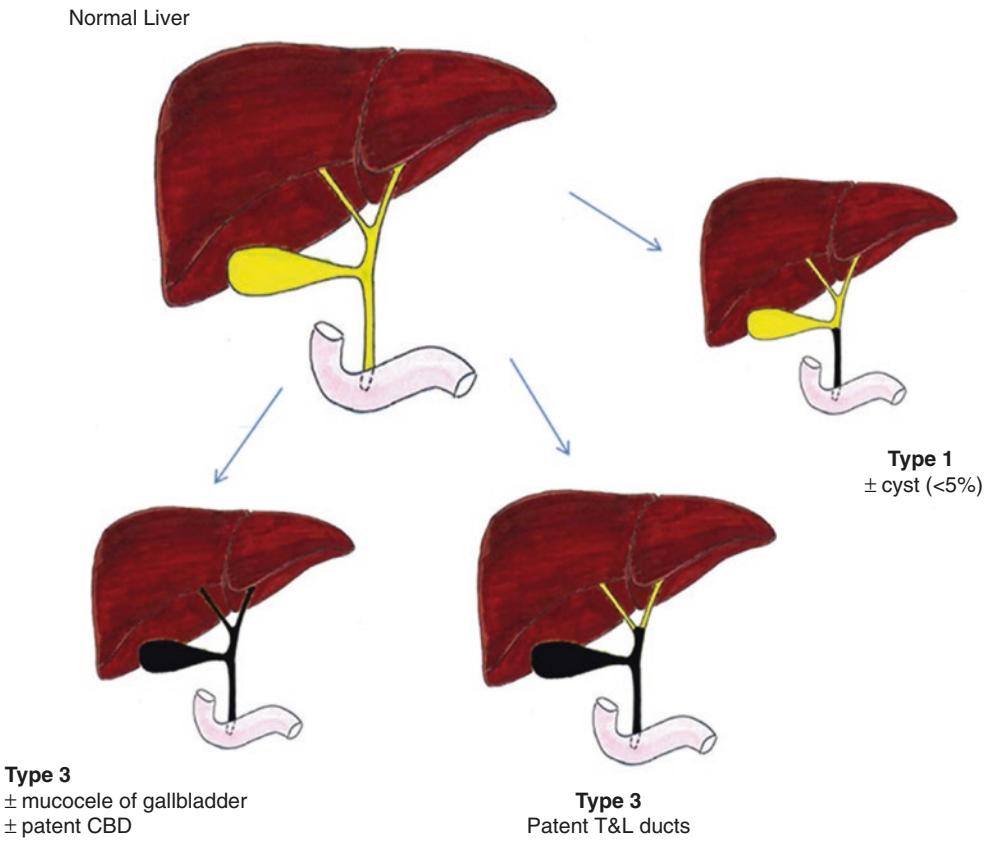

Fig. 7.3 Pathological classification of biliary atresia (NB atretic bile ducts shown in black)

A pro-inflammatory molecular profile was reported in a large-scale gene expression analysis of liver biopsies from infants with BA. This study suggested a genetic footprint in which genes involved in the Th1 helper cell response were activated at an early stage, with simultaneous but transient suppression of markers of humoral immunity [22].

A novel mechanism of immune damage has been suggested by Muraji et al. [23] based on the observation that male BA infants have a threefold increase in maternal origin cells in their livers. These were later shown to be maternal origin chimeric CD8+ T cells and CD45 NK cells and certainly appear capable of initiating immune cholangiolar damage. This has been termed *maternal microchimerism*, and it may explain why the destructive process seems time-limited and most potent shortly after birth.

Recently an intriguing explanation of outbreaks of biliary atresia in animals has been advanced demonstrating a possible environmental cause which may have human implications. Sheep farms around the Burrinjuck Dam, New South Wales, Australia, reported [24] recurrent outbreaks of biliary atresia in lambs where their pregnant mothers had been allowed to graze on the foreshores of the dam which had become exposed to drought conditions. It appeared that a particular weed known as the red crumbweed (*Dysphania glomulifera* subsp. *glomulifera*) in these conditions had proliferated and was the major source of maternal nutrition. In later years whenever the exact combination of exposed foreshore, weed proliferation and grazing pregnant livestock occurred then affected offspring were born.

This concept was further developed in the laboratory using the popular zebrafish model. In this the genome can be manipulated; organ development can be tracked in vivo because the larvae are transparent and furthermore they have a short lifespan and a fully developed biliary system by 5 days postfertilization. Potential hepatotoxic compounds derived from the various isoflavonoids found in the red crumbweed were tested in this zebrafish model. One, now known as **biliatresone**, caused biliary maldevelopment [25] and provided a chemical environmental explanation to the Burrinjuck conundrum.

Is this possible in humans? It appears highly unlikely that it results from maternal exposure to this particular weed although there may be similar compounds or metabolism of non-toxic precursors such as beta-vulgarin found in more common plant foods such as sugar beet, beetroot and chard [26].

In conclusion, the aetiology and pathogenesis of BA remain a land ripe for discovery with several intriguing possibilities for the different clinical phenotypes on show.

7.1.4 Clinical Features and Diagnosis

Conjugated jaundice is the key feature of BA. This together with pale stools and dark urine in an otherwise healthy infant should really set alarm bells ringing (Fig. 7.4).

Such infants despite the absence of gastrointestinal bile usually thrive initially, masking the serious underlying cause of what is after all a common observation in neonatal life, jaundice, and deceiving the child's medical advisers. Recognition that jaundice persisting after 2 weeks in a term infant is not normal should encourage suspicion and further examination of stool and urine. The latter at this age should be colourless and should not stain the nappy [27].

Screening programmes have been developed in countries such as Taiwan and parts of Japan and, nearer to home, in parts of Switzerland and the Netherlands. These rely on stool colour observation by the parents and return of a completed stool colour card distributed to all mothers. They have reported a remarkable improvement in the time it takes to diagnosis BA where there had been delays. Some European countries such as Switzerland or regions such as North Netherlands are also practising screening though the results have not been published.

In all other countries, late presentation of infants with established cirrhosis is still common, beset by diagnostic inertia and confusion particularly with breast-fed jaundice.

The physical signs, apart from jaundice, in the first weeks of life may be minimal and consist only of soft hepatomegaly. Late signs include failure to thrive, ascites and cutaneous signs of chronic liver disease with splenomegaly. In some infants, the actual presenting feature is fat-soluble vitamin K deficiency leading to coagulopathy and bleeding. Sometimes this is innocuous gastrointestinal haemorrhage but in some can be catastrophic and intracranial.

The biochemical characteristics of BA include conjugated (direct) hyperbilirubinaemia, raised hepatocellular enzymes, raised alkaline phosphatase and γ-glutamyl transpeptidase, but there is a significant overlap with many other causes of neonatal conjugated jaundice, and no test is specific.

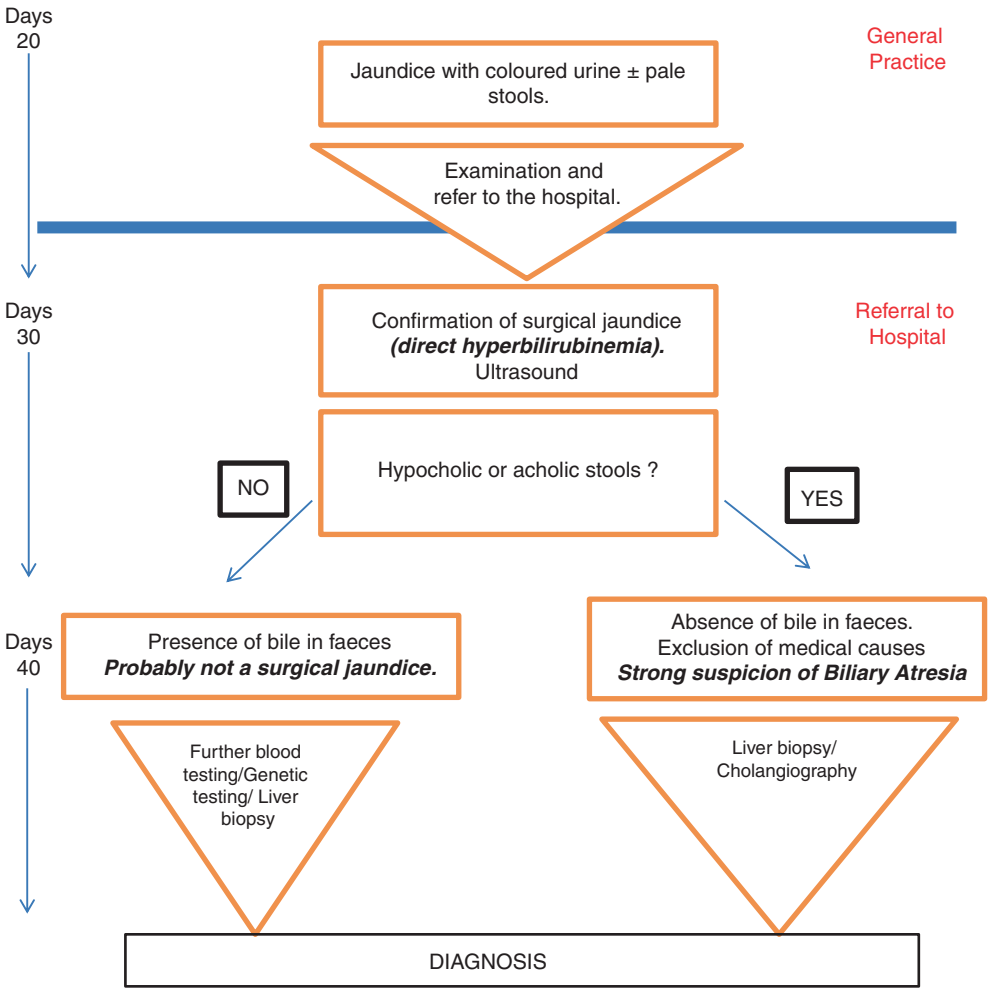

Fig. 7.4 Flow chart for diagnosis of biliary atresia

Ultrasonography (USS) is usually the next step. This typically shows absence of biliary tract dilatation with non-visualization of the gallbladder. One feature that has been suggested as specific is the so-called triangular cord sign illustrating the cone-shaped periportal fibrous mass cranial to the bifurcation of the portal vein [28].

There is no single pathognomonic preoperative finding of BA, but reasonable suspicion necessitates progression to more invasive tests. In our practice percutaneous liver biopsy after exclusion of medical causes of cholestatic jaundice (e.g. α-1-antitrypsin deficiency, Alagille's syndrome and neonatal hepatitis) is then indicated. Negative USS and positive histology results establish the correct preoperative diagnosis in more than 85% of cases of BA [29]. Key histological features might include bile duct proliferation, a small cell infiltrate, portal fibrosis and absence of sinusoidal fibrosis [30].

A 24-h duodenal aspiration and analysis for bile have been used for diagnosis in some Asian centres, but its accuracy has never been published. Other non-invasive tests such as radionuclide scans using a variety of technetium-labelled imino-diacetic acid derivatives are now less commonly used because discrimination between medical and surgical causes can be poor. The use of endoscopic retrograde cholangiopancreatography (ERCP) is possible in infants but is currently confined to highly specialized centres [31]. In our experience, infants with equivocal biopsy results undergo ERCP, although it should be noted that this diagnosis depends crucially on failure to show a biliary tree, and hence appropriate experience and judgement are essential. Furthermore there is currently a dearth of appropriately sized endoscopes available with manufacturers pulling out of production, and this doesn't bode well for being able to continue with this method in the future.

Operative visualization of biliary tree at laparotomy or laparoscopy with on-table cholangiography remains "the last resort" when all non-invasive methods have finished.

7.1.5 Treatment

In most centres and in most infants, the usual management of BA is a surgical attempt to restore bile flow using the Kasai portoenterostomy (KPE) technique [4, 5]. If this fails for one reason or another and if facilities are available, then liver transplantation should be considered. The aim of KPE is to restore, albeit imperfectly, the residual intrahepatic biliary system with the gastrointestinal tract and abbreviate any ongoing tendency to liver fibrosis.

The preoperative management includes correcting the coagulopathy and maybe an antibacterial bowel preparation. Perioperative antibiotics should be effective against aerobic and anaerobic flora.

Initially, the diagnosis is confirmed through a limited right upper quadrant muscle-cutting incision, allowing access to the gallbladder. A cholangiogram may need to be done, but as the first thing one usually sees is an atrophic gallbladder with no lumen, then this may be actually impossible, and the appearance in itself should be regarded as enough of a positive sign to proceed further. This may not be possible in some simply because the gallbladder has no lumen—but this, in itself, is indicative of BA and allows progression. Neonatal sclerosing cholangitis or various hypoplastic biliary appearances (typically seen with Alagille's syndrome) can be seen in some cholangiograms showing patency with proximal intrahepatic ducts. Little more can be done in these circumstances and surgery may be terminated.

Although visible bile-containing ducts may be evident in Type 1 or 2 BA and a hepaticojejunostomy performed, it is probably better that further proximal tissue is resected completely leading to the need of a portoenterostomy. Sometimes on-table evidence of cirrhosis and variceal change may seem to make a portoenterostomy futile. However this is rarely absolutely predictable, and there are insufficient criteria to confidently decide when a late KPE is too late. Late KPE has been variably defined as age >90, 100 or 120 days, and the reported survival with native liver in these patients is 42% at 2 years, 23–45% at 4–5 years, 15–40% at 10 years and <10% at 20 years. The decision to perform KPE after day 100 may be relevant, as KPE in infants with cirrhosis and ascites may precipitate hepatic decompensation, and the procedure is associated with an increased risk for bowel perforations and biliary complications at the time of LT.

Some authors have found that higher stages of fibrosis, a ductal plate configuration and a moderate to marked bile duct injury at KPE were independently associated with a higher risk of transplantation. Nevertheless there is uncertainty on whether liver histology can predict outcome after surgery as the key determinant is restoration of bile flow, something that is only evident after surgery.

A reasonable working rule might be that in infants older than 100 days primary LT may be considered more judicious (obviously where it is available) particularly if there is clinical and USS evidence of nodularity on the liver substance and moderate to severe ascites [32–34].

If the BA diagnosis is confirmed, we believe that the most consistent and efficient dissection of the porta hepatis is facilitated by mobilization of the liver (Fig. 7.5). This need not involve division of all the suspensory ligaments and can be limited to just the falciform and the left triangular, but this still allows the entire organ to be everted onto the anterior abdominal cavity. The fibrotic remnant of the extrahepatic bile ducts is dissected free, dividing first the common bile duct to allow it to be tracked back to the porta hepatis. It is then transected at the level of the liver capsule. This transected portal plate is then anastomosed to a retrocolic 40 cm jejunal Roux

loop to restore biliary continuity. A liver biopsy is performed at the conclusion of the operation in order to document hepatic histology. The goals of the operation are to restore the bile flow to the intestine, reduce jaundice and halt ongoing liver damage.

Almost 15 years has now passed since Esteves et al. [35] reported the first laparoscopic KPE. Further reports have been published though none has shown any significant advantage over open KPE and in one German study it worsened the outlook [36]. This laparoscopic approach has still not been taken up by the larger centres in Japan, Europe and North America.

The use of steroids is controversial but appealing given the possible role of inflammation in the aetiology of BA. Davenport et al. [37] in the first randomized placebo-controlled trial of oral prednisolone (2 then 1 mg/kg/day in first month) reported definite improvements in early clearance of jaundice but a lack of real effect on final results and need for transplant. The same authors followed this using an open-label trial structure and a higher dose (starting at 5 mg/kg/day) which showed a statistically significant 15% increase in clearance of jaundice compared to control and placebo in those <70 days at KPE [38]. In 2014, Bezerra et al. [39] studied the effects of a 13-week course of steroids on clearance of jaundice with the native liver at 6 months after Kasai. This was multicentre and had an older population than the UK trials, and though the difference between active and placebo groups was also 12–15% because of their lower numbers in the comparison groups, they declared that there was no statistical difference. Nonetheless subsequent meta-analysis has shown statistically significant evidence of benefit of high-dose steroid regimens (Fig. 7.6) [40].

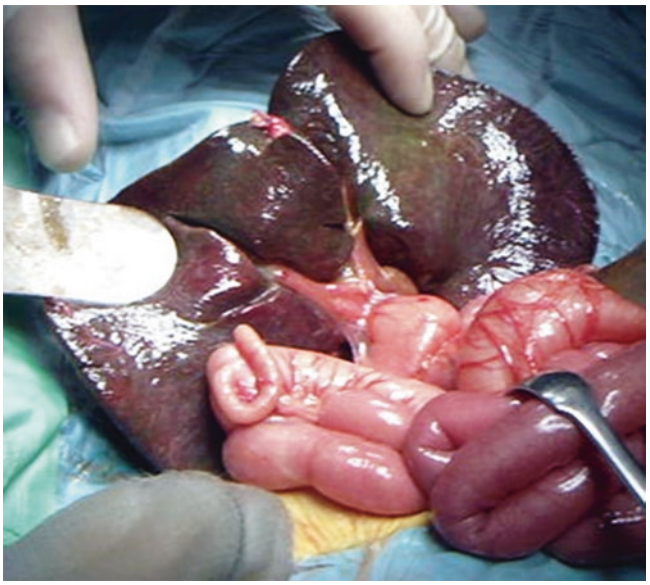

Fig. 7.5 Mobilization of the liver to facilitate porta hepatis dissection in Kasai portoenterostomy

Ursodeoxycholic acid (UDCA) is widely thought to be beneficial but only if surgery has already restored bile flow to reasonable levels. UDCA "enriches" bile and has a choleretic effect, increasing hepatic clearance of supposedly toxic endogenous bile acids and may confer a cytoprotective effect on hepatocytes.

7.1.6 Complications

Ascending cholangitis is the more frequent complication after Kasai portoenterostomy especially in the first postoperative year and is probably due to the restoration of direct communications between intrahepatic bile ducts and the small bowel. Clinical presentation of cholangitis is with fever, jaundice and abdominal pain. Acholic stool and a deterioration in liver function tests should also be present. Early diagnosis is very important to prevent the loss of remaining

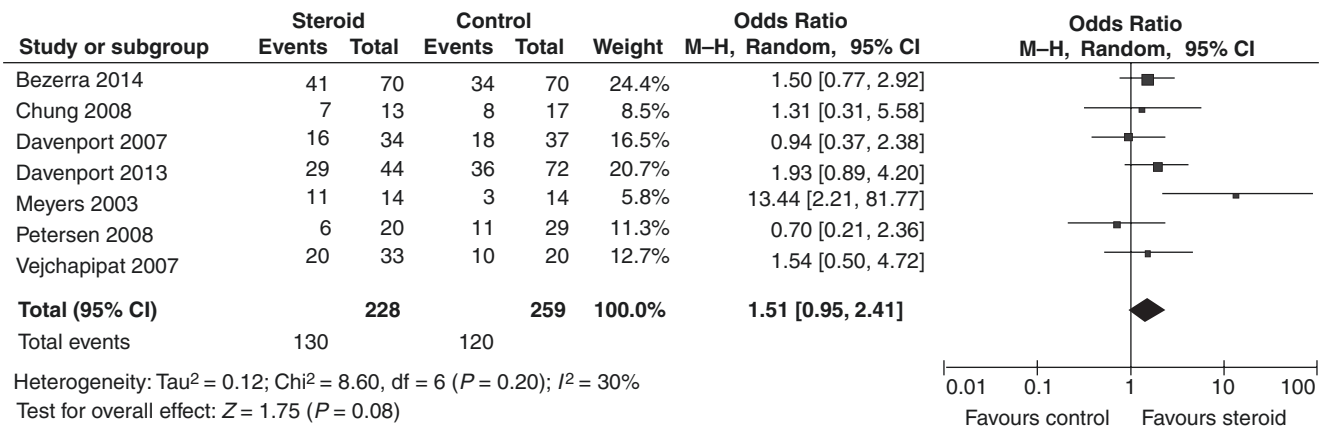

Fig. 7.6 Meta-analysis of steroids in biliary atresia. Forest plot showing improved clearance of jaundice with steroids (reproduced with permission from [24])

patent bile ducts and to preserve the native liver function. Percutaneous liver biopsy may be done to identify the causative organism, but this is uncommon. Cholangitis should be treated aggressively with intravenous antibiotics against Gram-negative organisms.

A prophylactic regimen with oral antibiotics such as amoxicillin, trimethoprim and cephalexin might be considered in all children who have undergone KPE in order to prevent cholangitis. In cases of children with recurrent cholangitis, following clearance of jaundice, liver scintigraphy may detect a Roux loop obstruction. This is important as it is surgically correctable.

Portal hypertension and oesophageal varices are two serious complications after KPE, and they are due to the progressive liver fibrosis causing sustained elevation of portal venous pressure. Progressive hepatosplenomegaly, gastrointestinal bleeding, ascites, encephalopathy and portopulmonary syndrome may all be signs of portal hypertension. Among adult survivors with native liver, the incidence of portal hypertension varies from 50 to 90% [41].

Portal venous pressure is often already high before surgery. Some studies have shown that infants with this early high level of portal venous pressure have worse outcomes in terms of native liver survival and risk for varices and variceal bleeding. Duche et al. also showed that the presence of ascites, serum bilirubin concentration >20 μmol/L, prothrombin ratio <80% and portal vein diameter >5 mm are significant risk factors for bleeding [42]. Although bleeding is unusual before 9 months, each child should probably undergo periodic endoscopic surveillance and endoscopic variceal ligation or injection sclerotherapy if necessary. Sometimes primary prophylaxis as prevention of variceal bleeding may be warranted. Occasionally, emergency treatment of bleeding varices using a Sengstaken tube is necessary. There is a wide variation in estimation of the complications of portal hypertension—from 10 to 60% of patients' transplant-free survival present with at least one episode of gastrointestinal bleeding during 5 years of follow-up [43]. Developing fibrosis and cirrhotic nodules are the natural progression of the liver affected by biliary atresia. Perhaps, one of the most dangerous complications of cirrhosis is the development of hepatocellular carcinoma. Fortunately it seems that only a small percentage of children with BA develop this kind of neoplasm and, in absence of the extrahepatic involvement, liver transplantation is the effective treatment [44].

7.1.7 Prognosis

Several factors may influence the outcome of infants with biliary atresia. Age at surgical intervention remains a critical issue, and it is widely accepted that late age at surgery contributes to a worse outcome in the long term. The age at surgery also reflects on the effectiveness of the referring primary care system and efficacy of the diagnostic process. The current accepted standard in Europe and North America is to perform KPE at the earliest possible age and carried out by an experienced biliary surgeon. The experience of the centre performing the operation also appears as a major prognostic factor. Centralization of hepatobiliary services occurred in England and Wales at the end of the 1990s, and results following this showed significant improvement on national outcome for this disease [45–47] and have been followed by a similar policy shift at least in Northern European countries (Fig. 7.7).

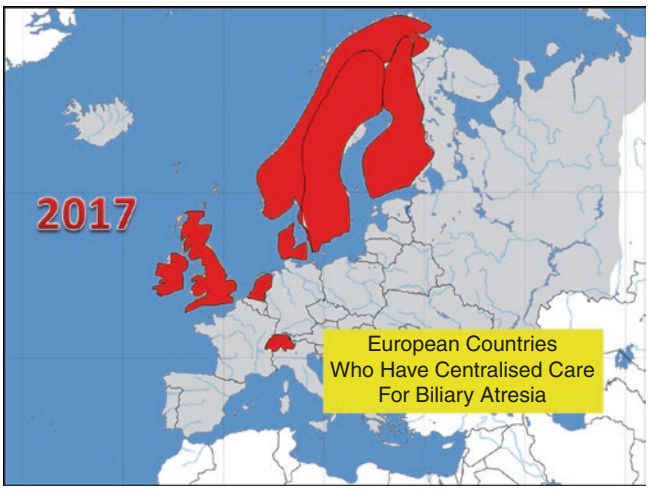

Fig. 7.7 Centralization of biliary atresia centres in Europe

7.1.8 Implications for Liver Transplantation

BA is the most common indication for liver transplantation (LT) in the paediatric population accounting for about half. Optimal timing is crucial to achieve a successful outcome and avoid deaths on the waiting list. The main factor affecting indication and timing of LT is the success of KPE. Children not achieving clearance of jaundice in the first few months after surgery are usually transplanted by 2 years of age. If jaundice has resolved by 3 months after KPE, the 10-year transplant-free survival rate has been shown to range from 75 to 90%, whereas if jaundice persists after KPE, the 3-year transplant-free survival rate is only 20% [48]. In a recent North American study of the Childhood Liver Disease Research Network (ChiLDReN), infants with bilirubin >2 mg/dL (≈34 μmol/L) at 3 months from KPE had diminished weight gain and greater probability of developing ascites, hypoalbuminaemia and coagulopathy and were more

likely to die or require LT [49]. Thus, children who do not demonstrate good bile flow and clearance of jaundice by 3 months after KPE should be evaluated early for transplantation, ideally by 6–9 months of age [50].

Infectious complications may sometimes threaten the life of a child with BA who had a successful KPE. Repeated episodes of ascending cholangitis were associated with a threefold increased risk for early failure after KPE. This complication should prompt listing to LT in case of recurrent episodes despite aggressive antibiotic therapy, multiresistant bacterial organisms, episodes of life-threatening sepsis or severely impaired quality of life due to frequent hospitalizations [51].

Portal hypertension (PH) accompanies the rapid progression of end-stage liver disease in children with a failed KPE, raising the issue of surveillance endoscopy of these patients while awaiting LT. However in most patients, the risk of bleeding starts after the first year of life [52]. Considering that varix treatment is difficult in infants (due to the lack of a suitable banding device), that variceal bleed is rarely associated with death and that in most centres LT is performed by 12–18 months of age, a conservative approach to PH based only on clinical observation in these patients seems reasonable. Despite a much slower course, PH develops almost invariably even after a successful KPE. A study from the USA, analysing 163 children with BA who survived with their native liver to a mean age of 9.2 years, showed that PH could be identified in 67%. Variceal bleeding had occurred in 20% of subjects, although the majority (62%) had only one episode [53]. In Canada and Europe, up to 96% of adult patients with BA had features of PH, with 65% having evidence of varices, 91% splenomegaly and 14% ascites. A French study showed that 99% of BA survivors with their native liver into adulthood had evidence of cirrhosis and 70% had significant PH [41, 54]. Extrahepatic complications of portal hypertension, such as spontaneous bacterial peritonitis, hepatopulmonary syndrome, porto-pulmonary hypertension and spontaneous bacterial peritonitis, represent a clear indication to promptly place the patient on the transplant list [55].

Deciding the best timing to list for LT in a BA patient who had a failed Kasai may be challenging and probably depends more on the transplant programme setting rather than on an individual patient's features. A tool validated in children with chronic liver disease is the paediatric end-stage liver disease (PELD) score. PELD score is calculated based on the age, growth failure, albumin, international normalized ratio and total bilirubin level and is an excellent predictor for the outcome of paediatric LT patients. However, it has been reported that the PELD score in BA patients does not accurately represent the true mortality risk associated with complications of portal hypertension, variceal bleeding, refractory ascites and hepatopulmonary syndrome. The US experience showed that BA patients have a median wait time on the list of 90 days and a median calculated PELD score of 15 at the time of transplant (UNOS data); 15% of children with chronic liver disease have either died on the waiting list or been removed because they were too ill to transplant. These figures are probably related to the fact that in the US network, only approximately 10% of eligible donor livers are split, missing an opportunity to expand access to transplant for BA patients and leading to a high mortality on the list in children younger than 2 years of age [56–58]. This is not the case in countries, such as Italy, where the split technique is widely adopted; thus many left lateral segment grafts are offered to the centres, and the mortality on the list of recipients below 2 years of age is close to 0% [59] (Table 7.1).

Table 7.1 Indications for liver transplantation in biliary atresia

• Failure of Kasai portoenterostomy
–Persistent jaundice
–Recurrence of jaundice
• Late diagnosis: Primary LT
• Failure to thrive despite aggressive nutritional support
• Recurrent/life-threatening bacterial cholangitis
• Recurrent hospitalizations impairing quality of life
• Refractory variceal bleeding
• Hepatopulmonary syndrome
• Porto-pulmonary hypertension
• Significant ascites and episodes of spontaneous bacterial peritonitis
• Hepato-renal syndrome
• Hepatic malignancy

7.2 Part II: Congenital Choledochal Malformation

7.2.1 Introduction

Congenital choledochal malformation (CCM) is a term used to describe biliary malformation where the distinguishing feature is dilatation of some part. Usually and typically these are not actually obstructed to discriminate from situations of biliary dilatation due to intraluminal stones, for instance.

Many CCM are associated with an abnormal union between the pancreatic and distal common bile duct (Fig. 7.8). An example was first described by Abraham Vater in 1723, but there is much about its aetiology and pathophysiology which can still be debated. CCM may cause symptoms at any age but typically present with obstructive jaundice in infants and recurrent abdominal pain often due to pancreatitis in children. Other recognized complications include cholangitis, cholelithiasis and malignant degeneration though this is only really found in adults.

Fig. 7.8 Congenital choledochal malformation with abnormal pancreatobiliary junction (common channel)

7.2.2 Epidemiology

CCM are rare malformations with an incidence in the Western population of anywhere between 1 in 100,000–150,000 births though this is entirely guesswork [60]. It is known to be remarkably higher in Asian populations though the reason is still unclear. There is also a female-male preponderance of up to 4:1, and more than two-thirds of cases are diagnosed in children <10 years of age.

Alonso Lej et al. [60] proposed the first classification for CCM in 1959, describing three types of bile duct dilatation. In 1977, Todani [61] expanded this classification to include intrahepatic and multiple cysts. Our own version of this is a little simpler and is as follows (Fig. 7.9):

- **Type 1** (75%)—extrahepatic dilatation.
  - Predominantly **cystic** dilatation (**1C**), with distinct demarcation at the top and bottom.
  - Predominately **fusiform** dilatation (**1F**), less dilated and more indistinct.
- **Type 2** (<1%)—extrahepatic **supraduodenal diverticulum** of the bile duct.
- **Type 3** (< 1%)—**choledochocele**, a localized dilatation of the intramural duodenal bile duct.
- **Type 4** (20%)—combination of type 1C/F and intrahepatic dilatation.
- **Type 5** (4%)—intrahepatic biliary dilatation.
  - **Caroli's disease:** genetic origin, R and L lobes, liver fibrosis and renal disease (cysts or fibrosis).
  - Isolated intrahepatic dilatation, usually peripheral.

7.2.3 Aetiology and Pathogenesis

The aetiology of CCM, particularly Types 1 (C&F) and 4, is still unclear, although many theories have been proposed. Two deserve wider explanation. The first and oldest would suggest that there is a congenital distal bile duct stenosis which causes increased proximal intrabiliary pressure and dilatation. This is a common scenario in many congenital atresias such as jejunal and oesophageal atresia. The alternative, first suggested by Donald Babbitt, an American radiologist, on the basis of noticing that there was reflux from the bile ducts into the pancreatic duct via the common channel at the time of on-table cholangiography. He surmised that this could go the other way and activated proteolytic pancreatic juice could damage the wall of the bile duct causing weakness and dilatation [62].

Clinical research at King's tends to refute this as an aetiological theory [63–65]. Thus, we have routinely measured choledochal pressure and bile amylase levels (as a surrogate of pancreatic reflux into the biliary tree) at the time of surgery and first showed an inverse relationship between the pressure within the choledochal malformation and bile amylase levels [64, 65]. Most recently, we looked at the histological appearance of the biliary lining in 73 patients with CCM and correlated it with their pressures and bile amylase levels [65]. This showed that those with the most damaged and abnormal epithelium were those with the highest pressures and the *lowest levels of bile amylase* (and by extension other pancreatic enzymes) (Fig. 7.10). These observations strongly suggest that Babbitt's aetiological speculations are invalid.

7.2.4 Clinical Features and Diagnosis

The majority (80%) of CCM are diagnosed in childhood. Some may be detected at routine prenatal USS examination as early as 15 weeks' gestation and may be confused with duodenal atresia, ovarian cysts or intestinal duplication [19]. The CCM antenatally diagnosed are typically and almost exclusively Type 1C lesions (Fig. 7.11).

Clinical presentation of CC varies depending on age of patient. The classic triad of jaundice, abdominal pain and right upper quadrant mass is uncommon and seen mainly in children. Abdominal pain is a more prominent symp-

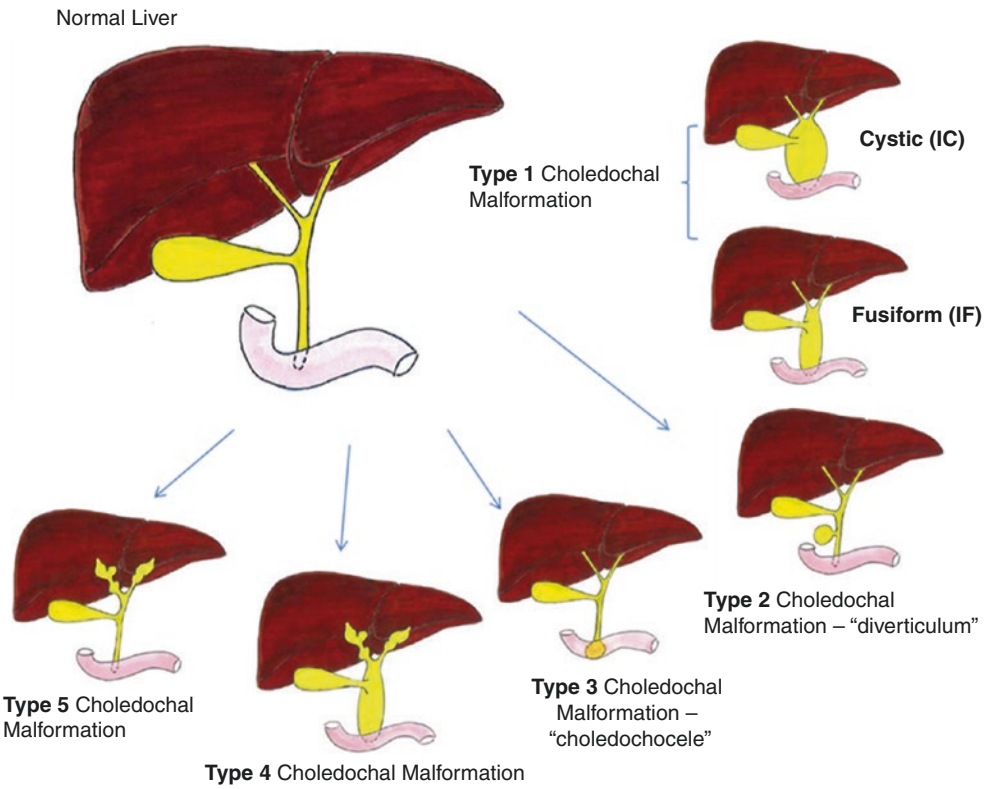

Fig. 7.9 Schematic version of King's College Hospital classification of congenital choledochal malformation

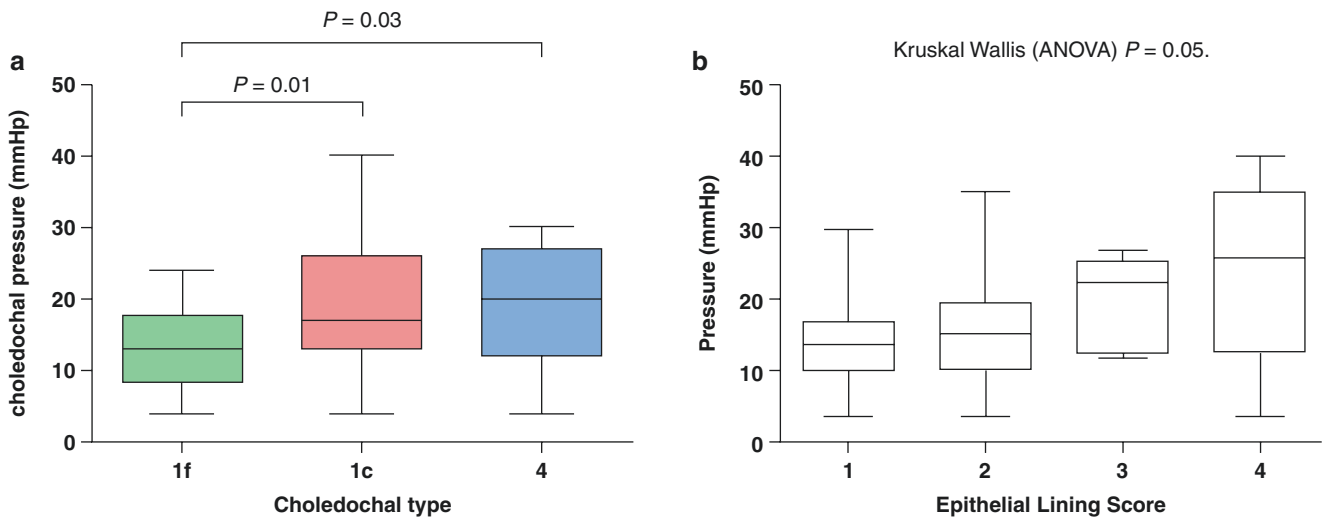

Fig. 7.10 Choledochal pressure: morphology and epithelial consequences. (**a**) Choledochal pressure (mmHg) in relation to the type of choledochal malformation in 47 patients (20 Type 1f, 20 Type 1c and 7 Type 4). (**b**) Choledochal pressure (mmHg) vs. epithelial lining score where 1 = normal and 4 = epithelial necrosis and bile impregnation. Modified from [65]

tom in older children and jaundice in the young. Biliary amylase levels may be elevated and correlate with an initial clinical presentation with acute pancreatitis [63]. Caroli's disease typically presents with cholangitis and stone formation.

Infants are most likely to present with painless, obstructive jaundice. Vomiting, failure to thrive and an abdominal mass also may be noted. Even in the presence of the concomitant common channel, hyperamylasaemia may not be found in infants as its concentration in pancreatic juice at birth and after is low only reaching significant levels at about 1–2 years of age [63]. An incidental presentation is perhaps less common in the paediatric population but seen in nearly one-third of adult CCM patients [66].

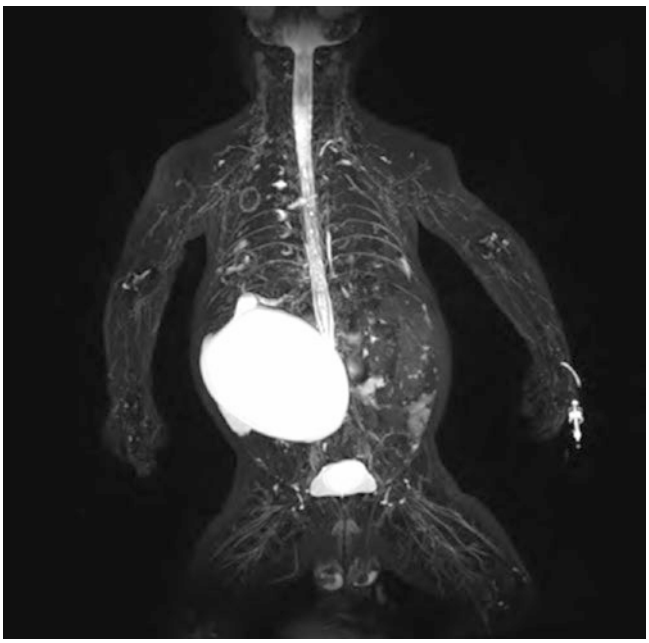

Fig. 7.11 MRCP of huge cystic choledochal malformation (Type 1C)—antenatally diagnosed

Biliary peritonitis secondary to rupture of a CCM is uncommon and described in <2% of cases [67]. They are usually children (only about 20–30% present as adults) with the classic triad of palpable abdominal mass, pain in right upper quadrant and jaundice. Perforations may be single or multiple, and there is no apparent relationship between cyst size and rupture.

Irwin and Morrison [68] reported the first CCM-associated malignancy in 1944. The mechanism remains unclear; however, pancreatic reflux, biliary stasis and formation of mutagenic secondary biliary acids are thought to play a role. Although a malignancy may develop anywhere within the biliary tree, over 50% of tumours develop within the cyst itself. In a review of 5780 CCM cases in the literature, Sastry et al. reported that 7% of patients had cancer—cholangiocarcinoma (70%) and gallbladder cancer (23%). The incidence of malignancy at <18 was 0.42 versus 11% in adults [69]. We looked at two possible contributory factors in order to try and identify those children who might be susceptible to later development of malignant change after resection of the extrahepatic portion during childhood [70]. These were levels of CA 19-9, a known biomarker of pancreatic and hepatobiliary malignancy, in bile at the time of surgery, and the histological expression of MIB-1 on resected choledochal mucosa, which is regarded as marker of epithelial instability. Both proved surprisingly uninformative. High levels of CA 19-9 (>10,000 iu/L) were found unexpectedly in bile, completely independently of bile amylase, and later staining showed that it was expressed in all parts of normal biliary mucosa. Furthermore there were 8 infants and children (of 43 patients) with moderate and high levels of MIB-1 expression without any kind of unifying factor or explanation.

The diagnosis of CCM is typically suspected using USS and can allow an accurate evaluation of size, contour and position of the biliary malformation. Uncommon complications such as cholelithiasis, perforation or even ascites may be noted. Diagnosis requires demonstration of continuity of the cyst with the biliary tree so that it can be differentiated from other intra-abdominal cysts such as pancreatic pseudocysts, echinococcal cysts or hepatic cysts. Technetium-99 HIDA scans may also be used to show bile content of cysts and then degree of obstruction and drainage. This scan will show an initial area of photopenia at the cyst, with consequent filling and then, usually, delayed empting into the bowel [71].

Cross-sectional imaging may be used including MRI, to derive an MRCP (magnetic retrograde cholangiopancreatogram). This is now considered to be the standard to diagnose CCM and can create images by differential signal intensity of stagnant pancreatic fluid and bile compared with surrounding structures [72]. CT with contrast clearly shows any cyst and dilated intrahepatic bile ducts and may be useful in those with acute pancreatitis and perhaps where an associated malignancy is suspected. Currently, endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) are best reserved because of their invasive nature but may be used to decompress an obstructed bile duct or define more complex pancreatic duct arrangement in the setting of recurrent pancreatitis.

7.2.5 Treatment

Primary excision of the dilated part of the extrahepatic biliary system should be performed soon after diagnosis. Early surgery provides the opportunity to exclude cystic biliary atresia in infants and hepatic complications such as fibrosis while reducing the risk of cholangitis and perforation.

Intraoperative cholangiography should always be done prior to any dissection and provides key anatomical details of biliary variation. Excision and hepaticojejunostomy are the treatment of choice in virtually all circumstances. Extrahepatic duct excision should extend proximally to the confluence of the right and the left, leaving a single ring to anastomose. Choledochoscopy performed after duct excision helps to identify intrahepatic bile ducts, stenosis and stone formation and can also be done in the dilated common channel to confirm absence of obstruction and debris. While there are flexible dedicated cholangioscopes, a small flexible ureteroscope or bronchoscope should suffice.

A long (40 cm) Roux-en-Y hepaticojejunostomy is the preferred method of enteric bile drainage and has an excellent long-term outcome. If cyst excision of the distal portion proves difficult due to recurrent inflammation and scarring, removal of just the mucosa is acceptable, in order to avoid damage to the underlying pancreatic duct and portal vein. A liver biopsy is performed at the conclusion of the operation in order to document hepatic histology.

Excision of the diverticulum of a Type 2 CCM should be relatively straightforward leaving the common bile duct intact.

Large choledochoceles, often only a problem in adulthood, can be removed transduodenally in those with Type 3 CCM, and smaller ones can be treated by sphincteroplasty or endoscopic sphincterotomy [73–75].

There is an increasing experience throughout the world with laparoscopic excision and reconstruction though it has to be said that most proponents with anything like decent series are in the Far East. Liem et al. [76] from Hanoi in Vietnam have reported their experience with an almost unbelievable 400 cases of laparoscopic cyst excision and hepaticoduodenostomy or HJ reconstruction for CCM. Anastomotic leaks occurred in <5%, and conversion to open surgery was only required in two children. This experience will never be repeated in Western Europe or North America because the cases are just not there. They were able to show good results with low conversion rate and outcomes similar to those with open surgery [77].

One way of making the most difficult and challenging part of the procedure, the hepaticojejunostomy, easier is to do it robotically. The team from Leeds, UK, has reported an experience of 27 children of which 22 were successfully completed robotically with extracorporeal jejunal anastomosis. The conversions were for anatomical concerns or technical reasons, and one was for a bile leak [78]. Of course you have to spend up to two million dollars to buy yourself a robot so it can never be cost-effective in any realistic paediatric environment.

7.2.6 Complications

Surgical treatment of CCM achieves consistently good results, even in small infants. Early postoperative complications such as anastomotic leakage, bleeding, pancreatitis and intestinal occlusion are uncommon. The long-term complication rate in the literature ranges between 5 and 15%, and reoperation rates range between 1 and 20%. Cholangitis occurs in 1–9% of the patients, stricture of the biliary anastomosis occurs in up to 9% of the patients, and there is a reoperation rate of 1–20% [79, 80].

7.2.7 Liver Transplantation and Caroli's Disease

Caroli's disease (CD) is a rare autosomal recessive inherited disorder characterized by macroscopic saccular or segmental ectasias of the intrahepatic bile ducts. CD is frequently associated with congenital hepatic fibrosis and autosomal recessive polycystic kidney disease, and the clinical course is determined by the extent of underlying pathologic abnormalities. Biliary cystic dilatation and narrowing lead to cholestasis and cholangitis. CD may also be complicated with the formation of extra- and intrahepatic bile duct stones with development of hepatic abscess and portal hypertension [81]. The surgical treatment of CD consists in drainage of biliary obstruction and/or abscess, partial hepatic resection in case of localized lobar disease and the liver transplantation in case of diffuse, bi-lobar symptomatic disease and of concomitant portal hypertension due to hepatic fibrosis. Excellent survival rates [82] are reported regarding liver transplantation in those patients with Caroli's disease that are principally complicated by recurrent cholangitis and concomitant renal disease.

7.3 Part III: Spontaneous Bile Duct Perforation

SBP in infancy was first described by Dijkstra in 1932 [83], and small series of affected infants have been reported [84] since, with the largest being that of Chardot et al. [85] from Paris who described 11 infants seen over a 22-year period. Spontaneous biliary perforation (SBP), together with inspissated bile syndrome, and after biliary atresia are other possible causes of surgical jaundice in early infancy [29]. Perforation may occur more commonly in the anterior part of the duct where the cyst meets the common hepatic duct but also has been reported at the back adjacent to portal vein [86]. Anomalous entry of the CBD into the duodenum, bile duct stenosis or intraluminal obstruction with bile plugs may predispose to a sudden rise in duct pressure leading to "blow-out". Anterior perforations lead to bile ascites and may be obvious in boys by causing bile discolouration of hydroceles and hernias. Posterior perforations leak around the tissues supporting the portal vein and spill into the lesser sac being much more constrained [29]. As a consequence diagnosis may be difficult. Late portal vein thrombosis is a late complication of this posterior perforation [86].

Liver function tests may be normal, though jaundice is usual, and serum alkaline phosphatase and γ-glutamyl transferase levels are mildly raised. Ultrasound is abnormal showing some kind of paraductal mass and varying degrees of bile ascites. Posterior perforations may show more a complex echogenic mass around the duct into the lesser sac. The dif-

ferential diagnosis must include perforation in a pre-existing usually cystic choledochal malformation. Radionuclide hepatobiliary scanning shows zones of persistent radioactivity around the common bile duct, as well as generalized abdominal radioactivity caused by leakage of bile into the general peritoneal cavity.

The current management of SBP is still laparotomy in the absence of sufficiently small ERCP stents. Simple drainage of the peritoneal cavity is reasonable outside of specialist centres, following cholangiography through the gallbladder. More invasive surgery should be left to experts and might include primary duct repair, T-tube insertion, choledocojejunostomy or cholecystojejunostomy [84, 85].

7.4 Part IV: Ciliated Hepatic Foregut Cyst

Although congenital cysts of the liver are uncommon, with the widespread use of US, particularly during prenatal period, their prevalence appears to be increasing [87]. Ciliated hepatic foregut cyst (CHFC) is a rare cystic malformation of the liver described first by Wheeler and Edmonson in 1984 [88]. The histogenesis is still unclear, but most authors think that CHFC probably arises from the remnants of embryonic foregut, similar to that of bronchial and oesophageal cysts. CHFC has been reported in about 60 patients, but only a small proportion are children despite its supposed congenital origin [89–91]. The differential diagnosis in childhood includes choledochal malformations and cystic neoplasm, but detailed imaging investigations (US and MRCP) are usually able to establish the correct diagnosis (Fig. 7.12). Increasing cyst size and sign and symptoms of biliary drainage obstruction remain recognized indications for surgery [91].

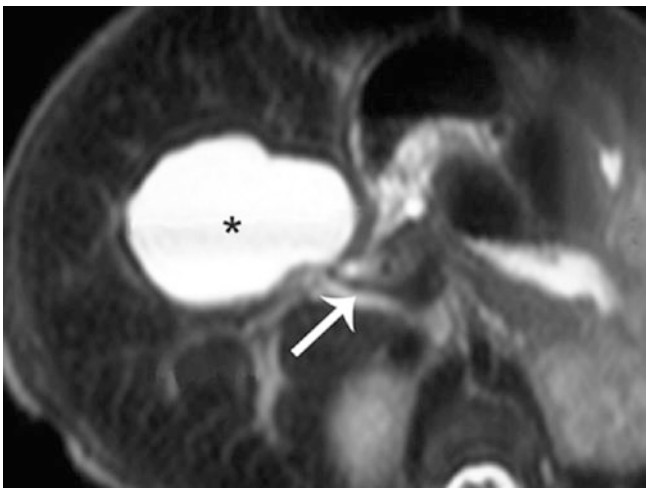

Fig. 7.12 MRI of ciliated hepatic foregut cyst (*asterisk*). *NB No communication with the normal biliary tree* (arrow)

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