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GUIDELINE

# Japanese clinical practice guidelines for congenital biliary dilatation

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**Abstract** Until now, there have been no practical clinical guidelines for congenital biliary dilatation (CBD). In this review article, the Japanese Study Group on Congenital Biliary Dilatation (JSCBD) propose to establish clinical practice guidelines for CBD. Because the evidence-based literature is relatively small, we decided to create guidelines based on the consensus of experts, using the medical literature for reference. A total of 20 clinical questions (CQs) were considered by the members of the editorial committee responsible for the guidelines. The CQs included the distinct aspects of CBD: (1) Concepts and Pathology (three CQs); (2) Diagnosis (six CQs); (3) Pancreaticobiliary Complications (three CQs); Treatments and Prognosis (eight CQs). Each statements and comments for CQs were made by the guidelines committee members. CQs were finally approved after review by members of the editorial committee and the guidelines evaluation board of CBD. These guidelines were created to provide assistance in the clinical practice of CBD management; their contents focus on clinical utility, and they include general information on CBD to make this disease more widely recognized.

**Keywords** Anomaly · Choledochal cyst · Congenital biliary dilatation · Pancreaticobiliary maljunction

## Introduction

The purpose of this research is the preparation of clinical practice guidelines (CPG), which encompasses diagnostic guidelines based on scientific grounds and agreement with the goal of improving the level of treatment of childhood-onset intractable hepatobiliary pancreatic diseases. In congenital biliary dilatation (CBD), it is known that the majority of cases are accompanied by pancreaticobiliary maljunction (PBM), and since the Japanese Study Group on Congenital Biliary Dilatation (JSCBD) commenced nationwide patient registration in 1990, approximately 3,000 cases of PBM have been registered to date. In addition, in 2012, Japanese CPG for PBM was reported. However, the definition and diagnostic criteria of CBD are yet to be established, neither have CPG been prepared.

Thus, a working group was formed to prepare the CBD CPG with the aid of the Health and Labor Sciences Research Grant. The dual purpose of this study was: (1) the establishment of the definition and diagnostic criteria of CBD; and (2) preparation of the CPG of CBD according to Minds 2014. Regarding specific policies, the definition and CPG of CBD have been deliberated and prepared at the guidelines committee of the JSCBD and announced as the CBD CPG 2015. Regarding the CPG preparation, a part of the Japanese CPG for PBM [1] was extracted and partially modified to create

20 clinical questions (CQs) regarding CBD. Specifically, they are Concepts and Pathology (three CQs), (2) Diagnosis (six CQs), (3) Pancreatobiliary Complications (three CQs), and (4) Treatments and Prognosis (eight CQs). Statements and comments on each CQ were newly prepared by each committee member. In addition to the literature searched under Japanese CPG for PBM, literature searches made by 2016 under Pubmed were added, with each cited reference categorized according to the research design, and a systematic review used in the GRADE system was conducted. From the level classification of the cited reference, the level of the evidence as a whole was determined, and the level of recommendation of the statement was also determined. Furthermore, consensus was formed through the votes of eight committee members using the Delphi method in order to complete the CBD CPG. It is notable that regarding CBD, there exists minimal literature with a high level of evidence. Thus, regarding statements of which it is difficult to gauge the level of recommendation in terms of literature, assessment was made with consideration to expert opinion.

The CPG are reference material and are not intended to regulate the discretion of physicians. However, regarding the treatment of CBD, which is a rare disease, it is expected that there would be difficulties in the diagnosis and treatment due to a lack of experience. It is hoped that the guidelines provided herein will deepen the understanding of the pathology of CBD and benefit the patients, their families and the daily treatment by medical professionals.

## Guideline preparation method

### Literature search, systematic review

In addition to the literature searched under the PBM guidelines, literature searches up to 2016 from Pubmed were added, and cited references which were adopted for each CQ were classified and noted. The evidence quality at the time of assessment was classified into high, medium and low. Next, the important outcome included for each CQ was presented, and the articles related to the outcome were divided into groups. Using the systematic review method used in the GRADE system, an assessment was made in order to determine the level of the overall evidence and was noted "Level *."

### Determination of the recommendation level

The level of recommendation was determined based on the results of the evidence level for each CQ. With recommendation level "1," the notation was "implementation recommended," and for recommendation level "2," the notation was "implementation suggested." For CQ irrelevant to diagnosis and treatment, the recommendation level was not given and only the evidence level was noted. Regarding the consensus-reaching method, the Delphi method was generally used, and if consensus could not be reached at one time, the results were announced and votes were taken twice and three times until over 70% of the approval was obtained.

## Diagnostic criteria for congenital biliary dilatation 2015 [2]

### Definition

CBD is a congenital malformation involving both local dilatation of the extrahepatic bile duct, including the common bile duct, and PBM. However, cases associated with intrahepatic bile duct dilatation can be included in this entity.

### Pathophysiology

Various kinds of pathological conditions, such as flow disturbances of bile and pancreatic juice, reciprocal reflux between bile and pancreatic juice, and malignancy of biliary systems, can occur in the hepatobiliary system and pancreas secondary to bile duct dilatation and PBM.

### Diagnostic criteria

For a diagnosis of CBD, both abnormal dilatation of the bile duct and PBM must be evident by either imaging or anatomical examination. Acquired or secondary dilatation of the bile duct, which is caused by obstruction due to biliary stones or malignancy, is strictly excluded.

### Diagnosis of biliary dilatation

Diagnosis of biliary dilatation must be established by using the diameter, site, and characteristic form of dilatation of the bile duct.

#### *Diameter of the bile duct*

Measurement of the diameter of the bile duct must be obtained by non-pressure imaging modalities on the biliary system, such as ultrasonography, magnetic resonance cholangiopancreatography (MRCP), and computed tomography (CT; including multi-planar reconstruction [MPR]

images provided by multi-detector row computed tomography [MD-CT], etc). The inner diameter of the most dilated site of the common bile duct must be estimated as the maximum diameter for the patient. The standard diameter of the bile duct, measured by ultrasonography, significantly correlates with age, and diagnosis of dilatation is considered based on the upper limit of bile duct diameter in each patient.

*Site of bile duct dilatation*

The common bile duct must be included as the site of bile duct dilatation. In addition, cases involving intrahepatic bile duct dilatation can be included in CBD.

*Form of bile duct dilatation*

Cystic dilatation and cylindrical (fusiform) dilatation of the common bile duct can be classified subjectively. CBD is expressed as Ia, Ic, and IV-A according to Todani's classification.

Diagnosis of PBM

Diagnosis of PBM is essential for diagnosis of CBD, and it must be diagnosed strictly based on the Diagnostic Criteria for Pancreaticobiliary Maljunction 2013.

## Chapter I: Concepts and pathology

CQ-I-1: What is the pathogenesis of CBD?

- The pathogenesis of CBD is yet to be elucidated. However, it is closely associated with the development of PBM.
- Regarding the pathogenesis of PBM, there is a convincing hypothesis suggesting that it involves a dysplasia of the ventral pancreas that is formed from the bilobed ventral pancreatic anlagen by the 4th week of gestation.
- Convincing evidence regarding the development of biliary dilatation states that it is associated with the mechanisms involved in lumen formation in the primitive gut.

Comments

CBD is thought to occur in the process of the development of PBM. Because the pathogenesis of PBM has not been elucidated, the details regarding the pathogenesis of CBD is likewise unknown. The current state is that we can only make an assumption based on what is presently understood regarding the development of the pancreas and the biliary tract.

The biliary system develops from the hepatic diverticulum that originates from the foregut. The hepatic diverticulum itself transforms into the common bile duct, cystic duct and gallbladder. The bilobed ventral pancreatic anlagen (cranial and caudal), each communicating with the foregut through a duct, develops from a part of the hepatic diverticulum that is close to where the hepatic diverticulum is attached to the foregut, and they subsequently fuse into a monolobed ventral pancreas at about the 4th week of gestation [3]. With the rotation of the intestinal tract, the ventral pancreas and dorsal pancreas are fused at about the 6th week, and bile is produced from about the 12th week of gestation [4].

PBM is understood to develop due to a dysplasia of the ventral pancreas which is formed from the bilobed ventral pancreatic anlagen, at about the 4th week of gestation, a process that is considered to affect the formation of the hepatic diverticulum. Normally, the cranial pancreatic anlagen duct disappears. If the cranial pancreatic anlagen duct remains, a complex PBM is formed in which the pancreatic duct system and the biliary system join at two points. If a dysplasia of the ventral pancreatic anlagen causes the end of the common bile duct of the same site to be occluded, PBM with biliary dilatation, namely CBD, will occur. If the dysplasia of the dorsal ventral pancreatic anlagen occurs, the result is PBM without dilatation of the biliary system, namely biliary non-dilatation PBM [1].

The lumen of the primitive gut, especially that of the foregut that generates the hepatic diverticulum, becomes occluded due to epithelial proliferation, although the very same epithelium subsequently recanalizes to finally form the lumen of the intestine. The abnormal dilatation of the biliary tree is thought to occur in the common bile duct, cystic duct, and gallbladder (all of which originate from the hepatic diverticulum), as well as in the hepatic duct (which originates from the hepatic diverticular epithelia) when the continuity between the hepatic diverticular epithelia and that of the primitive gut is lost [5]. Furthermore, when the bile duct bud and the ventral pancreatic anlagen are fused together and the subsequent fusing with the pancreatic duct branches take place, a vacuolization disorder in this region takes place. There is a theory that when vacuolization does not take place in the lower bile duct (transection type occlusion of the bile duct), the result is CBD, when the vacuolization disorder is minor, the result is PBM with minor dilatation of the bile duct, and if there is no vacuolization disorder, the result is non-dilatation PBM.

Regarding the pathogenesis of the dilatation of the bile duct, there exist such theories as the theory of pancreatic juice reflux accompanying PBM, the theory of a fragile bile duct due to premature elastic fiber of the bile duct wall, the theory of biliary obstruction arising from congenital stenosis of the peripheral bile duct [6–8], etc. However, there are many obscure points at the present time.

CQ-I-2: Are there any differences in the incidence of CBD between the different sexes or in distinct regions?

- The male-female ratio in CBD is approximately 1:3, and it is especially predominant in young women (Level C).
- Orientals are considered to be more susceptible to this disease than Occidentals (Level D).

Comments

According to the results of a nationwide study conducted by the Japanese Study Group on Pancreaticobiliary Maljunction (JSPBM), women are three times more likely to be affected by this disease than men, and women up to their 20s account for the majority of patients [1]. While the exact incidences in various ethnic groups are unknown, there are often reports from Japan, China, South Korea, and the incidence of CBD appears to be higher in Orientals than in Occidentals [9]. Approximately one in every 1,000 persons is affected by this disease in Japan [10], and the incidences of CBD and PBM are 0.3% and 4.1%, respectively, in South Korea [11]. In Western countries, it is reported that CBD occurs in one of every two million births, and in one of every 50,000–150,000 individuals [12–14].

CQ-I-3: What are pancreatobiliary reflux and biliopancreatic reflux in CBD?

- In PBM, the reciprocal reflux of pancreatic juices and bile occur because the papillary sphincter fails to control the pancreaticobiliary junction (Level B).
- The reflux of pancreatic juices into the biliary tract is evident from abnormally high levels of pancreatic enzymes in bile, which may subsequently be one of the causes of biliary tract carcinogenesis (Level B).
- It is clear that reflux of bile into the pancreatic duct also occurs, although further research is necessary to determine its involvement in disease states such as pancreatitis (Level D).

Comments

In PBM, the pancreatic and bile ducts join at a site that lies outside the area of influence of the papillary sphincter, and this phenomenon leads to the reciprocal reflux of pancreatic juices and bile. Normally, the intraductal pressure in the pancreatic duct is higher than in the bile duct [15] and thus, the idea that pancreatic juices reflux into the biliary tract is beyond dispute. Pancreatic juice reflux into the biliary tract is also apparent from the findings that the bile samples from the gallbladder or bile duct of patients with PBM contain abnormally high levels of pancreatic enzymes such as amylase and lipase [16]. In recent times, it has become possible to track the reflux through images such as secretin-stimulated dynamic MRCP [17]. The pancreatic enzymes flowing into the biliary tract are activated by enterokinase in the bile, and it is thought that the repeated cycle of biliary epithelium disorder and regeneration leads to carcinogenesis [18, 19].

On the other hand, there are only a few reports regarding the reflux of bile into the pancreatic duct. In PBM, it is well known that the pancreatic duct is enhanced in direct cholangiography, such as that performed through a T-tube. However, as this procedure is a condition in which artificial pressure is applied, it is unclear whether the reflux is physiological. In the T-tube cholangiography, even in patients with no PBM, the pancreatic duct is enhanced with contrast medium in 13.3%–27% of cases [20–22].

Fumino et al. [23] reported that with drip infusion cholangiography with CT (DIC-CT) the pancreatic duct could be seen in six out of 15 patients with PBM, visualizing the reflux of bile into the pancreatic duct by means of imaging. However, it is not clear under what conditions such reflux against the pressure gradient can occur. Similarly, it remains unclear what kind of clinical condition the reflux of the pancreatic juices causes, and whether this reflux contributes to the onset of pancreatitis; both of these issues require further study.

## Chapter II: Diagnosis

CQ-II-1: What kind of clinical manifestations are associated with CBD?

- The main symptoms include abdominal pain, vomiting, jaundice, and fever (Level B).
- Abdominal pain, jaundice and an abdominal mass have been referred to as the triad of manifestations in CBD; however, all three manifestations are seldom present at the same time (Level D).

Comments

A survey was carried out by the JSPBM during the 10 years between 1990 and 1999 on 1,627 cases nationwide [16]. Adults with dilatation of 10 mm or wider, and pediatric patients with dilatation of 5 mm or wider were categorized as having biliary dilatation, and they were subdivided into those with biliary dilatation (1,239 cases) and those without (388 cases), and the former group was categorized as CBD and the latter group was categorized as non-dilation PBM. Of those with CBD, 86.1% were symptomatic, and the main symptoms were abdominal pain (78%), vomiting (36%), jaundice (22%), and fever (22%).

Abdominal pain, jaundice and an abdominal mass have been referred to as the triad of manifestations; however, the proportion of patients who manifest all symptoms are variable. In pediatric patients, there is a correlation between the symptoms and the age of onset, and the differences seen according to the age were prominent. In addition, the symptoms were also related to biliary dilatation form. Many patients with neonatal/infant onset have been classified as the cystic type, whose main symptoms are jaundice and abdominal mass, while patients with onset during early childhood mostly have a fusiform/cylindrical type of biliary dilatation, manifesting mainly abdominal pain [1]. Among the triad of manifestations, a massive cystic-type abdominal mass is seldom seen in adults, thus limiting the triad of symptoms to children.

CQ-II-2: What type of blood tests should be conducted for CBD?

- During asymptomatic periods, abnormal results do not appear in blood tests. When the patient becomes symptomatic, it is recommended that serum levels of amylase, direct bilirubin, biliary enzymes be measured (Recommendation level 1, Level C).

Comments

In CBD, PBM and biliary complications (stones, stenosis, etc), bile from meals and dehydration, and dynamic or qualitative changes in pancreatic juices may cause symptoms to appear temporarily. In other words, the occurrence of symptoms is thought to stem from complications, and abnormalities in the blood test are seen transiently during symptomatic periods. Because test values return to normal when symptoms disappear, most abnormalities in the blood test are attributed to complications. Examination items that manifest abnormal values and the mechanisms thereof are as described below.

*Amylase*

Abdominal pain occurs when pancreatic juices are retained and is usually accompanied by hyperamylasemia. The younger the patient, the higher the frequency of pancreatitis-like symptoms such as abdominal pain, nausea and vomiting. The majority of pancreatitis occurs when the protein plug in the common duct is impacted in the papilla, causing pancreatic juices and bile to be retained, elevating the internal pressure of the pancreatic duct and biliary tract, causing abdominal pain. There is experimental data indicating that pancreatic juices enter the biliary system, further refluxing into the blood stream due to elevation of the internal pressure of the biliary tract [24].

*Bilirubin*

There is elevation of mainly the direct bilirubin. When stones or protein plugs exist within the biliary system or common channel due to temporary bile retention, occlusive jaundice may occur. However, while jaundice seen in biliary atresia is continuous, jaundice seen in CBD is intermittent.

*Biliary enzymes*

Elevation is seen when biliary obstruction occurs. According to the PBM patient registration [25], specific factors in the blood tests and the percentage of patients manifesting abnormal values (number of patients with abnormal values/number of patients studied) were: amylase 20.4% (182/894), elastase 1 31.8% (89/280), trypsin 35.5% (55/155), phospholipase A2 33.3% (34/102), total bilirubin 29.4% (225/766), direct bilirubin 23.3% (200/859), alkaline phosphatase 45.4% (435/959), and γ-GPT 42.7% (395/925).

CQ-II-3: Is ultrasound (US) effective in CBD screening?

- US detects the dilatation of the common bile duct, intrahepatic bile duct and the thickening of the hypoechoic inner layer of the gallbladder, presenting the first opportunity to diagnose CBD. It is useful to screen for CBD and implementation is recommended (Recommendation level 1, Level B).

Comments

In the diagnosis of CBD, US is a simple and non-invasive form of imaging, and is a vital and useful screening method [26, 27]. When conducting an US on cases that are not clinically recognized as jaundice, and severe dilatation of the bile duct is observed, CBD is suspected,

requiring the diagnosis of PBM using MRCP, endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) [26, 27]. In comparison to dilatation of the bile duct accompanied by biliary occlusion due to choledocholithiasis or malignant tumor, the dilatation of the bile duct in CBD is characterized by being localized, with sudden transition to a normal-size bile duct.

In CBD, with the influence of the accompanying PBM, a thickening of the gallbladder wall can often be observed. In PBM, a mixture of pancreatic juices and bile is retained in the gallbladder, causing repeated inflammation and recovery of the gallbladder epithelial wall. The resulting enhanced cell proliferation in the gallbladder wall is thought to provoke hyperplasia and subsequent dysplasia, which is assumed to trigger carcinogenesis in the gallbladder [28, 29]. In studying pathological tissue samples, hyperplasia often takes a papillary form, and the membrane height reaches about 1 mm [29], and the area is often identified by the US as a thickening of the low echo layer of the inner gallbladder wall [27]. In US, PBM cannot be depicted; however, from dilatation of the bile duct and thickening of the gallbladder wall, CBD can be detected.

CQ-II-4: Is MRCP useful in the diagnosis of CBD?

- MRCP is useful for diagnosis, as it depicts the overall biliary system including the enhanced image of the intrahepatic/extrahepatic bile ducts as well as the depiction of PBM. In particular, it is a non-invasive test for pediatric patients and implementation is recommended (Recommended level 1, Level B).
- However, for infants and patients with a short common channel, diagnosis may at times be difficult.

Comments

In the diagnosis of CBD, MRCP is superior to ERCP in the depiction of the overall biliary tract including the enhanced image of the intrahepatic and extrahepatic bile duct. In particular, it is a non-invasive test for pediatric patients, and in cases where CBD is suspected, it is thought to be the first test that should be carried out. However, discretion is required for infants and patients with a short common channel due to the fact that diagnosis may be difficult in such cases.

The rate of MRCP accurately detecting CBD is reported to be 38%–100% [30–36]. In addition, the diagnostic criteria of MRCP for PBM is equivalent to ERCP; however, the definitive detection rate thereof is reported to be 60%–100% [30–38]. The detection rates of PBM for adults and children are reported to be 82%–100% [32, 34, 35, 37] and 40%–80% [30, 31, 33, 36–38], respectively. In cases where the common channel is 15 mm or longer, the detection rate is reported to be 82% [32]. It should be noted that ERCP is indispensable to reach a definitive diagnosis.

The reason for false-positive diagnosis is often due to mistakenly diagnosing the overlap of the bile duct and pancreatic duct for maljunction. As MRCP does not possess such a high spatial resolution as X-rays, it is unclear how precisely it depicts complicated junctions [30–38].

CQ-II-5: Is ERCP useful in the diagnosis of CBD?

- ERCP is useful in the diagnosis of the dilatation of the extrahepatic bile duct and PBM, and implementation is proposed (Recommended level 2, Level B).
- However, in pediatric patients, it is an invasive test and adaptation should be carefully considered along with other image findings.

Comments

In CBD, dilatation of the extrahepatic bile duct including the common bile duct is local, and the dilatation of the extrahepatic bile duct is cystic, cylindrical or fusiform. In cases of extrahepatic bile duct dilatation, there is often stenosis in the hepatic hilum, and there is a sudden move of the dilated region of the extrahepatic bile duct to a normal-size upper bile duct. In cystic dilatation, there is a narrow segment at the end of the bile duct, where the bile duct and pancreatic duct join at right angles (bile duct [junction] type). In cylindrical and fusiform cases, the narrowing at the end of the bile duct is minor, and the pancreatic duct joins the bile duct at an acute angle (pancreatic [junction] type). When the dilatation transcends the junction of three ducts to the hepatic side, there is local dilatation at origin of the cystic duct.

MRCP and DIC-CT are superior in depicting the dilated bile duct and intrahepatic bile duct seen in CBD. On the other hand, in order to grasp the whole picture of the biliary system of CBD by means of ERCP, injection of a great quantity of contrast media is required, and it is common for it to cause pain due to a sudden rise in the internal pressure of the biliary tract.

ERCP is useful in the diagnosis of accompanying PBM. In PBM, it is observed that the pancreatic duct and bile duct are joined by an abnormally long common channel, or are joined in an abnormal manner [39]. In PBM, the action of the papillary sphincter does not extend to the junction of the

pancreatic and bile ducts. Therefore, the communication between the pancreatic and bile ducts is maintained not only during the relaxation phase of the papillary sphincter, but also during the contraction phase. Localized dilatation is often seen in the common channel; however, the dorsal pancreatic duct appears normal [40]. Sometimes, a protein plug is observed in the common channel. In recent years, through MRCP, 3D-DIC-CT, EUS and MPR MD-CT images, it has become possible to diagnosis PBM by observing the outer wall junction of the long common channel or pancreatic tube with the bile duct [39]. However, in cases where the common channel is short or there is a complex junction, a definitive diagnosis of PBM is required by means of direct cholangiography such as ERCP [39].

ERCP is able to clearly depict the details of the pancreatic and biliary junction. However, it is a test accompanied by procedural accidents such as pancreatitis. Particularly in the diagnosis of CBD in pediatric patients, adaptation should be carefully considered along with other image findings.

CQ-II-6: Is it possible to diagnose CBD prenatally?

- There are many cases of prenatal diagnosis; however, this is not possible in all cases (Level C).

Comments

The majority of CBD cases diagnosed prenatally are the Ia type, and they are detected as a cystic lesion adjoining the tubular structure heading towards the lower surface of the liver [41] in prenatal fetal US checkups. Increasing numbers of cases are presently being diagnosed prenatally [41–43]. Detection by means of prenatal fetal US checkups have become possible from the 20th week of gestation [44], and in some cases, diagnosis at 15 weeks of gestation has become possible, at the earliest [42].

Points to verify in the fetal US checkups for definitive diagnosis are: (1) continuity of the cyst to the intrahepatic bile duct [41]; (2) increase in the bile duct diameter corresponding to the number of weeks of gestation [45, 46]; and (3) detection of a cyst [46, 47].

Differential diagnosis must rule out duodenal atresia, renal cyst, ovarian cyst, hepatic cyst and lymphangioma; however, biliary atresia (I cyst) present a problem. With an US checkup, it is considered difficult to differentiate between CBD and I cyst biliary atresia [48]. Therefore, even when the prenatal diagnosis is CBD, some cases are diagnosed for the first time as biliary atresia intraoperatively. It is important to differentiate the increase in bile duct diameter corresponding to the number of weeks of gestation (particularly from the 35th week onwards) to biliary atresia in which the bile duct diameter does not increase [46, 49].

Prenatal MRI [50] and 3D US checkups [51] are useful as auxiliary methods of diagnosis. In MRI, the dilated bile duct appearing to taper off in the cranial-caudal direction is useful in the diagnosis [50]. One characteristic of prenatal diagnosis is that there are few cases of intrahepatic biliary dilatation in comparison to other age groups [41].

## Chapter III: Pancreatobiliary complications

CQ-III-1: How common are gallstones in the biliary tract in association with CBD and what are their characteristics?

- Biliary tract stones are found in 17.9% of patients with CBD (Level C).
- Among the biliary tract stones, gallstones in the bile duct are most frequently found in patients with CBD (Level C).
- Of the different types of gallstones found in patients with CBD, bilirubinate gallstones are most frequently seen (Level D).

Comments

Biliary tract stones develop in 17.9% of patients with CBD [16]. They are observed in 24.1% of adults and 9.0% of pediatric patients, indicating that this is a frequent complication in adults [52]. It is reported that in CBD, the ratio of occurrence is: gallbladder stones 12.7%, common bile duct stones 65.8%, and intrahepatic stones 21.5% [53]. According to another report, among the PBM cases, 100% of biliary stones occurring with cystic dilatation are bile duct stones [54]. From the foregoing, it can be said that the greater number of biliary tract stones accompanying CBD are bile duct stones.

In patients with CBD, cholesterol gallstones were found in 16.7% of cases, while mixed stones were found in 25% of cases, and bilirubinate gallstones were found in 58.3% of cases, indicating the greater ratio of bilirubinate stones [54].

CQ-III-2: How often does acute pancreatitis develop in conjunction with CBD?

- It is reported that the frequency of acute pancreatitis occurring in patients with CBD is 10.5%–56% for adults and 23% for children (Level C).

Comments

It is reported that the frequency of acute pancreatitis occurring in patients with CBD is: 10.5%–56% for adults [55, 56], and 23% [57] for children. The correlation between the pathogenesis of pancreatitis occurring in conjunction with CBD has been suggested [58], and the frequency of pancreatitis accompanying PBM is approximately 9% in adults and approximately 28%–43.6% in children [52]. Temporary abdominal pain due to protein plugs and hyperamylasemia is characteristic of PBM [59]; therefore, there is a possibility that these may also be diagnosed as acute pancreatitis.

CQ-III-3: What is the incidence of biliary tract cancer in CBD and what are its characteristics?

- The frequency of biliary tract cancer occurring in children (15 years or younger) is unknown; however, seven cases of bile duct cancer and one case of gallbladder cancer have been reported as occurring in patients with CBD (Level C).
- The frequency of biliary tract cancer occurring in adults with CBD is extremely high at 21.6%, and the ratio of main malignancies is 62.3% for gallbladder cancer and 32.1% for bile duct cancer (Level C).
- The age range when adult patients are predisposed to develop biliary tract cancers is 50–65 years. This indicates that this age range is 15–20 years earlier than the usual cancer onset age (Level D).

Comments

Patients with CBD have a high rate of biliary tract cancers [16]. In Western countries, the rate of CBD is 20%, but this is based on a few cases ($n$ = 20) [60]. In Japan, the nationwide survey taken during 1997–2007 regarding the incidence of biliary tract cancer concurrent with CBD is the greatest in scale ($n$ = 2,561). In the aforementioned survey, biliary tract cancer is detected in 21.6% of adult patients with CBD [52]. The main malignancies are gallbladder cancer 62.3%, bile duct cancer 62.5%, and gallbladder + bile duct cancer 4.7%, indicating that gallbladder cancer is most frequently found in association with these conditions [52].

Regarding pediatric patients younger than 15 years of age in Japan, only nine cases of biliary tract cancer have been reported (seven bile duct cancers and two gallbladder cancers), and eight were CBD cases [61–66]. The main malignancies in conjunction with CBD were seven bile duct cancers and one gallbladder cancer.

It is reported that CBD patients are a high risk group for developing biliary tract cancers [16], and the age range that these CBD patients are predisposed to developing gallbladder cancer is 60.1 ± 10.4 years, 52.0 ± 15.0 years for bile duct cancer, and 55.0 ± 14.6 years for gallbladder cancer + bile duct cancer. Comparing these figures to cases without cancer, the patients are more than 10 years older. However, when considering that the age range when people in general in Japan are predisposed to developing biliary tract cancers is 75–79 years, patients with CBD develop biliary tract cancers about 15–20 years earlier than usual [52, 67].

## Chapter IV: Treatments and diagnosis

CQ-IV-1: When is it recommended to operate on patients with CBD?

- There are no clear evidence-based recommendations as to when patients with CBD should undergo surgery. However, as CBD enhances the risk of developing biliary tract cancer and as juvenile patients can develop cancer, immediate surgery is recommended once a definitive diagnosis is established (Recommendation level 2, Level C).
- Symptomatic neonates and infants should be operated on as soon as possible, whereas elective operations at around 3–6 months of age may be considered for asymptomatic cases while liver functions, etc. are monitored carefully (Recommendation level 2, Level C).

Comments

According to the nationwide survey conducted by JSPBM between 1990 and 2007 [52], the rate of developing biliary tract cancers is significantly higher in patients with CBD in comparison to the general Japanese population (0.0141%). Considering the incidence rate of concurrent cancer in patients 15 years and older, the youngest average age of concurrent biliary tract cancer with CBD was 52.0 ± 15.0 years, and in this cohort, the youngest patient was a boy of 3 years of age [66]. Therefore, from the perspective of cancer prevention, there is no clear evidence indicating the timing of surgery. However, as there are reports of children and young adults with concurrent cancer, surgery should be performed as soon as a definitive diagnosis is reached.

Timing of surgery for neonates and infants should be determined carefully, with consideration to prenatal diagnosis and symptomatic changes such as jaundice and hepatic dysfunction. In neonates and infants, there may be a sudden progress in liver failure, intracranial hemorrhage

[68], or hepatic fibrosis or cirrhosis may be observed histologically. Thus, surgery should be performed as soon as possible in symptomatic cases. In asymptomatic individuals, many recommend that it is better to wait until they are 3–6 months old or older to avoid the risk of ruptured sutures or anastomotic stricture, both of which are attributed to the small diameter of their bile ducts [69].

CQ-IV-2: How should protein plugs be handled?

- When a protein plug is persistently incarcerated in the narrow distal segment or in the common channel, the symptoms may become exacerbated or protracted (leading to a worst-case scenario of biliary tract perforation), requiring biliary drainage or emergency surgery (Recommendation level 2, Level C).
- In general, protein plugs are fragile, and they have disappeared spontaneously in about 50% of patients by the time they undergo radical surgery. Protein plugs that persist until the time of surgery can generally be eliminated by lavage through a biliary drainage tube inserted in the narrow distal segment, or they can be removed with a spoon-shaped sonde (Level C).
- The future formation of protein plugs can be avoided with concomitant complete resection of the intrapancreatic bile duct is performed during a biliary diversion procedure (Level C).

Comments

In CBD, symptoms such as abdominal pain, vomiting, jaundice, and hyperamylasemia arise due to increase in the pancreatic intraductal pressure and in the biliary tract pressure that result from the obstruction of the common channel or the narrow segment by protein plugs. The majority of obstructions are caused by protein plugs, but in rare cases, they are caused by fatty acid calcium stones [59, 70]. Obstruction by protein plugs occurs primarily during childhood; however, they occur through the same mechanism in adulthood [71]. Hyperamylasemia does not really reflect true pancreatitis, but rather, in most cases it is considered to be the result of amylase flowing back from the bile into the blood through cholangio-venous reflux [72]. Protein plugs are made of lithostathine. Lithostathine is a protein discovered in pancreatic stones; thus, it was initially named pancreatic stone protein. Lithostathine is secreted from the pancreas and is soluble. However, it flows back into the biliary tract through due to PBM, and is broken down by trypsin, which also flows back at the same time and becomes activated, thereby making lithostathine insoluble. Insoluble lithostathine forms raw fibers through self-assembly by means of electrical coupling, which are gathered together to create protein plugs [73]. Experimentally, electric coupling is eliminated by acid and base, and protein plugs are dissolved [74].

Protein plugs are X-ray negative, and are translucent on cholangiopancreatography. MR detects tomographic images more easily. They are detected in more than 30% of pediatric cases [59]. Since most protein plugs are fragile and disappear naturally, and the symptoms are transient. When protein plugs are repeatedly produced, intermittent symptoms appear. When protein plugs are persistent and remain incarcerated in the common channel or the narrow distal segment, symptoms worsen or are protracted. In such situations, biliary drainage or emergency surgery becomes necessary [59]. There are reports that such biliary drainage as percutaneous transhepatic biliary drainage, laparotomic/laparoscopic external drainage (such as T-tube drainage or external cholecystostomy), and drainage performed through endoscopic procedures (indwelling transnasal tube, stenting, sphincterotomy) have been performed [59, 75]. Symptoms rapidly disappear with drainage, and at the same time, there is the advantage that information regarding the pancreatic duct, intrapancreatic bile duct, hepatic-side bile duct may be obtained [59]. Most protein plugs seen in the drainage disappear naturally, or disappear by means of lavage through the indwelling tube, making surgical removal unnecessary. Of protein plug detection cases, only 20%–30% of protein plugs remain in the common channel or pancreatic duct until the diversion procedure. Even if such plugs persist, most of them can be removed through the narrow distal segment of the lower bile duct, only a few cases requiring pancreatic ductotomy [76, 77]. If complete resection of the pancreatic duct is performed, care is required so as to avoid postoperative pancreatic duct stenosis [76]. There are also reports on the use of small-diameter endoscopy in the protein plug removal in the common channel [77]. However, while there is a consensus on the need for protein plug removal during the diversion procedure, it is not known how frequently pancreatitis and other postoperative problems result when protein plugs remain.

If the pancreatic bile duct is completely resected through surgery, no symptoms from postoperative reformation of protein plugs will occur [78]. Conversely, if there are protein plugs remaining in the intrapancreatic bile duct, protein plugs will recur even after the diversion procedure. In addition, there are reports pointing out that even if papillary sphincterotomy and sphincteroplasty are performed due to attributing the protein plugs to the papillary function, if remnants in the intrapancreatic bile duct exist, protein plugs will recur [79, 80]. In other words, with regard to the pancreatic juice discharge function, the papillary functions of

maljunction patients are normal and irrelevant to the formation of protein plugs. However, if there are remnants of the bile duct, lithostathine breakdown results, leading to the reformation of protein plugs, although the mechanism is yet unclear.

CQ-IV-3: What are methods of surgery for CBD?

*Q1: What is the most recommended method of surgery for CBD?*

- Extrahepatic bile duct resection encompassing the gallbladder is recommended, as the incidence for concurrent biliary tract cancer is high (Recommendation level 1, Level B).
- Cyst-enterostomy (internal drainage operation) should be ruled out and is not recommended (Recommendation level 1, Level B).

*Q2: To what extent should the intrapancreatic bile duct be resected?*

- It is recommended that the pancreatic bile duct be resected just above the pancreatic duct junction, leaving as little as possible (Recommendation level 1, Level B).

*Q3: When the dilated lesion includes the intrahepatic bile duct, to what extent should resection be made?*

- There is no unified view. There are reports of hepatectomy, but it is regarded as excessively invasive in pediatric patients (Level D).

Comments

CBD is accompanied by PBM, triggering biliary tract cancer, cholangitis, pancreatitis, and other disorders of the biliary tract and pancreas. In particular, biliary tract cancers occur in the dilated bile duct and gallbladder at a high rate [81], and according to a nationwide survey in Japan, the incidence of concurrent biliary tract cancer was 10.6%, and restricting this figure to adults, the rate became higher at 21.6%. Of these, the incidence of gallbladder cancer was 62.3% and bile duct cancer was 32.1% [52]. From the foregoing, the standard surgical procedure is extrahepatic bile duct resection and biliary tract reconstruction, including the gallbladder where there is a tendency for carcinogenesis tends to develop [82, 83]. Internal drainage operation (cyst-enterostomy) enhances the risk of postoperative bile duct inflammation and carcinogenesis, and should be avoided [83, 84]. However, there are reports that the hepatico-enterostomy itself is a risk factor for bile duct cancer [85] and that cancer developed after hepatic bile duct resection from the intrahepatic bile duct and intrapancreatic remnant bile duct [86, 87] requiring a long-term postoperative follow-up.

There are reports on postoperative carcinogenesis, pancreatitis and pancreatic stones from the intrapancreatic remnant bile duct [88, 89]. From the foregoing, it is thought to be vital to resect the lower common bile duct close to the pancreatic duct junction, so as to leave as little intrapancreatic duct as possible [78]. In a cystic dilatation, the narrow segment at the end of the bile duct can be observed, making the resection near the pancreatic junction relatively simple. However, with the fusiform or cylindrical dilatation cases, the narrow segment is obscure, creating a risk for pancreatic duct damage, becoming the source of postoperative pancreatic juice drainage, pancreatitis or pancreatic duct stenosis. In order to avoid these complications, there are reports of confirmation being made using an intraoperative cholangiography with a metal clip [78] or a biliary endoscopy [90].

In recent times, an increase is reportedly seen in the number of heptatectomies performed in the initial intervention when the dilated lesion extends to the intrahepatic bile duct [91–94]. There are also reports that in the IV-A type where intrahepatic bile duct dilatation is observed, comparing the groups that underwent extrahepatic bile duct resection and hepatectomy in the initial intervention, adults in comparison to children had significantly less reoperations for intrahepatic stones and stenosis when hepatectomy was performed at the same time [93]. In addition, reports indicate that in view of the risk of intrahepatic bile duct carcinogenesis, hepatectomy should be an additional consideration for adults [94]. If there are no risks involved, hepatectomy on the initial surgery may be considered. However, there is no consensus in this regard, and in pediatric patients, due to the excessive invasiveness, oftentimes, only cyst resection is performed on the initial surgery and progress observed. However, at the present time, there is little evidence on this matter and no consensus has been reached.

CQ-IV-4: How should hepatic hilum and intrahepatic bile duct stenosis be dealt with?

*Q1: Should hepatic hilum and intrahepatic bile duct stenosis be dealt with during the initial intervention?*

- Because intrahepatic stones after an extrahepatic bile duct resection may cause intrahepatic stones, it is recommended

that this be dealt with during the extrahepatic bile duct resection (Recommendation level 1, Level C).

*Q2: What is an effective way of dealing with bile duct stenosis?*

As approaches in dealing with bile duct stenosis, two methods are recommended, that of performing resection from inside the common hepatic duct, or that of making an incision in the lateral wall of the bile duct, cranial to the stricture (Recommendation level 2, Level C).

*Q3: How should stenosis that are inaccessible from the hepatic hilum be effectively dealt with?*

- There is no definite view. If hepatectomy solves the problem of cystic dilatation or stenosis of the intrahepatic bile duct, the procedure may be considered. However, hepatectomy is thought to be excessively invasive for pediatric patients (Level C).

Comments

It is thought that cholangitis and intrahepatic stones that occur after the extrahepatic bile duct resection are primarily due to stenosis of the anastomotic part, intrahepatic bile duct dilatation and bile duct stenosis [95]. In CBD, stenosis of the hepatic hilum and intrahepatic bile duct are reported to occur frequently, in 80% of cases [96]. Bile duct stenosis are mainly membranous or septal, and since stenosis exist close to the hepatic hilum and cause cholangitis and intrahepatic stones after the extrahepatic bile duct resection, it is recommended that the stenosis be resected or reconstructed during the initial surgery [96]. According to reports, in order to remove the stenosis, the restiform body or membranous stenosis may be resected from inside the lumen of the common bile duct [97], or hepaticojejunostomy may be performed by making an incision into the lateral wall of the hepatic duct, cranial to the stenosis [83, 98]. In hepatic bile duct dilatation cases, because anastomosis at the common bile duct level leads to relative stenosis, some reports recommend performing a bilio-jejunal anastomosis, that is, making an incision in the right and left hepatic ducts to create a wider anastomotic stoma [99]. However, while there is consensus regarding the need to deal appropriately with stenosis, there is little literary basis verifying the effects thereof. There is one comparative article using historical control which reports that by making an incision into the right and left hepatic ducts, cholangitis due to intrahepatic stones decreased from 11.8% to 0% [89]. This remains to be a future issue.

There is no fixed method in dealing with intrahepatic bile duct stenosis during the initial surgery in cases where access from the hepatic hilum is difficult. In recent years, there is reportedly an increase in hepatectomy during the initial intervention [91–93]. In a non-randomized controlled trial article on the IV-A type in which intrahepatic bile duct dilatation is observed, comparing the group which had only an extrahepatic bile duct resection and the group which had both an intrahepatic bile duct resection and hepatectomy, in pediatric patients, good progress was seen in the group which had only an intrahepatic bile duct resection, whereas in adults, the group which also had hepatectomy had significantly less reoperatioans from intrahepatic stones or stenosis [93]. If it is possible to remove cystic dilatation or stenosis in the intrahepatic bile duct by also having a hepatectomy, this procedure may be considered; however, it is regarded as excessively invasive for pediatric patients. There is no fixed view at present. In many cases, if intrahepatic stones occur after the extrahepatic biliary resection or in cases of stenosis when access from the hepatic hilum is difficult, hepatectomy is generally adopted [100].

CQ-IV-5: What approaches are used for biliary tract reconstruction?

*Q1: What is the recommended approach for biliary tract reconstruction?*

- Intestinal tracts used in biliary tract reconstruction are roughly divided into jejunum and duodenum, and the reconstruction method most often adopted and recommended in Japan is hepaticojejunostomy with Roux-en Y anastomosis (Recommendation level 1, Level B).

*Q2: Which method is better, hepaticojejunostomy or hepaticoduodenostomy?*

- Hepaticojejunostomy with Roux-en-Y anastomosis prevents reflux gastritis in comparison to hepaticoduodenostomy; however, there is no uniform view as to which method is better (Level B).

Comments

Intestinal tracts used in the reconstruction of the biliary tract are roughly divided into jejunum and duodenum, and the typical reconstruction method is hepaticojejunostomy with Roux-en-Y and hepaticoduodenostomy. Hepaticoduodenostomy, in comparison to hepaticojejunostomy, offers certain advantages as being simple procedure with a single anastomosis of the physiological biliary outflow tract and little

likelihood of developing postoperative ileus [98]. However, because there are concerns over complications due to the reflux of duodenal contents into the biliary tract, hepaticoduodenostomy with Roux-en-Y is most widely performed. In addition, cases of gastritis due to bile reflux into the stomach have been reported [101, 102]. However, there is no evidence suggesting carcinogenesis with hepaticoduodenostomy.

In a meta-analysis based on six observational studies, the outcome was categorized as: bile leak, cholangitis, anastomotic stricture, reflux/gastritis, adhesive intestinal obstruction, reoperation rates, operative time and hospital stay. There were no significant differences in bile leak with relative risk (RR): 1.50 [0.51–4.36] ($P = 0.46$), no significant differences in cholangitis with RR: 1.07 [0.41–2.81] ($P = 0.89$), and no significant differences in anastomotic stricture with RR: 1.45 [0.36–5.79] ($P = 0.60$). However, hepaticojejunostomy had significantly little reflux/gastritis with RR: 0.08 [0.02–0.39] ($P = 0.002$). In addition, there were no significant differences in adhesive intestinal obstruction with RR: 2.77 [0.27–27.92] ($P = 0.39$), no significant differences in reoperation rates with RR: 2.14 [0.67–6.89] ($P = 0.20$), and there was only one entry for operative time. There were no significant differences in hospital stay with MD: 0.30 [0.22–0.39] ($P = 0.29$) [103]. As a result, apart from being able to prevent reflux gastritis with hepaticojejunostomy, no conclusion was reached as to the superiority or inferiority of the procedures [103, 104].

However, due to the spread of laparoscopic surgery, for technical reasons, hepaticoduodenostomy is the preferred method in Western countries.

In Japan, based on the fact that the majority of institutions perform hepaticojejunostomy, hepaticojejunostomy with Roux-en-Y is generally the recommended procedure.

### CQ-IV-6: What is an effective treatment for cases with bile duct perforation?

- It is suggested that external biliary drainage should be performed for the time being, and then to perform a radical operation once the patient's condition has stabilized (Recommendation level 2, Level C).

### Comments

PBM significantly influences the etiology of biliary tract perforation [105]. However, a definite mechanism of biliary tract perforation is unknown. The standard treatment is undefined. In general, an urgent external biliary drainage is first performed, and once the patient's condition has stabilized, a cholangiography is carried out to confirm the morphological diagnosis. Thereafter, many consider it safe to perform a radical operation as a secondary measure [106].

Various surgical procedures have been reported as follows: (1) intraperitoneal drainage only [107], (2) biliary drainage through a perforation site [108], (3) construction of a tube biliary fistula, (4) suture closure of the perforation site [109], (5) closure by placing a gallbladder patch on the perforation site, (6) sewing a caulescent gallbladder wall as a patch on the perforation site [110], T tube insertion into the common bile duct, (7) cholecystoduodenostomy or cholecystojejunostomy [111], (8) if the perforation site is the gallbladder, cholecystectomy; if the perforation site is the bile duct, choledochojejunostomy (choledochoduodenostomy), (9) choledochojejunostomy (choledochoduodenostomy), (10) T tube biliary fistula, (11) extrahepatic biliary resection after several months [112], (12) extrahepatic biliary resection according to the general physical condition of the patient [113], etc.

### CQ-IV-7: What are the early and late postoperative complications and their frequencies?

- Early postoperative complications include ruptured suture, bleeding from the resection surface, acute pancreatitis, pancreatic fistula, gastrointestinal bleeding, and ileus, most of which result from inadequate surgical procedures and are infrequent (Level C).
- Late postoperative complications include cholangitis, hepatolithiasis, residual biliary tract cancer, pancreatic stones, pancreatitis, and ileus. Hepatolithiasis and residual cholangiocarcinoma are the most serious of these complications, often appearing several years or more than a decade after the operation (Level C).

### Comments

Early postoperative complications include bleeding, pancreatic fistula, acute pancreatitis, gastrointestinal bleeding, and ileus, all of which are infrequent. Acute pancreatitis or pancreatic fistula may occur postoperatively due to the exfoliation of the intrapancreatic bile ducts, although they are rare complications and generally resolve with conservative treatment.

It has been reported that cholangitis, hepatolithiasis, pancreatic stones, and pancreatitis represent late postoperative complications, which may also include biliary tract cancer. Cholangitis and hepatolithiasis often result from cholestasis due to anastomotic stricture, intrahepatic bile duct stenosis, or the remnants of intrahepatic bile duct dilatation [95]. In particular, there are many IV-A type cases with hepatic bile

duct dilatation, and although the frequencies depend on the differences in the surgical procedures of the institutions or the follow-up term, hepatolithiasis is detected in approximately 10% of patients with late postoperative complications [95, 114–116]. Acute or chronic pancreatitis following cyst excision is attributed to intrapancreatic residual bile duct, dilated common duct, complex duct morphology, or malfusion of the pancreas divisum, etc.

Residual biliary tract cancer: in other words, cancer that develops in the residual hepatic duct on the hepatic side, in the intrahepatic bile duct, or in the residual intrapancreatic bile duct following cyst excision, is an increasing problem. There are reports demonstrating that cholangiocarcinomas develop in approximately 0.7% of patients who undergo cyst excision, an incidence which is 120–200 times higher than the incidence in the population at large [86, 87]. Bile duct digestive tract anastomosis itself is a risk factor for bile duct cancer [85]; however, repeated cases of cholangitis, hepatic stones or cyst remnants due to inadequate intrahepatic bile duct excision are oftentimes the causes of such carcinogenesis [86, 87].

CQ-IV-8: What is the frequency of cholangiocarcinomas following a biliary diversion procedure?

- The incidence of biliary tract cancer following biliary diversion procedure for CBD is reported to be 0.7%–5.4% (Level C).

Comments

There are no major studies regarding the development of bile duct cancer following the diversion and undiversion procedures.

Of the 997 adult cases of CBD during the 18 years between 1990 and 2007 studied by JSPBM, there were 79 cases which had concurrent bile duct cancer at the time of diagnosis (7.9%) [52]. This is the coexistence rate of bile duct cancer at the time of CBD diagnosis. However, knowing the future carcinogenic rate of bile duct cancer without the performance of a diversion procedure for CBD is helpful. On the other hand, regarding the development of bile duct cancer after the diversion procedure for CBD, Watanabe et al. [87] report 0.7%. Furthermore, Kobayashi et al. [86] report the rate of incidence at three cases out of 56 (5.4%) and adds that the RR of developing bile duct cancer after the diversion procedure has not declined. All of the above are based on a few cases, and it is no appropriate to make a definitive statement regarding the incidence rate thereof. On the other hand, regarding the rate of bile duct development after the so-called "internal drainage procedure" which is generally not performed at present, Todani et al. [84] report that at least two-thirds of the patients who underwent this procedure developed biliary tract cancer within 10 years. Moreover, the age at onset of cancer in patients who underwent an internal drainage procedure was reported to be up to 15 years younger than the age of those who developed cancer without being operated on. In the internal drainage operation in patients with CBD, intestinal juices flow into the dilated bile duct that has not been resected, and thus, the postoperative pathological state of the bile duct is different from that experienced in patients who have not undergone an operation on the dilated bile duct. However, it may be fair to conclude at present that the incidence of biliary tract cancers following biliopancreatic undiversion is higher than that after a biliary diversion procedure.

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