Minireview

Etiological classification and treatment strategies for secondary bile duct dilatation

Yunfu Lv, Ning Liu, Hongfei Wu and Zhuori Li

Department of General Surgery, Hainan General Hospital (Hainan Medical College Affiliated People's Hospital), Haikou 570311, China
Corresponding author: Yunfu Lv. Email: yunfu_lv@126.com

Impact statement

This minireview clearly defines the concept and three characteristics of secondary intra- and extrahepatic bile duct dilatation, which are rarely reported in the literature. It also provides an objective and comprehensive overview of the many causes of secondary intra- and extrahepatic bile duct dilatation by classifying them from various viewpoints. Moreover, this is the first study to clarify the relationship between biliary pressure, dilatation, and jaundice, which indicates that efforts must be made to reduce biliary pressure to avoid bile duct dilatation and jaundice. Finally, the findings suggest that treatment should be "tailored" to the cause. These new information will enhance the understanding of secondary intrahepatic and extrahepatic biliary tract expansion, providing important help in the diagnosis and treatment of its causes, and have profound clinical significance.

Abstract

Secondary intra- and extrahepatic bile duct dilatation is a very common condition that can be caused by several diseases. However, it has been rarely discussed in the specialized literature. Moreover, no distinct etiology can be determined in some cases, which hampers the diagnosis and treatment. Here, we discuss the etiological classification and treatment strategies of secondary intra- and extrahepatic bile duct dilatation based on an extensive literature review, as well as our experimental research and clinical experience. The etiology of secondary intra- and extrahepatic bile duct dilatation can be classified in different ways. From a clinicopathological perspective, it can be classified into obstruction-, lesion-, and compression-induced dilatation. Treatment varies depending on the cause. For example, endoscopic dilation or stenting is used for biliary strictures, laparoscopic choledochectomy for stone removal, and resection for cholangiocarcinoma.

Keywords: Bile duct dilatation, intra- and extrahepatic, secondary, etiological classification, diagnosis, treatment

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Introduction

In a healthy adult, the diameter of the common bile duct (hereafter termed "bile duct") is <8 mm (it is <1 mm in newborns; and the inner diameter of the extrahepatic bile duct is 3 mm in infants and young children and 5 mm in children). Bile duct dilatation occurs when its widest diameter is ≥8 mm. A diameter of 8–12 mm is defined as "mild," 12–16 mm as "moderate," 16–20 mm as "severe," and >20 mm as "very severe" dilatation. Right and left hepatic ducts, interlobular bile ducts, and bile ducts in hepatic segments are called levels one, two, and three bile ducts, respectively, which are distributed in a dendritic manner. Normal right and left hepatic ducts have a diameter of 3.5 and 3.3 mm, respectively. If the diameter of the right and left hepatic ducts is greater than normal, and/or level-two or level-three bile ducts are widened, this is called "dilatation of intrahepatic bile ducts."[1] Intra- and extrahepatic bile duct dilatation can be classified into "congenital"[2–4] and "secondary" dilatation. Secondary (also known as "acquired") intrahepatic and extrahepatic bile duct dilatation is caused by diseases or acquired factors.[5] It has three characteristics: (i) dilatation occurs after the primary disease or the predisposing factors; (ii) the bile duct above the lesion is wholly dilated (versus local dilatation in congenital cases); the closer it is to the lesion, the more marked is the dilatation; (iii) in general, it does not develop into cancer. Extrahepatic bile duct dilatation, in general, occurs before intrahepatic dilatation. However, only intrahepatic dilatation will occur if the lesion is in the hepatic hilum or within the liver. There are several causes of secondary intra- and extrahepatic bile duct dilatation. Most of them, such as biliary stones, parasites and tumors, can be determined by medical history, physical examination, and imaging. However, the etiology is not known in a few cases. It is difficult for clinicians to deal

with patients who present with unexplained bile duct dilatation (with or without subjective symptoms). A missed diagnosis or misdiagnosis can sometimes occur even with an experienced surgeon. Therefore, it is necessary to summarize the etiology and treatment of secondary intra- and extrahepatic bile duct dilatation.

Etiology

Clinical data were collected from 1340 patients with secondary intra- and extrahepatic bile duct dilatation admitted to our hospital from January 2000 to December 2014. These cases accounted for 93.7% of patients with bile duct dilatation diagnosed in this period, indicating that the vast majority of bile duct dilatation is secondary in nature. Specifically, the diameter of the bile duct was 8–12 mm in 380 cases (28.4%), 12–16 mm in 479 cases (35.8%), 16–20 mm in 341 cases (25.4%), and >20 mm in 140 cases (10.4%). The top-five causes of bile duct dilatation were stones in the bile duct ($n = 476$, 33.3%), cancer of the pancreatic head ($n = 179$, 12.5%), periampullary carcinoma ($n = 159$, 11.1%), cholangiocarcinoma ($n = 89$, 6.2%), and chronic pancreatitis or a cyst in the pancreatic head ($n = 86$, 5.6%).[6] The etiology of secondary bile duct dilatation in this patient cohort is summarized in Table 1.

Classification

Secondary intra- and extrahepatic bile duct dilatation can be classified by several methods.

Classification by characteristics of bile duct obstruction

As suggested by Nakeeb *et al*.,[7] secondary bile duct dilatation can be classified into four categories according to the characteristics of bile duct obstruction. The first category is complete obstruction. This can be caused by cancer of the pancreatic head, cholangiocarcinoma, papillary cancer, ampullary cancer, ligation of the bile duct, liver parenchymal tumor (primary or secondary), gallbladder cancer invading the bile duct, or bile duct compression by lymph node metastasis. The second category is intermittent obstruction. This can be caused by biliary stones, duodenal diverticulum, biliary papilloma, papillary carcinoma, a cyst in the bile duct, polycystic liver, intrahepatic/biliary parasites, or hemobilia. The third category is chronic incomplete obstruction. This can be caused by stenosis in the bile duct (congenital, traumatic, or iatrogenic), stenosis of a biliary-enteric anastomosis, stenosis in the sphincter of Oddi, chronic papillitis, chronic pancreatitis, or cystic fibrosis. The fourth category is segmental obstruction. This can be caused by trauma (including iatrogenic trauma), hepatolithiasis, intrahepatic biliary stricture, sclerosing cholangitis, or intrahepatic cholangiocarcinoma. Patients with complete obstruction of the bile duct present with jaundice. Patients with intermittent obstruction may have other symptoms (e.g. pain, skin itching, fever, biochemical changes) without jaundice. Patients with chronic incomplete obstruction can eventually develop liver fibrosis and biliary sclerosis.

Classification by disease type

Eight types of disease[8] that can lead to bile duct dilatation have been identified: stones (found in 35% of cases), compensation (4%), parasites (4%), inflammation (5%), tumor (22%)), external wall pressure (21%), injury (2%), and others (2%).

Classification by biliary pressure

Secondary bile duct dilatation can be divided into six types according to biliary pressure. It can be induced by high pressure, stones, compression, infection, compensatory mechanisms, or adhesion.[6] With regard to stone-induced dilatation, the research team of Yunfu *et al*.[9] inserted stones from the human bile duct into the bile duct of 10 dogs. One month later, sclera jaundice and significantly increased serum levels of bilirubin were observed in six dogs. Methylene blue saline injected above the stones in the bile duct flowed back into the liver in these dogs. The other four dogs did not have sclera jaundice and had normal serum levels of bilirubin. In these four dogs, methylene blue saline injected above the stones in the bile duct flowed into the duodenum through the gaps between the stones (Figure 1). This phenomenon is called by Yunfu *et al*.[9] the "sandstone filtration effect" (like water at the upper end of a pipe flowing to the lower end through a gap between sandstones). The biliary pressure in a healthy adult is 8–12 cmH_2O (5.34–8.00 mmHg = 0.784–1.176 kPa). After bile flowed into the duodenum through the gap between

Table 1. Etiology of 1340 cases of bile duct dilatation.

Etiology	Number	%	Etiology	Number	%
Stones in the bile duct	476	35.5	Relaxation of the sphincter of Oddi	6	0.4
Post-cholecystectomy	51	3.8	Stenosis of the biliary-enteric anastomosis	15	1.1
Biliary parasites	51	3.8	Chronic cholecystitis with incarcerated gallstones in the neck	28	2.1
Cholangitis	53	4.0	Gallbladder cancer	30	2.2
Biliary stricture	14	1.0	Periampullary carcinoma	159	12.0
Extrahepatic cholangiocarcinoma	89	6.6	Cancer of the pancreatic head	179	13.5
Mirizzi syndrome	10	0.7	Hepatic hilar metastasis	17	1.3
Hemobilia	10	0.7	Chronic pancreatitis or cyst pancreatic head	80	6.0
Stenosing papillitis	9	0.7	Ulcer in the duodenal bulb	16	1.2
Duodenal papilla cancer	40	2.9	Peripapillary diverticulitis	7	0.5

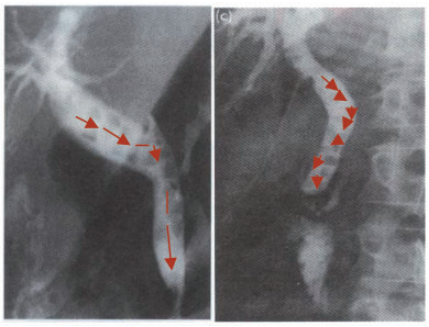

Figure 1. Bile flows into the duodenum through the gap between stones.

the stones or parasites, the biliary pressure did not increase or increased slightly but remained below the threshold for obstructive jaundice (20 mmHg or 2.94 kPa),[10] and did not lead to jaundice. In this case, dilatation is a gradual expansion of the bile duct due to the formation and enlargement of stones. Most cases of bile duct dilatation without jaundice reported in the literature belong to this type.[11]

Clinicopathological classification

From a clinicopathological perspective, dilatation can be induced by obstruction, lesions, or compression according to Lv *et al*.[1] Obstruction-induced dilatation can be caused by obstruction of the lumen of the bile duct by stones, parasites, or other foreign bodies. The causes include intra- and extrahepatic bile duct stones, Mirizzi syndrome, biliary parasites, and severe acute cholangitis. Lesion-induced dilatation is dilatation of the proximal bile duct caused by lesions on the bile duct wall, ectopic pancreas, or tissue destruction of the bile duct wall due to inflammation. These actions result in stenosis at the lesion site. The causes include bile duct polyps, bile duct adenoma, cholangiocarcinoma, biliary papilloma, biliary ectopic pancreas, chronic cholangitis, periampullary carcinoma, duodenal papillary tumor, gallbladder cancer invading the bile duct, primary hemangioma of the bile duct wall, stenosis of a biliary-enteric anastomosis, traumatic biliary stricture, or injury to the biliary–pancreatic junction. Compression-induced dilatation is caused by compression or traction of the bile duct wall by external lesions. The causes include acute/chronic pancreatitis, pancreatic pseudocyst, cancer of the pancreatic head, peripapillary diverticulitis, compression by a metastatic tumor, multiple hepatic cysts, post-bulbar duodenal ulcer compressing the bile duct, biloma, peribiliary aneurysm, duodenal ectopic pancreas, pancreaticoduodenal aneurysm,[12] lymphoma,[13] or cavernous transformation of the portal vein.[14]

Classification by the site of dilatation

The site of dilatation can be divided into intrahepatic, extrahepatic, intra- or extrahepatic bile duct. The causes include stones, parasites, tumors, peribiliary hemangioma, mass compression, inflammation, or injury to the bile duct.

Other classifications

Bile duct dilatation can also be divided into: endogenous and exogenous dilatation; dilatation caused by benign or malignant lesions; dilatation caused by functional and organic lesions.

Relationship between biliary pressure, dilatation, and jaundice

Four main findings have been established from our experiments regarding the relationship between biliary pressure, dilatation, and jaundice. First, after biliary obstruction, there is an increase in biliary pressure, followed by bile duct dilatation to reduce the biliary pressure and, finally, jaundice.[15] Second, the magnitude of bile duct dilatation is positively correlated with biliary pressure. However, biliary pressure reaches a plateau and decreases when it reaches 34 mmHg. Similarly, the diameter of the bile duct does not increase after it reaches 7.5 mm. Hence, the increase in biliary pressure and diameter of the bile duct is self-limiting.[16] The widest diameter of the bile duct in patients with biliary obstruction is >50 mm. The reason is that the bile duct wall expands compliantly with gradual increases in biliary pressure. Compliant dilatation is not only related to the level of biliary pressure, but may also be related to its long duration.[17] Third, when the biliary pressure increases to 20 mmHg, which is close to the threshold for obstructive jaundice in humans (22 mmHg = 2.94 kPa = 30 cmH_2O), bile stained with methylene blue in the bile duct flowed back into the liver, thereby suggesting jaundice. Fourth, the degree of obstructive jaundice is positively correlated with the degree of bile duct dilatation and the level and duration of biliary pressure. It can be inferred from the findings stated above that any diseases or factors that can cause increased biliary pressure can cause secondary bile duct dilatation and jaundice. Therefore, it is necessary to reduce biliary pressure to avoid damage from intra- and extrahepatic bile duct dilatation and jaundice.

Bile duct dilatation and serum levels of total bilirubin

The degree of secondary bile duct dilatation is related to the serum level of total bilirubin. For bile duct dilatation caused by cancer, in general, the more severe the dilatation, the higher is the serum level of total bilirubin and the more profound is the jaundice. However, this scenario is not entirely true for bile duct dilatation caused by stones in the bile duct. We documented 80 cases (22%) of stones in the bile duct with almost no jaundice (serum level of total bilirubin <30 μmol/L). Among them, 9 patients had a diameter of the bile duct of 8–12 mm, 55 had a diameter of 12.1–16.0 mm, 5 had a diameter of 16.1–20.0 mm, and 11 a diameter of >20 mm, accounting for ~10% (11/111) of all patients with a diameter of the bile duct >20 mm. The reason may be the sandstone filtration effect,[9] which prevents biliary obstruction. These findings suggest that the degree of bile duct dilatation is not proportional to jaundice in this subgroup of patients. In other words, patients

with a dilated bile duct may not have jaundice. The ability of bile to flow into the duodenum through the gaps between gallstones is affected by the size, shape, number, and location of the stones. If the stones are conical and incarcerated in the terminal portion of the bile duct, leading to disappearance of the gap between the stones, bile cannot flow into the duodenum. In this case, the degree of bile duct dilatation is proportional to jaundice. Jaundice was not present in 75% of cases of bile duct dilatation caused by chronic pancreatitis. Even if jaundice was present, the maximum serum level of total bilirubin was $\leq$171 μmol/L. Jaundice was also absent in some cases of bile duct dilatation caused by cancer. In addition to early detection of the lesion (which prevents complete biliary obstruction), whether the tumor originates directly from the bile duct wall or indirectly compresses the bile duct wall is important. For example, jaundice has been shown to be present in >90% of cases of bile duct dilatation caused by cholangiocarcinoma because it is a progressive cancer that originates directly from the bile duct wall and, thus, causes biliary stricture readily.[18] In contrast, most pancreatic cancers compress the bile duct wall indirectly, so jaundice was not present in 37% of this subset of patients. In addition, jaundice was not present in some cases with a late diagnosis of cancer because there was necrosis in the center of the tumor, which formed a hollow channel to allow the passage of bile. Smith *et al*.[19] believe that dilatation of the bile duct and pancreatic duct may indicate pancreatic disease, and that obstructive jaundice is highly likely to be caused by pancreatic cancer. Homasset *et al*.[20] reported that of 830 cases with a biliary stricture, normal levels of bilirubin and liver enzymes (alkaline phosphatase and alanine aminotransferase) were measured in 6% of patients with primary hepato-pancreatico-biliary cancer, 21% of cases with pancreatic cancer, 13% of patients with ampullary carcinoma, 7% of cases with distal cholangiocarcinoma, and 9% of patients with hilar cholangiocarcinoma.

Diagnosis

In addition to upper abdominal discomfort or pain, poor appetite, jaundice, and increased serum levels of bilirubin, the diagnosis of intra- and extrahepatic bile duct dilatation is based mainly on imaging: B-ultrasound, computed tomography, magnetic resonance imaging, percutaneous transhepatic cholangial drainage, endoscopic retrograde cholangiopancreatography, and isotope labeling.[21–25] In particular, the Medical Image Three-Dimensional Visualization System provides an accurate diagnosis of intrahepatic calculi.[26]

Treatment strategy

Experimental studies have shown that collagen content in the liver increases significantly one week after bile duct obstruction, obvious fibrosis appears after two weeks, and liver cirrhosis develops after three to four weeks. Mathie *et al*.[27] reported that after two weeks of ligation of the bile duct in dogs, blood flow in the hepatic artery decreased by 36%, portal blood flow decreased by 44%, total hepatic blood flow decreased by 41%, and portal vascular resistance increased by 187% as measured by an electromagnetic flow probe. The reduction in hepatic arterial blood flow was due to the decreased response of the peripheral blood vessels to increased pressure, which resulted in a decrease in systemic blood pressure. The decrease in portal vein blood flow was the result of increased portal vascular resistance. An increase in hepatic arterial blood flow in late obstructive jaundice is not sufficient to compensate for the further decrease in portal blood flow. As a result, the total hepatic blood flow is reduced, leading to liver cirrhosis and portal hypertension which, in turn, causes life-threatening upper gastrointestinal hemorrhage. Moreover, prolonged dilatation of the bile duct and bile stasis can lead to biliary cirrhosis, impaired liver function, and decompensation.[28] For example, the synthesis of plasma albumin and clotting factors, the secretion of immunoglobulins, and the ability of the liver to remove inflammatory mediators, damaged blood cells, cell debris, fiber-degradation products and endotoxins decrease, and the levels of proinflammatory cytokines increase, which increases the risk of biliary tract infections, and leads to a series of adverse consequences, including a possible need for liver transplantation at a late stage.[29] Therefore, a surgical procedure should be undertaken once the cause of bile duct dilatation has been identified. The purpose of the surgical procedure is to eliminate the cause and remove the lesion to establish adequate bile drainage by surgical or endoscopic means.[30]

Treatment methods vary depending on the cause. Surgical or endoscopic treatment should be undertaken in most cases of bile duct dilatation. Conservative treatment is indicated only for compensatory bile duct dilatation, and bile duct dilatation due to biliary parasites, dysfunction of the sphincter of Oddi, peripapillary diverticulitis, or chronic inflammation, but a surgical procedure should be carried out if improvement is not observed.[31,32] Common surgical procedures include choledochectomy for stone removal, lesion resection and biliary-enteric drainage, Oddi sphincterotomy, stenting for biliary strictures, and pancreaticoduodenectomy for cancer of the lower bile duct, periampullary cancer, duodenal papilla cancer, and cancer of the pancreatic head. Endoscopic surgery,[33] laparoscopic surgery,[34] liver transplantation, and robotic surgery can also be applied.[35,36]

AUTHORS' CONTRIBUTIONS

YFL, NL, HFW, and ZRL, contributed equally to this work. All authors participated in the design, read literature, statistics, data analysis, and manuscript review. Specifically, Lei said that YFL is mainly responsible for project design, collecting and analyzing data, and writing papers; NL and HFW are mainly responsible for collecting data, statistical analysis; ZRL mainly assisting in design and funding.

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ORCID iD

Yunfu Lv https://orcid.org/0000-0003-0451-399X

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