Current concept about postoperative cholangitis in biliary atresia

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Background: **Postoperative cholangitis characterized by fever and acholic stool and positive blood culture is a common and serious complication following Kasai's operation for biliary atresia. The aim of this review was to describe the pathogenesis, clinical manifestations, medical treatment and outcome of postoperative cholangitis.**

Data sources: **Articles on biliary atresia retrieved from Pubmed and MEDLINE in the recent 10 years were reviewed.**

Results: **The pathogenesis of postoperative cholangitis is still controversial. Recent methods for the diagnosis of postoperative cholangitis include urinary sulfated bile acids (USBA) and magnetic resonance cholangio-pancreaticography (MRCP). High-dose steroids and oral antibiotics have been used to reduce the incidence of postoperative cholangitis, and recurrent cholangitis leads to a lower survival rate.**

Conclusions: **Cholangitis is one of the most important determinants of long-term survival after the Kasai's procedure. The knowledge on postoperative cholangitis has been increasing in the past 10 years, showing a lower incidence of the disease and better therapeutic results.**

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Key words: **biliary atresia;**
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Postoperative cholangitis characterized by fever, acholic stool and positive blood culture is a common and serious complication following Kasai's operation for biliary atresia. Among the mechanisms for postoperative cholangitis, ascending infection has been widely accepted, but the precise mechanism of cholangitis is unclear. Patients with one or more episodes of cholangitis usually have a greater risk for cirrhosis. Prevention of cholangitis is essential to the maintenance of bile flow that is related to the postoperative mortality. Prophylactic oral antibiotics, combined with adjuvant high-dose steroids, and ursodeoxycholic acid have played an important role in the management of the disease. Moreover, recent progress in immunology and molecular biology has led to better understanding of the pathogenesis of the disease and its causative agents, diagnostic techniques and treatment.

Clinical feature

Postoperative cholangitis is characterized by fever, acholic stool, abdominal pain with or without jaundice, and positive blood culture ruling out other causes of infection. It usually develops in the first year after operation. The estimated incidence is reported between 40% and 93%.[1] There is a significant correlation between the time of the first attack of cholangitis and the frequency of episodes: the earlier the first episode occurs, the more frequently the patient may develop cholangitis afterwards. Thus the more episodes the patients have, the lower the survival rates are.

Pathogenesis

Reduced lymph drainage at the porta hepatis, portal venous infection, dehydration with reduced bile flow, ascending bacterial infection from the enteric conduit, insufficient volume of bile flow, and a partially obstructed biliary tree were recognized as possible causative factors for the disease before the 1990s. Subsequently, several new ideas arose, for instance, hepatolithiasis, cystic dilatation of the intrahepatic bile duct, partial bile drainage, and changes in intestinal movement.

Translocation of micro-organisms from the gut

In the mechanisms for postoperative cholangitis following bile duct reconstruction, ascending infection

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from the bilioenteric conduit (BEC) has been widely accepted for a wide range of pathogens involved. The responsible organisms are intestinal flora including *E. coli, P. aeruginosa, K. pneumoniae, E. cloacae, A. baumani* and *S. typhi*. But *P. aeruginosa* seems to be more frequent.[2] In patients who have undergone the Kasai's operation, many factors facilitate the spread of the bacteria such as obstructive jaundice, dilated biliary tree, bacterial inhabitation in the bilioenteric anastomosis and deteriorated health.

Bacteria ascend early to the liver from the BEC after the operation, particularly at the presence of obstructive jaundice.[3] This phenomenon proceeds for some time following biliary drainage of extrahepatic biliary obstruction. Dilatation of the biliary tree, followed by bile duct ligation, might contribute to ascending cholangitis. Furthermore, the heavily colonized BEC is also a risk for postoperative cholangitis, while a concomitant increase of bacteria appears in the liver. Hepatic bacterial proliferation after bile duct reconstruction is significantly affected by microbial overgrowth in the bilioenteric anastomosis and is associated with deteriorated liver function and leucocytosis. The consequence of bacterial overgrowth is not only associated with leukocytosis or anemia,[4] but also a reduced albumin synthesis and an elevated ammonia level, which aggravate the infection in reverse.

Hepatolithiasis

Hepatolithiasis may develop more frequently after portoenterostomy. Bile stasis and bacterial infection have been recognized as important factors for the formation of calculi especially in the bile lakes. On one hand, repeated cholangitis causes the bile duct to be obstructed, favoring the formation of calculi. On the other hand, the calculi lead to ongoing inflammatory process and biliary obstruction, which results in cholangitis. In 2006 Tainaka et al[5] found that among 8 patients presenting with bile bacterial infection, 7 (88%) had a history of ascending cholangitis, suggesting a close relationship between hepatolithiasis and cholangitis.

Cystic dilatation of the intrahepatic bile duct

Dilatation of the biliary tree might be another factor for ascending cholangitis, which is similar to Caroli disease, characterized by multiple and segmental dilatations of the bile ducts which are often complicated by recurrent episodes of bacterial cholangitis.

An animal experiment[3] showed that jaundiced rats are more susceptible to *E. coli* infection in the BEC and concomitant colonization of the liver than those not subjected to bile duct ligation. Bile duct dilatation and lithiasis favor bacterial persistence after the initial biliary tree colonization, which leads to difficulty in medical treatment of bacterial cholangitis.

Intraluminal pressure

In 2003 Ernest et al[1] reported two patients who developed cholangitis with fever and clinical jaundice a few days after the onset of ileus. When presenting with ileus they had no fever or any other evidence of cholangitis, but cholangitis occurred during the initial conservative management of intestinal adhesion. High intraluminal pressure in the bowel was proposed to affect bile drainage and result in cholestasis, bacterial overgrowth, and ascending cholangitis. In both patients, fever resolved within 3 days after laparotomy and antibiotic therapy.

Partial bile drainage

Partial bile drainage is associated with an increasing risk of cholangitis.[6] Small biliary cysts at the porta hepatis or relatively large intrahepatic bile ducts that drain insufficiently may be prone to developing biliary stasis and cholangitis. Intrahepatic bile ducts that drain well and bile ducts that are completely fibrosed are relatively resistant to this complication.

Patients with intrahepatic bile ducts that are partially drained seem to have an ongoing risk for cholangitis until these ducts are completely fibrosed or good drainage is established. The patient with 17 episodes of cholangitis in the first 3 years after operation reported by Ernest et al[1] supports this hypothesis. In this patient, after this period there was complete fibrosis of one half of the liver but no recurrence of cholangitis. Because of the good drainage of the other half of the liver, the serum bilirubin levels remained normal. Hence if hepatic fibrosis and cirrhosis get worse, it may result in liver failure, portal hypertension, and esophageal varices.

A gap on epithelial lining

Autoanastomosis between major intrahepatic-duct epithelium and coaptated intestinal mucosa takes about 6 weeks.[7] Before it the transected microscopic ducts are prone to inflammatory closure. It is still unknown whether such a gap on the epithelial lining between the bile duct and the jejunum at the anastomosis is an important cause of frequent cholangitis in some patients. One possibility is that small intestinal defects and ischemic tissue necrosis associated with types of suture may inhibit intestinal flora.

Intestinal movement

To clarify the mechanism and changes in intestinal movement after biliary reconstruction by Roux-en-Y

anastomosis, electromyography (EMG) was used to study the motility of the reconstructed intestine in dogs.[8] Electromyography analysis was made to monitor basic electrical rhythm (BER) and migrate myoelectric complexes (MMC) while most of the Y-loop MMCs were propagated smoothly to the anal side according to the continuity of the intestine, and the intestinal content was transported without stagnation. The intestinal movement was useful as a biliary drainage route to prevent ascending cholangitis. A comparison of short- and long-term intestinal motility after biliary reconstruction showed adaptation of the intestinal movement after the procedure. The outflow of bile appeared to accelerate intestinal motility because of prolongation of the MMC interval in the duodenum and oral jejunum without bile flow.

Advances in diagnosis

The diagnostic criteria for cholangitis include fever, increasing jaundice or acholic stools excluding other causes of infection. Increased level of serum bilirubin is often confirmatory for the diagnosis of postoperative cholangitis. However, it is not always easy to make a prompt and accurate diagnosis of cholangitis since the serum bilirubin level does not necessarily increase. Although blood culture can directly detect the organism causing cholangitis, the positive rate of blood cultures is low.[2] Some researchers have proposed liver biopsy,[9] but such a procedure is too invasive. Recently a measurement of urinary sulfated bile acids (USBA) is introduced as simple and noninvasive.

Urinary sulfated bile acids

In 2005, Shinohara and his colleagues[10] advocated USBA for the diagnosis of bacterial cholangitis. Sulfated bile acids with a high water solubility can be immediately excreted into the urine if the serum concentration of these bile acids increases sufficiently. After an obstruction due to inflammatory cell infiltration around the intrahepatic bile ducts, excretion of bile from hepatocytes into bile canaliculi and drainage of bile are impaired, and cholestasis occurs while increasing the level of serum bile acid and renal excretion as USBA increases. In Shinohara's study, the R-USBA value increased immediately in cholangitis, but not in non-cholangitis. The episodes of increased R-USBA showed that cholestasis occurred when the body temperature increased. However, conventional tests including test of total bilirubin determination did not reveal cholestasis. Possibly these are episodes of cholangitis with cholestasis. Nevertheless, fever associated with cholestasis does not correspond to cholangitis. To solve this problem, a prospective study using USBA to detect cholangitis is necessary in the future.

Diagnostic imaging

Most patients with cholangitis have such potential factors as dilatation of intrahepatic bile ducts and stones. Conventional methods include ultrasound and CT scan. But in recent years, magnetic resonance cholangiopancreaticography (MRCP)[11] and technetium 99m PMT hepatobiliary scintigraphy[12] have been used widely, especially the former.

Because MRCP creates high contrast between the high intense signal of bile and the low signal of surrounding structures, it can provide complete visualization of the biliary tree. MRCP shows typical signs of bile duct distension and narrowing in parts of the liver, which are consistent with those of sclerosing cholangitis secondary to recurrent infection.

Unlike endoscopic retrograde cholangio-pancreaticography and percutaneous transhepatic cholangiography, MRCP is noninvasive and free of complications such as pancreatitis, perforation, cholangitis, sepsis, bile leakage, and intraperitoneal hemorrhage.

In conclusion, MRCP is accurate in the diagnosis of biliary disease, fully comparable to invasive cholangiography, and may be even superior in the evaluation of postoperational cholangitis.

Treatment strategy

Kasai's operation and its modifications

Although several surgical modifications of the original portoenterostomy technique described by Kasai and Suzuki are suggested to reduce the risk of cholangitis, the results do not confirm this reduction. The most commonly employed modification includes exteriorization of the BEC or placement of an intussusception's antireflux valve in the interposed segment. However, neither "venting" nor "valving" is effective in lowering the incidence of ascending cholangitis.

Intussusception-type antireflux valve (ARV) which has been introduced to prevent postoperative ascending cholangitis in the management of biliary atresia is recognized effective in the prevention of cholangitis. However, a recent study[13] showed that the valve is probably useful in preventing reflux, but the prevention of cholangitis might be another issue. One possible explanation is that cholestasis with cystic dilatation of the intrahepatic bile duct could be a potential target of bacteria.[14] Consequently, the functioning ARV could

not prevent the infection.

According to the report,[15] the incidence of cholangitis in patients without a valve was significantly higher than in the group with longer limbs (P=0.038). Therefore, a longer Roux-en-Y limb is vital for an antireflux effect. Since 1993, a 50-cm Roux-en-Y limb has become the golden rule.

Cavitron ultrasonic suction aspirator (CUSA)

In 1997, it was a new approach to Kasai's operation using CUSA[16] to efficiently isolate biliary remnants and facilitate enteric anastomosis. CUSA was described as effective for achieving persistent and complete disappearance of jaundice without reoperation while lowering the need for liver transplantation. CUSA was later widely used in surgical practice such as liver resection. However, no application in Kasai's operation was reported afterward.

Medicine administration

Adjuvant therapy using intravenous antibiotics and high-dose steroids (ursodeoxycholic acid) may accelerate the clearance of jaundice, which is the major factor determining the clinical outcome of biliary atresia.

During the last two decades, the protocol for antibiotic treatment was changed. In the early 1980s, second-generation cephalosporins (cefuroxime and cefamandole) with or without aminoglycosides (gentamicin and amikacin) were used. Third-generation cephalosporins showed adequate biliary levels via a passive secretory route, giving another advantage at 12-24 hours intervals for home therapy. The sensitivity test justified empirical therapy with ceftriaxone. Since 1989, third-generation cephalosporins (usually cefoperazone) were widely used sometimes with the addition of aminoglycosides, unless the patients were allergic to one of them.

Unfortunately, the efficacy of cefoperazone in the treatment of cholangitis post-Kasai's operation has decreased in the past years from 88.9% to 75%. This suggests a need for a more effective first-line empirical antibiotic. In 2003, TMP/SMZ or neomycin was found to be effective according to Bu's study.[17] In 2004, meropenem was introduced as a suitable candidate.[18] A further prospective study is necessary to find the best substitute for cefoperazone.

Steroids have been used to augment antibiotic treatment of refractory cholangitis in patients with biliary atresia for more than 20 years. In 1985 Karrer and Lilly[19] reported the use of a short-term "blast" of steroid administration to augment bile flow.

Steroids offer both choleretic and anti-inflammatory benefits. The choleretic effect of steroids involves induction of Na-K-ATPase,[20] which increases canalicular electrolyte transport and stimulates bile flow independent of the bile salt concentration. Moreover, when given in high doses, steroids have pronounced anti-inflammatory and immunosuppressive effects decreasing edema and collagen deposition, inhibiting scarring, and arresting migration of infiltrating monocytes and lymphocytes. Chemokines including interleukin-8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1) have been identified in the inflammatory infiltrate of cholangitis. Glucocorticoid treatment is effective in modulating IL-8 and MCP-1 expression and ameliorating inflammatory cell infiltration.[21] Expression of intracellular adhesion molecule-1 (ICAM-1) by the bile duct epithelium may play a role in the recruitment of lymphocytes. Serum ICAM-1 levels decrease in patients with biliary atresia after steroid therapy. GcRs mediate the effects of glucocorticoid steroids.[22] The increase and degree of GcRα expression are associated with the severity of liver injury and may be correlated with the dose of prednisolone required to sustain bile flow.

Kobayashi[20] recommended a protocol of steroid usage that seems to be more effective: the initial dose of 4 mg/kg per day was tapered by half for several days but increased if bile drainage appeared to decrease. Stool color is a good indicator of bile excretion, and stool color monitoring of bile flow facilitates the timing of restarting prednisolone. However, a different idea about the effectiveness of steroids has emerged recently. In Escobar's study,[23] steroids were found to improve clearance of postoperative jaundice and lower serum bilirubin levels but had no effect on the incidence of cholangitis. A prospective study with standardized steroid administration and a longer period of follow-up is necessary to assess the effectiveness of steroids after portoenterostomy.

In addition to steroids, choleretic agents including dehydrocholic acid, glucagons, prostaglandin E2, and ursodeoxycholic acid are also available at the present. Among them ursodeoxycholic acid is often studied and is shown to significantly improve essential fatty acid deficiencies and decrease bilirubin levels.[24] Ursodeoxycholic acid is now used routinely with good effect, and no side effects have been reported.

Outcome

Recurrent cholangitis may result in progressive cirrhosis, portal hypertension, severe gastroesophageal bleeding, and ongoing sepsis. Clinically, these complications are preceded by the portal vein thrombosis[25] induced by a bout of ascending

cholangitis. In this episode, the patient presents with an acute decompensation of his portal hypertension due to acute intrahepatic portal vein thrombosis. As a result, liver infarction eventually causes hepatic failure. Intrahepatic portal vein thrombosis can aggravate pre-existing pre-sinusoidal resistance caused by progressive parenchymal fibrosis. Indeed, patients with cirrhosis resulted from biliary atresia are at risk of bleeding from varices and presenting these complications at a younger age. With active bile drainage, varices spontaneously regresses. The portal vein increases in both caliber and total length per unit hepatic volume, and portal volume normalizes.[26]

Cholangitis is considered one of the most important determinants of long-term survival after a successful hepatic portoenterostomy.

In conclusion, recurrent cholangitis is a common complication after Kasai's procedure and contributes to a poor prognosis. After decades of study, the precise pathogenesis of postoperative cholangitis is still unclear. Recent advances in the diagnosis and treatment of this disease improve the outcome to some extent, but the current situation is far from satisfactory. Further investigation requires international cooperation and interaction.

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Flowers by Xiang Sheng-mo (1597-1658), Ming Dynasty