**Choledochal cysts**

**Part 1 of 3: Classification and pathogenesis**

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Much about the etiology, pathophysiology, natural course and optimal treatment of cystic disease of the biliary tree remains under debate. Gastroenterologists, surgeons and radiologists alike still strive to optimize their roles in the management of choledochal cysts. To that end, much has been written about this disease entity, and the purpose of this 3-part review is to organize the available literature and present the various theories currently argued by the experts. In part 1, we discuss the background of the disease, describing the etiology, classification, pathogenesis and malignant potential of choledochal cysts.

Although cystic disease of the biliary tree has been described since 1723, much about its etiology, pathophysiology, natural course and optimal treatment remains under debate.

**EPIDEMIOLOGY**

Choledochal cysts (CCs) are rare medical conditions with an incidence in the western population of 1 in 100 000–150 000 live births, although the incidence has been reported to be as high as 1 in 13 500 births in the United States and 1 in 15 000 births in Australia. The rate is remarkably higher in Asian populations with a reported incidence of 1 in 1000, and about two-thirds of cases occur in Japan. The reason for this Asian preponderance is still unclear. There is also an unexplained female:male preponderance, commonly reported as 4:1 or 3:1. Distribution of the different types of CCs are as follows: 50%–80% are type I, 2% type II, 1.4%–4.5% type III, 15%–35% type IV and 20% type V.

**CLASSIFICATION**

Alonso-Lej and colleagues proposed the first classification system for CCs in 1959, describing 3 types of bile duct dilation, which has gained wide acceptance. Todani and colleagues expanded this system in 1977 to include the occurrence of intrahepatic and multiple cysts, and this modified classification is now most commonly used by clinicians. Type-I cysts have subsequently...
been subclassified into 3 types. Type IA shows marked cystic dilation of the entire extrahepatic biliary tree, with sparing of the intrahepatic ducts. The cystic duct and the gallbladder arise from the dilated common bile duct (CBD). Type IB is defined by focal, segmental dilation of the extrahepatic bile duct. Although by definition the cyst can arise from anywhere within the extrahepatic biliary tree, it is most commonly distal, with the cystic duct branching off a normal CBD. The biliary tree proximal to the gallbladder is usually normal. Type-IC cysts are smooth fusiform dilations of the entire extrahepatic bile duct, usually extending from the pancreaticobiliary junction to the intrahepatic biliary tree.

Type-II cysts are discrete diverticuli of the extrahepatic duct with a narrow stalk connection to the CBD. Type-III cysts are also called choledochocele owing to their similarity in morphology, and postulated etiology, to ureteroceles. They consist of dilation of the distal CBD that is confined to the wall of the duodenum, and often bulge into the duodenal lumen. Although the outer lining of the cyst is always lined by duodenal mucosa, the inner lining can either be duodenal or biliary epithelium. Sarris and colleagues have further subdivided choledochoceles into 5 types based on the cysts’ relations to the ampulla of Vater and the pancreatic duct. Although this system identifies the different configurations in which choledochoceles occur, the presentation and management of all subtypes are identical. Thus further characterizing type-III cysts into their subclassifications has not gained popularity among clinicians.

Type-IV cysts are multiple in nature and are further subdivided based on intrahepatic duct development. Type-IVA cysts are multiple intrahepatic and extrahepatic dilations. The intrahepatic duct dilation can be cystic, fusiform or irregular. Todani and colleagues have recommended further description of type-IVA cysts as cystic–cystic, cystic–fusiform or fusiform–fusiform to better delineate the nature of their intrahepatic and extrahepatic morphologies. Type-IVB cysts refer to multiple dilations of the extrahepatic biliary tree only, described radiographically as either a “string of beads” or “bunch of grapes” appearance.

Type-V CCs refer to Caroli disease, also known as communicating cavernous ectasia, which is multiple saccular or cystic dilations of the intrahepatic bile ducts. Simple Caroli disease is isolated biliary dilation, whereas Caroli syndrome is cystic disease associated with congenital hepatic fibrosis. Some authors have described Caroli disease with associated extrahepatic CC, but the distinction between this and type-IVA cysts is unclear. Levy and colleagues state that saccular dilation of the intrahepatic bile ducts and diffuse fusiform extrahepatic bile duct dilation less than 3 cm marks Caroli disease as separate from type-IVA cysts. Figure 1 shows the different types of CCs.

Lilly and colleagues described an entity that they called “form fruste” CCs. Patients with these cysts present with typical symptoms of abdominal pain and obstructive jaundice, without bile duct dilation, but exhibiting an abnormal pancreaticobiliary duct junction. These patients have the same symptoms, histological evidence of inflammation and malignancy potential as those with CCs, and so some authors believe they should be included within the spectrum of disease.

Kaneyama and colleagues described 4 patients, an incidence of 1.1% in that series, with a combination of type-I and type-II cysts. Intraoperatively, all 4 patients were morphologically identical, with a fusiform type-IC cyst with a type-II diverticulum arising from the middle portion of the cyst and the cystic duct draining into the right side of the diverticulum. The authors suggested that this may be a new clinical subtype. Four cases have also been reported of diverticular cysts of the cystic duct, which the authors suggested might be another subtype. The question arises, however, whether this is just a variant type-II cyst.

Visser and colleagues recently challenged the traditional classification system, stating that it grouped together separate disease entities, marked by differing etiologies, natural courses, surgical options and complication profiles. They also contended that type-I and type-IVA cysts are simply variations of the same disease, as in their experience all type-I cysts had some element of intrahepatic dilatation, and the degree of intrahepatic dilatation defining one type versus the other was arbitrary. They advocated using descriptive nomenclature instead of the traditional alphabetic classification, and this has been supported by subsequent authors.

**Pathogenesis**

The etiology of CCs is still unclear, although many theories have been put forth. Babbitt’s theory of cysts caused by an abnormal pancreaticobiliary duct junction (APBDJ) such that the pancreatic duct and the common bile duct meet outside the ampulla of Vater, thus forming a long common channel, has gained much popularity. This theory postulates that the long common channel allows mixing of the pancreatic and biliary juices, which then activates pancreatic enzymes. These active enzymes cause inflammation and deterioration of the biliary duct wall, leading to dilation. Furthermore, greater pressures in the pancreatic duct can further dilate weak-walled cysts. Many studies have measured the amylase level in CC bile, which is always higher in patients than in controls. Furthermore, higher levels of amylase were significantly associated with younger age of symptom onset and higher grade of dysplasia. This lends credence to the theory that pancreaticobiliary reflux not only exists in these patients, but also leads to inflammation and dysplasia. The authors also postulated that high levels of reflux (and thus amylase) results in earlier symptoms, whereas low levels result in chronic, insidious disease that presents with complications later in life. Although amylase may be a
marker for pancreatic reflux, it is more likely that the other enzymes actually cause epithelial breakdown. Therefore further studies have been conducted to assess trypsinogen and phospholipase A2 levels in CC bile, which were also found to be elevated.\textsuperscript{24,29–35} Interestingly, 61\% of the trypsinogen in the bile duct and 65\% of the trypsinogen in the gallbladder was activated to trypsin, which can only be accomplished by the presence of enterokinase.\textsuperscript{24} Although normal epithelium does not produce enterokinase outside of the duodenum, it is secreted by dysplastic biliary epithelium, including the epithelium of patients with APBDJ.\textsuperscript{29,31} Therefore it is theorized that enterokinase from diseased biliary epithelium activates trypsinogen to trypsin, which in addition to its digestive and irritating effects activates phospholipase A2. Activated phospholipase A2 hydrolyzes epithelial lecithin to lysolecithin, resulting in further inflammation and bile wall breakdown.\textsuperscript{14,35} Also supporting this theory are animal studies in which both ligation of the common bile duct and surgical creation of APBDJ lead to cystic dilation of the biliary tree in canine and murine models.\textsuperscript{34} Administration of secretin, which increases pancreatic secretion, has been shown to dilate the CBD and gallbladder in patients with CC, whereas controls showed duodenal filling only. This demonstrates pancreaticobiliary reflux in these patients.\textsuperscript{37,38} As described previously, the existence of form fruste CC supports the belief that APBDJ is related to the pathogenesis, symptoms and complications of overt CC.\textsuperscript{8}

Skeptics of this theory call it into question because only 50\%–80\% of CCs are associated with APBDJ, and immature neonatal acini do not make sufficient pancreatic enzymes to explain antenatally diagnosed CC.\textsuperscript{39,40} Counterarguments by supporters of Babbitt’s theory state that long common channels are arbitrarily defined in terms of length, with wide variation in measured length based on imaging modality and angles.\textsuperscript{41} In fact, different authors have defined a long common channel as anywhere from 10 to 45 mm. Therefore, APBDJ and a common channel may in fact exist in a much larger proportion of patients with CC, but may be underestimated owing to unrealistic long common channel definitions or inadequate imaging methods. Okada and colleagues\textsuperscript{35} recommend defining a

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**Fig. 1.** Choledochal cyst classification. (A) Type-IA cystic dilation of the extrahepatic duct. (B) Type-IB focal segmental dilation of the extrahepatic duct. (C) Type-IC fusiform dilation of the entire extrahepatic bile duct. (D) Type-II simple diverticula of the common bile duct. (E) Type-III cyst/choledochoccele distal intramural dilation of the common bile duct within the duodenal wall. (F) Type-IVA combined intrahepatic and extrahepatic bile duct dilation. (G) Type-IVB multiple extrahepatic bile duct dilations. (H) Type-V/Caroli disease multiple intrahepatic bile duct dilation.
long common channel as any pancreaticobiliary junction that lies outside of the duodenal wall and thus could result in pancreaticobiliary reflux and mixing.

There is a theory that CCs are instead purely congenital in nature. This theory states that embryologic overproliferation of epithelial cells results in dilation during the cannulation period of development. Davenport and Basu noted that all neonatal CCs they reviewed were cystic in nature, and pathologically had fewer neurons and ganglia. Their theory was that round cysts are congenital in nature, with distal obstruction due to aganglionosis and proximal dilation (similar to Hirschsprung disease). In this case, chronic inflammation and symptoms occur owing to biliary stasis within the dilation rather than pancreatic reflux. They believe that fusiform dilations are acquired lesions due to APBDJ. Ohkawa and colleagues discovered that elastin fibres in the biliary tree do not develop until 1 year of age. They assert that increased neonatal tendency for round dilation is due to APBDJ and increased pressure within the bile duct, which yields round dilation before 1 year of age with the absence of elastin and fusiform dilation after the age of 1 year. Contradicting this is Xei Jongs’ observation that neonatal CCs are round, whereas cysts associated with biliary atresia are fusiform, suggesting that round lesions are congenital and fusiform dilations are due to distal obstruction and thus acquired. Other authors speculate that all adult cysts are acquired due to distal obstruction, with longer, narrower stenosis leading to round lesions and shorter wider stenosis leading to fusiform lesions. The distal obstruction may be due to sphincter of Oddi dysfunction or scarring and stone formation. As mentioned previously, the inner lining of a choledochocoele can be biliary or duodenal epithelium, leading some authors to believe that these reflect either duodenal or biliary duplication cysts.

Choledochal cysts are associated with many different developmental anomalies, which have given rise to some additional etiologic theories. Such associations include colonic atresia, duodenal atresia, imperforate anus, pancreatic arteriovenous malformation, multisepalate gallbladder, OMENS plus syndrome, ventricular septal defect, aortic hypoplasia, pancreatic divisum, pancreatic aplasia, focal nodular hyperplasia, congenital absence of the portal vein, heterotropic pancreatic tissue and familial adenomatous polyposis. Embryologically, the pancreas forms when the ventral and dorsal pancreatic buds rotate, fuse and form connections with the biliary tree. Abnormal rotation and fusion may result in APBDJ and CC, pancreatic divisum and pancreatic aplasia. Although the relation with enteric atresia is not clear, hypotheses include common developmental malformations or embryological cyst compression of either the gastrointestinal tract itself or its blood supply. Familial adenomatous polyposis is associated with mutations in the adenomatosis polyposis coli tumour suppression gene, which leads to interference with normal biliary cell–cell adherence, and therefore may lead to cystic dilation. Reasons for the other associations remain unclear.

The above theories may explain the formation of type-I and type-IV cysts, but some authors contend that the etiologies of the other types are quite distinct. As described previously, type-II cysts are true diverticuli of the common bile duct, with histological evidence of little inflammation and carcinogenic potential. There also have been reports of “diverticular” cysts with no apparent communication with the biliary tree. Therefore the question arises as to whether this is truly a cystic dilation caused by the above mechanisms or if it simply reflects a biliary duplication cyst. The etiology of choledochoceles is also not clear. Wheeler suggested that obstruction of the ampulla of Vater may result in localized dilation of the distal intramural bile duct. Others believe that increased pressure owing to sphincter of Oddi dysfunction leads to such dilation. As mentioned previously, the inner lining of a choledochocoele can be biliary or duodenal epithelium, leading some authors to believe that these reflect either duodenal or biliary duplication cysts.

Type-V CCs, or Caroli disease, is a disease entity quite separate from other CCs, with very different theories of etiology. Embryology of the intrahepatic biliary tree is as follows: a single layer of cells called a ductal plate forms around the portal branches, which then duplicates to form a double layer. Remodelling and selective resorption of the ductal plate commences in the 12th week and progresses to form the large bile ducts at the hilum to the small ductules in the periphery. Arrest of this remodelling results in Caroli disease. When such duct plate malformation occurs at the level of the large ducts, Caroli disease results. Malformation that continues to later stages of development such that the peripheral ductules are affected results in Caroli syndrome, with intrahepatic cysts reflecting large duct arrest and congenital hepatic fibrosis reflecting ductule arrest. Caroli disease is associated with biliary atresia, which is also thought to be due to duct plate malformation. Caroli disease also is associated with both autosomal recessive and, less commonly, autosomal dominant polycystic kidney disease. It is postulated that the genetic mutations responsible for the renal malformations also result in hepatic duct plate malformation.

CARCINOGENESIS

It is well accepted that a CC is a premalignant state, with cancer not only occurring more often in these patients but also 10–15 years earlier. The overall risk of cancer has been reported to be 10%–15%, and increases with age. The risk rises from 2.3% in patients aged 20–30 years to 75% in patients aged 70–80 years, and histopathology shows increasing dysplasia with increasing age. Distribution of the types of cancer found in patients with CC are as follows: adenocarcinoma 73%–84%, anaplastic...
carcinoma 10%, undifferentiated cancer 5%–7%, squamous cell carcinoma 5% and other carcinoma 1.5%. The site of cancer is the extrahepatic bile duct in 50%–62% of patients, gallbladder in 38%–46%, intraductal bile ducts in 2.5%, and the liver and pancreas in 0.7% each. A review by Todani and colleagues found that 68% of cancers were associated with type-I, 5% type-II, 1.6% type-III, 21% type-IV and 6% type-V CCs. Abnormal pancreaticobiliary duct junction has a 16%–55% risk of malignancy with or without bile duct dilation, and cancer has been reported in 12%–39% of form fruste patients. Cancer usually occurs within the cyst in CC and in the gallbladder in form fruste CC, leading some authors to postulate that malignancy occurs at the site of bile stasis, irritation and inflammation (within the dilated cyst in CC and within the gallbladder when no cyst exists). Caroli disease is associated with a cancer risk of 7%–15%.

The incidence of malignancy with choledochocele is usually reported as 2.5%, but 1 study reported a 27% incidence. Although not typically associated with APBDJ, some authors claim that the choledochocele itself may be a site of pancreatic and biliary juice mixing, as the pancreatic duct and the CBD may both open into the cyst, thus creating the same inflammatory and precancerous milieu as with an APBDJ. Cancer occurs as a result of chronic inflammation, cell regeneration and DNA breaks, leading to dysplasia. The inflammation can be from either recurrent cholangitis or pancreaticobiliary reflux. Chronic inflammation also destroys the protective mucin-producing epithelial cells. Furthermore, chronic postobstructive infection by gram-negative bacteria such as Escherichia coli metabolizes bile acids into carcinogens. K-ras mutations and overexpression of p53, which have been demonstrated in many other malignancies, are also present in malignant, precancerous dysplastic and chronically inflamed bile ducts in CC and APBDJ. This suggests that pancreatic reflux causes K-ras mutation, cellular atypia, p53 overexpression and carcinogenesis. Although most CC-associated malignancy presents with abdominal pain, weight loss and obstructive jaundice, many can be asymptomatic, and therefore vigilant surveillance is necessary.

**CONCLUSION**

As described, CCs are part of a complicated disease entity about which many debates still ensue. Although the modified Alonso-Lej classification system is widely used by clinicians now, its validity is questionable. Apart from existing in the same anatomic area, the different subtypes of CCs have quite varied characteristics. As described in this article, and in the upcoming parts 2 and 3 of this review, the subtypes have different etiologies, carcinogenicity, ideal imaging modalities and optimal treatment strategies. Therefore clustering all of them within the same disease modality, based solely on anatomy, seems simplistic. Furthermore, the alphanumeric naming is esoteric, and universal comprehension of the pathology involved will be facilitated by descriptive nomenclature instead. The evidence supporting APBDJ as the common etiology for CCs is impressive, ranging from pathological to biochemical to animal models. The distinction should be made between the term “long common channel” and APBDJ, as pancreaticobiliary fluid mixing and enzyme activation seems to be the factor leading to cystic dilatation, and this may occur in the absence of a common channel that exceeds an arbitrarily defined “normal” common channel length. The patients with CC who fail to demonstrate a long common channel may be such patients who have a normal common channel length yet also have APBDJ and premature pancreaticobiliary mixing. In subsequent articles, we will examine the diagnosis and treatment of biliary cystic disease.

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**References**


