

Choledochal cysts–Classification, physiopathology, and clinical course

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Abstract

Although biliary canal cysts were first described around the 1720s, the aetiology, physiopathology, natural course, and treatment options of the disease remain controversial. These cysts are becoming more common and can now be more easily diagnosed thanks to recent developments in imaging methods. Nevertheless, if left un-diagnosed, the risk of progressive complications such as spontaneous perforation, cholelithiasis, choledocholithiasis, cholangitis, secondary biliary cirrhosis, portal hypertension, and development of malignancies should be considered. In this review, we discuss the epidemiology, classification, physiopathology, carcinogenesis, and clinical course of biliary cysts.

Introduction

Choledochal cysts (CCs) are rare medical conditions, which are congenital cystic dilatations of any portion of the bile ducts, most often occurring in the main portion of the common bile duct. Although choledochal cysts are considered a disorder of childhood and infancy, the ages in reported cases range from newly born to 80 years old; however 60% of such cysts are diagnosed in patients less than 10 years old [1-6].

Epidemiology

Choledochal cysts (CCs) are extremely rare with an incidence of about 1/100–150,000 in Western societies. The disease affects 1 in 13,500 live births in the USA and 1 in 15,000 live births in Australia. It is seen more frequently in Asians; two out of three cases are of Japanese origin despite the reported incidence of 1/1,000. There is significant female gender predominance (F/M: 3–4/1). The cause of this female and Asian origin predominance is unknown [6].

Classification

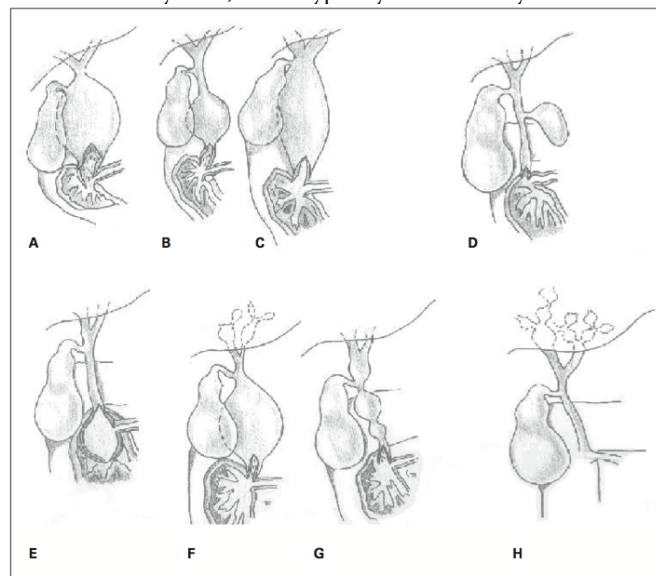
Alonso-Lej defined three types of biliary dilatations in 1959; this classification system has since been widely accepted. Todani expanded this classification in 1977 and divided the CCs into five subgroups. Todani re-modified the classification to include pancreatic junctional abnormalities, and the resulting system became the final and most commonly used classification method [6] (Table 1) (Figure 1). According to the Todani classification, CCs are classified as follows:

Table 1. Todani classification of the bile duct cysts.

Type IA	Cystic dilatation of the extrahepatic bile ducts
Type IB	Extrahepatic distal focal - segmental biliary dilatation
Type IC	Extrahepatic fusiform biliary dilatation
Type II	Extrahepatic biliary diverticula
Type III	Intrahepatic portion of the common bile duct dilatation (Choledococel)
Type IVA	Multiple cystic dilatation of the intrahepatic and extrahepatic bile duct
Type IVB	Multiple cystic dilatation of the only extrahepatic bile duct
Type V	Cystic dilatation of the intrahepatic bile ducts (Caroli's disease)

Type IA Choledochal Cysts: Characterised by cystic dilatation of the extrahepatic biliary tract; the intrahepatic biliary tract is preserved. Gallbladder opens into a dilated hepatic duct.

Type IB Choledochal Cysts: Characterised by focal-segmental dilatation in the extrahepatic biliary tree. Cyst may be located anywhere within the biliary tract, but is typically distal. The cystic duct of the



A: Type IA B: Type IB C: Type IC D: Type II E: Type III F: Type IVA G: Type IVB H: Tip V
Figure 1. Todani classification of the bile duct cysts

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gallbladder opens into a biliary duct of normal diameter which is proximal to the cyst. The intrahepatic biliary tree is preserved.

Type IC Choledochal Cysts: Characterised by a regular and fusiform dilatation extending from the pancreaticobiliary junction into the intrahepatic biliary tract.

Type II Choledochal Cysts: Characterised by a diverticulum originating from the extrahepatic biliary tract that is generally connected to the tract via a narrow peduncle.

Type III Choledochal Cysts: Characterised by a dilatation limited to the duodenal wall in the distal part; named as a choledochal cell since it resembles a ureterocele morphologically and aetiologically. The outer wall of the cyst contains almost exclusively duodenal mucosa while the inner wall may include duodenal or biliary epithelium. This lesion has been divided into five subgroups by some authors according to its associations with the choledochoceles, ampulla Vateri and pancreatic channel; this classification has gained much support [7].

Type IVA Choledochal Cysts: Characterised by multiple intra-extrahepatic dilatations. The intrahepatic dilatation may be cystic, fusiform or irregular. In addition, Tadoni reported that these cysts could be classified as cystic-cystic, cystic-fusiform or fusiform-fusiform according to the shape of the intrahepatic and extrahepatic dilatations [8].

Type IVB Choledochal Cysts: Characterised by multiple dilatations including only the extrahepatic biliary tracts. The morphology of this type of CC can be described as “beads” or as “a bunch of grapes” [9].

Type V Choledochal Cysts: These cysts, also known as Caroli disease, are characterised by multiple intrahepatic saccular or cystic dilatations. Caroli disease describes isolated biliary dilatations, while Caroli syndrome describes biliary dilatations along with congenital hepatic fibrosis [10]. Some authors have described Caroli disease in addition to extrahepatic CC; however, they were unable to differentiate this entity from Type IVA CC. On the other hand, some authors have reported that differentiation can be based on an extrahepatic fusiform dilatation diameter < 3 cm, in addition to intrahepatic saccular dilatation [11,12].

Furthermore, a subgroup known as the “coarse form” refers to cases that present with abdominal pain and obstructive jaundice and that include pancreaticobiliary junction abnormalities but no dilatation of the biliary tract. Patients in this group have the same clinical findings as with CCs; histological inflammation and malignancy potential are believed to represent another facet of the disease [13,14]. Other than these, combined types including Type I and II CCs have also been described [15].

Incidences have been reported as 50–80% for Type I, 2% for Type II, 1.4–4.5% for Type III, 15–35% for Type IV and 20% for Type V.

Physiopathology

Although the exact aetiology of CC is unknown, many theories have been proposed in the pathophysiology of the condition. The most widely accepted hypothesis is Babbitt's theory, which states that the long common channel develops due to a pancreaticobiliary junction abnormality. According to this theory, the long common channel allows mixing of the pancreatic secretions and bile for longer than usual, activating pancreatic enzymes. The activated enzymes then cause inflammation and destruction in the wall of the biliary tract, causing dilatation [16]. Also, high pressure inside the pancreatic channel causes

progressive dilatation of the weak wall of the cyst [17].

The amylase level in the cystic common bile duct has also been found to be higher in this patient population than in control groups in some studies [18,19]. Furthermore, high amylase levels have been associated with early clinical findings and the degree of dysplasia. According to this theory, symptoms are seen at an earlier age, when the severity of the pancreaticobiliary reflux and the amylase level are higher and the disease is more asymptomatic, and becomes complicated at an older age when the severity of reflux and the amylase level are lower.

Since amylase can be used to determine the severity of the pancreaticobiliary reflux, trypsinogen and phospholipase-A2 levels have also been investigated as disease markers and were found to be increased in patients with CC [19-21]. Interestingly, trypsinogen was found to be activated by trypsin, in 61% of cases in the biliary tract and in 65% of cases in the gallbladder [19]. Enterokinase is necessary for this activation and normally it cannot be produced in mucosa other than the duodenal wall. Enterokinase is secreted by the dysplastic biliary epithelium, which is secondary to the pancreatic reflux and is activated by trypsinogen and lecithin-lisolecithin activation through phospholipase-A2, inflammation and destruction in the wall of the biliary tract has been proposed. This theory is further supported by animal experiments in which a pancreaticobiliary junction abnormality is produced surgically, leading to a biliary tract dilatation [21,22].

The presence of a pancreaticobiliary reflux has been confirmed in patients with a CC following administration of secretin, which increases pancreatic secretions in those patients. Secretin causes dilatation of the biliary tract and gallbladder. In the control group, on the other hand, the duodenum alone was shown to be filled, confirming the presence of a pancreaticobiliary reflux. This also supports the hypothesis that the presence of a pancreaticobiliary reflux is responsible for the pathogenesis of the “coarse form” of the disease [23,24].

Only 50–80% of CCs demonstrate an association with a pancreaticobiliary junction abnormality. In addition, the presence of antenatally diagnosed CCs despite a lack of immature pancreatic secretions also suggests that this theory is not fully adequate [25,26]. Also, when evaluating the long common channel theory, it is unclear which length defines “long”, since common channels of 10–45 mm have been demonstrated. Therefore, it has been suggested by some authors that a junction at a level other than the duodenal wall should be accepted as long, since this might allow mixing of pancreatic secretions with bile, leading to reflux [21].

Another theory is related to the congenital origin of CCs. Excess growth of the immature epithelium in the biliary tract during the development phase or an absence at any phase has been suggested to cause biliary tract dilatation [27,28]. A study that evaluated neonatal cystic CCs found that the amounts of neurons and ganglia were decreased in these cases [29]. Based on this finding, cystic dilatations were suggested to develop secondary to a dilatation at the distal part of the biliary tract, similar to Hirschsprung disease, rather than fusiform ones that are acquired due to abnormal reflux. Another study found that elastin fibrils in the biliary tract are absent before the first year of life; cystic dilatations were proposed to develop before an individual is 1 year old, while fusiform dilatations were suggested to develop after 1 year of life secondary to increased pressure in the biliary tract [29,30].

Another theory proposes that dilatations seen in adults develop due to obstructions at the distal biliary tract secondary to various abnormalities (Oddi sphincter dysfunction, scar tissue and gallstones)

and that a long narrow stenosis results in a cystic dilatation while a short wide stenosis results in a fusiform dilatation [8,29]. According to this theory, both distal and hilar-intrahepatic stenoses are necessary for the development of Type IV A cysts.

In general, those theories are meant to explain Type I and Type IV CCs. Type II cysts, on the other hand, are diverticular cysts that demonstrate minimal inflammation and carcinogenic potential histologically. Therefore, it is unclear whether these cysts develop secondary to causes explained in the theories stated above or whether they are true biliary duplications [31].

Type II cysts (choledocoeles) have been proposed to develop secondary to a pressure increase in the distal intramural biliary tract due to an ampullary obstruction or sphincter dysfunction. Some authors, on the other hand, suggest that choledocoeles may actually be duodenal or biliary duplication cysts, since they can contain duodenal or biliary inner epithelium [32,33].

Carcinogenesis

The premalignant nature of CC has been widely recognised; not only is the development of malignancy more frequent, the age of development of malignancy is also earlier than in the normal population [34]. Malignancy is a result of chronic inflammation, which leads to dysplasia and may also develop secondary to recurrent cholangitis and pancreatic reflux [35-37]. The risk of malignancy associated with a CC has been reported to be 10 to 15% in the overall population; however, this rate increases with increasing age [21,38]. The risk of malignancy is 23% at the age of 20 to 30 years, while it can increase up to 75% at the age of 70 to 80 years [35,39]. Malignancies include adenocarcinomas in 73 to 84% of cases, anaplastic carcinomas in 10%, undifferentiated carcinomas in 5 to 7%, squamous cell carcinomas in 5%, and other types of carcinoma in 1.5% [40,41]. These malignancies affect the extrahepatic biliary tract in 50 to 62% of cases, the gallbladder in 38 to 46%, the intrahepatic biliary tract in 2.5%, and the liver and pancreas in 0.7% [35]. The presence of a pancreaticobiliary junction abnormality carries a risk of malignancy in 16 to 55% of cases, regardless of whether a biliary dilatation is present [35,42,43]. The malignancy risk in the coarse form without biliary tract dilatation is 12 to 39%. While malignancies usually develop inside the cyst, in the coarse form they develop in the gallbladder. Therefore, some authors have suggested that tumours are most common in areas of highest exposure to biliary irritation (inside the cyst in patients with CC, or in the gallbladder if there is no cyst) [36-38]. The risk of malignancy is 7-15% and 2.5% in Caroli disease and in a choledocoele, respectively [44-47].

Clinical course

Although the symptoms of biliary cysts can be seen at any age, they manifest before the age of 10 years in 80% of cases. Although the triad of abdominal pain, jaundice and an intraabdominal palpable mass is known as the classical clinical presentation, it is rare for a patient to present with all three signs (20%); however, two out of three of those symptoms are present in 8% of cases [48,49]. In the neonatal period, patients often present with abdominal pain and mechanical jaundice (< 12 months), while older patients present with abdominal pain, nausea and vomiting, and jaundice [50-52].

Clinical findings of CC develop secondary to ascending cholangitis and pancreatitis, which occur due to biliary stasis, development of gallstones, inflammation and development of secondary inflammation [49-66]. Pancreatitis develops due to obstruction of the pancreatic

channel secondary to gallstones and protein-rich secretions from the dysplastic epithelium [52,61]. The cause of recurrent cholangitis in patients with intrahepatic involvement (Types IVA and V) is bacterial colonisation secondary to gallstones and obstruction due to intrahepatic biliary stasis [44,67]. The clinical presentation in those patients may advance to portal hypertension and biliary cirrhosis. Portal hypertension may develop without cirrhosis due to mechanical pressure of the cyst on the portal vein [69-73].

The initial symptoms may be abdominal pain and signs of peritonitis due to cyst rupture in 1-2% of cases [74]. Cyst rupture is thought to be due to the fact that the cyst wall, which becomes more fragile secondary to a distal obstruction in the biliary tract or increased intraabdominal pressure, cannot withstand the tension [75]. Perforation is often seen at the junction of the cystic duct and the main hepatic duct, which has the weakest blood supply in the biliary tract [74-75]. In cases of perforation, although the clinical findings are extremely aggressive, radiographic diagnosis is challenging because dilatations in the biliary tract disappear.

Patients with a choledocoele (Type III) are usually asymptomatic. Rarely, findings of gastric outlet obstruction or duodenal obstruction may be seen in these patients due to cystic obstruction of the duodenal lumen [76-82].

Choledochal cysts are associated with many different developmental anomalies, which have given to rise some additional etiological theories. Such associations include colonic atresia, duodenal atresia, imperforate anus, pancreatic arteriovenous malformation, multiseptate gallbladder, OMENS plus syndrome, ventricular septal defect, aortic hypoplasia, pancreatic divisum, pancreatic aplasia, focal nodular hyperplasia, congenital absence of the portal vein, heterotopic pancreatic tissue and familial adenomatous polyposis [83-87].

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