Sphincter of Oddi Dysfunction and the Formation of Adult Choledochal Cyst Following Cholecystectomy

A Retrospective Cohort Study

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Abstract: To determine the causes underlying the formation of adult choledochal cyst.

Anomalous pancreaticobiliary junction is the most widely accepted theory regarding the etiology of choledochal cyst. However, choledochal cysts have been found in patients in the absence of this anomaly. Because the number of adult patients with choledochal cyst is increasing, it is important to address this controversy.

Bile amylase levels in the cysts of 27 patients (8 males and 19 females) who had undergone cholecystectomy were retrospectively evaluated. The average age of the 27 patients was 45.8 ± 10.1 years and the majority (85.2%) were diagnosed with Todani type I cysts. None of the patients had dilatation of the common bile duct prior to surgery. There were 6 (22.2%) patients with anomalous pancreaticobiliary junction. However, amylase levels did not significantly differ between patients with and without this anomaly (P = 0.251). According to bile amylase levels, pancreatobiliary reflux was present in 21 (77.8%) patients. The mean amylase level significantly differed in patients with pancreatobiliary reflux (23,462 ± 11,510 IU/L) and those without (235 ± 103 IU/L) (P < 0.001). In patients with pancreatobiliary reflux, only 4 patients had anomalous pancreaticobiliary junction. That is, the majority of patients (17/21, 81%) having pancreatobiliary reflux did not have an anomalous junction of the pancreatic and biliary ducts.

Since the only explanation for pancreatobiliary reflux in patients with a normal pancreaticobiliary junction is sphincter of Oddi dysfunction, we proposed that the formation of adult choledochal cyst is increasing, it is important to address this controversy.

Bile amylase levels in the cysts of 27 patients (8 males and 19 females) who had undergone cholecystectomy were retrospectively evaluated. The average age of the 27 patients was 45.8 ± 10.1 years and the majority (85.2%) were diagnosed with Todani type I cysts. None of the patients had dilatation of the common bile duct prior to surgery. There were 6 (22.2%) patients with anomalous pancreaticobiliary junction. However, amylase levels did not significantly differ between patients with and without this anomaly (P = 0.251). According to bile amylase levels, pancreatobiliary reflux was present in 21 (77.8%) patients. The mean amylase level significantly differed in patients with pancreatobiliary reflux (23,462 ± 11,510 IU/L) and those without (235 ± 103 IU/L) (P < 0.001). In patients with pancreatobiliary reflux, only 4 patients had anomalous pancreaticobiliary junction. That is, the majority of patients (17/21, 81%) having pancreatobiliary reflux did not have an anomalous junction of the pancreatic and biliary ducts.

Since the only explanation for pancreatobiliary reflux in patients with a normal pancreaticobiliary junction is sphincter of Oddi dysfunction, we proposed that the formation of adult choledochal cyst is mainly due to sphincter of Oddi dysfunction.

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ultrasonography, and the diagnosis was confirmed by serologic testing and histopathological findings. Patients with a bile duct diameter more than 10 mm at the time of cholecystectomy were excluded from the study. Patients with postoperative compensatory dilatation of the CBD, secondary biliary dilatation due to a CBD stone or distal CBD stricture, or endoscopic sphincterotomy-treated patients were also excluded. A total of 27 out of 86 patients who underwent cholecystectomy fulfilled all of the inclusion and exclusion criteria.

APBJ was defined as the junction between the pancreatic and bile ducts located outside the duodenal wall with a common channel length $>1.5$ cm. This anomaly was further divided into P–B type (where the pancreatic duct joins the CBD; Fig. 1) and B–P type (where the CBD joins the pancreatic duct; Fig. 2).

When the biliary amylase level was $>1000$ IU/L, pancreatobiliary reflux was considered present. The amylase level was measured using a colorimetric method with an automatic Roche/Hitachi (cobas c701 module) analyzer (Mannheim, Germany). The normal range of serum amylase using this system is $<150$ IU/L.

**Statistical Analysis**

Descriptive statistics were used to summarize the data. Independent sample $t$ tests were used to examine group differences in average amylase levels. Statistical analyses were performed with IBM SPSS Version 20 (SPSS Statistics V20, IBM Corporation, Somers, NY). The statistical significance level was set at a $P$ value $<0.05$.

**RESULTS**

The demographic and clinical characteristics of the 27 patients evaluated in this study are presented in Table 1. The average age of the 27 patients (8 males and 19 females) was 45.8 $\pm$ 10.1 years, and the majority were diagnosed with Todani type I cysts (85.2%). Of the 27 patients, there were 15 patients with gallstones, 9 patients with gallbladder polyps, and 3 patients with both gallbladder polyps and gallstones. During cholecystectomy, 44.4% of patients had a CBD diameter in the 6 to 8 mm range and 55.6% of patients had a CBD diameter in the 8 to 10 mm range. Following cholecystectomy, over half of the patients had abdominal pain (88.9%), fever (51.9%), and cholangiolithiasis (51.9%). The average duration between cholecystectomy and a definitive diagnosis of CC in the 27 patients was 115.1 $\pm$ 35.0 months. During CC excision, the mean CBD diameter was 38.1 $\pm$ 10.3 mm.

As shown in Table 2, APBJ was found in 6 (22.2%) patients. However, amylase levels did not significantly differ between patients with APBJ and those without APBJ ($P = 0.251$).

| Parameters | Values |
|------------|--------|
| Age (y), mean $\pm$ SD | 45.8 $\pm$ 10.1 |
| Gender, male/female, $n$ | 8/19 |
| Todani classification, $n$ (%) | I 23 (85.2), IV-A 4 (14.8) |
| Indication for cholecystectomy, $n$ (%) | Gallstones 15 (55.6), Gallbladder polyps 9 (33.3), Gallbladder polyps with gallstones 3 (11.1) |
| CBD diameter during cholecystectomy, $n$ (%) | 6–8 mm 12 (44.4), 8–10 mm 15 (55.6) |
| Complications following cholecystectomy, $n$ (%) | Abdominal pain 24 (88.9), Fever 14 (51.9), Jaundice 8 (29.6), Cholangiolithiasis 14 (51.9) |
| CBD diameter during cyst excision, mean $\pm$ SD, mm | 38.1 $\pm$ 10.3 |

CBD = common bile duct, SD = standard deviation.
the CC, pancreatobiliary reflux was present in 21 (77.8%) patients. The mean amylase level significantly differed between patients with pancreatobiliary reflux (23,462 ± 11,510 IU/L; \( P < 0.001 \)) and those without pancreatobiliary reflux (235 ± 103 IU/L; \( P < 0.001 \)). Of note, in patients with pancreatobiliary reflux, only 4 patients presented with APBJ. That is, occult pancreatobiliary reflux accounted for the majority of patients (17/21, 81%) who presented with reflux of pancreatic juice into the biliary tract. Figure 3 shows a normal pancreaticobiliary duct junction in a 38-year-old man presenting with adult CC which was confirmed at surgery. Figure 4 shows a 42-year-old woman who presented with a CC 68 months after receiving a cholecystectomy.

**DISCUSSION**

Our results showed that, based on bile amylase levels, pancreatobiliary reflux was present in 21 (77.8%) patients with CCs and of those 21 patients, only 4 had APBJs. That is, occult pancreatobiliary reflux accounted for the majority of patients (17/21, 81%) who presented with reflux of pancreatic juice into the biliary tract and it appears that pancreatobiliary reflux was responsible for formation of CCs.

The present study demonstrated that pancreatobiliary reflux cannot be fully explained by the theory of an APBJ. In addition to APBJs, other mechanisms can lead to the reflux of pancreatic enzymes into the biliary tract that may trigger the formation of adult CC. Due to bile duct dilatation after cholecystectomy, an association between gall-bladder resection and the formation of adult CC is also possible.

The CBD and main pancreatic duct open into the duodenum either at separate points or via a common channel. At the lower end of the bile and pancreatic ducts, the sphincter of Oddi regulates the flow of bile and pancreatic juice into the duodenum. When the common channel exceeds 15 mm in length (ie, an anomalous junction), the sphincter of Oddi is inoperative. As a consequence, the pancreatic enzymes flow freely into the biliary system causing pancreatobiliary reflux. Although it is well known that pancreatobiliary reflux is frequently associated with the formation of CC, patients with an anomalous junction of pancreatic and biliary ducts may not present with CC. It is also possible to observe CC in patients without an anomalous junction of the pancreatic and biliary ducts. In the present study, we found over 80% of the patients with pancreatobiliary reflux had an anatomically normal pancreaticobiliary junction. This phenomenon of pancreatobiliary reflux found in patients with a normal pancreaticobiliary junction was defined as occult pancreatobiliary reflux.

It has been suggested that sphincter of Oddi dysfunction is the only plausible explanation for pancreatobiliary reflux in patients with a normal pancreaticobiliary junction. Ponce et al utilized endoscopic manometry to investigate the motility of pancreatobiliary reflux.

| TABLE 2. Comparison of Amylase Levels | APBJ | PBR |
|--------------------------------------|------|-----|
| n = 6                                | n = 21 | n = 6 | n = 21 |
| Amylase, IU/L: mean ± SD             | 24,225 ± 21,559 | 16,608 ± 11,342 | 23,462 ± 11,510 | 235 ± 103 |
| \( P \)                              | 0.251 | <0.001 |

APBJ = anomalous pancreaticobiliary junction, PBR = pancreatobiliary reflux, SD = standard deviation.
of the sphincter of Oddi and observed that patients with biliary cystic dilatation and those with CC both showed an elevated basal pressure but the frequency of phasic contractions of the sphincter of Oddi was abnormal only in patients with CC. Craig et al.12 provided manometric evidence of an elevated basal sphincter pressure of 59 mm Hg in an adult patient found to have CC but who did not show an APBJ by endoscopic retrograde cholangiopancreatography (ERCP) and suggested an etiological role of an abnormal sphincter of Oddi in the formation of CC.

The sphincter of Oddi is a cylindrically shaped smooth muscle located where the distal CBD and the main pancreatic duct meet at the entrance to the duodenum.14 The role of the sphincter of Oddi is to regulate the flow of bile and pancreatic enzymes into the duodenum by antegrade phasic contractions.27 Therefore, sphincter of Oddi dysfunction is a term referring to the malfunction of sphincter of Oddi contractility,14 which results in retrograde contractions allowing the regurgitation of pancreatic enzymes into the biliary tree. In the present study, we found elevated biliary amylase levels, a biochemical marker of pancreatic enzymes into the biliary tree. In the present study, we found retrograde contractions allowing the regurgitation of pancreatic enzymes into the biliary duct. When the stomach is empty, the contraction of the sphincter of Oddi within the ampulla of Vater contracts (closes) and bile duct pressure elevates. Since the regulatory function of the gallbladder has been removed, secondary biliary ductal dilatation will occur to relieve the bile duct pressure, which is the cause of secondary biliary ductal dilation after cholecystectomy. During eating, the papillary sphincter is relaxed through neurohumoral regulation, the bile drains into the duodenum and the bile excretion is increased through the contraction of smooth muscle within the bile duct wall; the balance of the bile duct pressure can, therefore, be maintained through the contraction of the smooth muscle within the bile duct wall. Thus, although gallbladder resection leads to secondary biliary ductal dilation, the dilation is not serious due to good functioning of the smooth muscle within the walls of the biliary ducts and normal functioning of the sphincter of Oddi. At this time, the biliary system is in compensatory balance after cholecystectomy, and normal biliary function is maintained.

Several conditions are responsible for the dysfunction of the sphincter of Oddi that results in pancreaticobiliary reflux.7,35,36 From clinical observations, patients with pancreaticobiliary reflux do not necessarily have cystic dilatation of the bile duct. When the degree of pancreaticobiliary reflux is relatively mild, the amount of refluxed pancreatic juice is small. A small amount of pancreatic juice that flows into the bile ducts has a relatively weak erosive effect on the bile ducts and also has a relatively weak destructive effect on the smooth muscle within the bile duct wall as it is diluted by large amounts of bile stored in the gallbladder. At this time, the erosive effect of the pancreatic juice is mainly exerted on the gallbladder that stores the bile, with the clinical symptoms of enlarged gallbladder volume and decreased gallbladder contractility and is responsible for the initial clinical manifestations of pancreaticobiliary reflux, that is, cholecystitis. At this time, the biliary system can still maintain relatively normal physiological function, so some patients with a relatively mild degree of pancreaticobiliary reflux do not develop CCs. However, if these patients have their gallbladder removed, the balance is broken, the erosive effect of regurgitated pancreatic juice transfers from the gallbladder to the bile duct and the long-term erosive effect of pancreatic juice causes a gradual loss of bile duct smooth muscle.7,37 Thus, the role played by the bile duct in maintaining bile duct pressure through its smooth muscle contraction is also gradually lost. Under these conditions, the bile duct pressure gradually elevates, and the bile duct gradually dilates leading to the formation of CCs. Therefore, we advocate that the structure and function of the biliary system, as a whole, be maintained as much as possible.

With the popularity of laparoscopic techniques, the number of cholecystectomies has increased significantly. At our
center, for example, before 2000, cholecystectomy was primarily performed by conventional laparotomy with an average of 150 to 200 surgical cases per year. Since 2000, cholecystectomy has been performed primarily by laparoscopic technique and the number of surgical cases has increased. At present, approximately 1000 cholecystectomies are performed per year at our center. The clinical data also show that the number of adult cases of CC has increased every year since 2000, developing from approximately 10 cases per year before 2000 to 69 cases per year in 2012. This growth trend is very significant. Among the adult cases with CC treated in recent years, the number of patients who had received cholecystectomy has also increased. Therefore, a certain relationship exists between cholecystectomy and the formation of adult CC.

The most serious consequence of CC formation is the development of hepatobiliary cancer. The bile and pancreatic juice within the CC from pancreatobiliary reflux not only causes cystic dilatation of the bile duct but also causes prolonged erosion of the bile duct system by activated pancreatic trypsin. The addition of long-term cholestasis and inflammatory stimulation secondary to cholangitis results in carcinogenesis within the cystic ducts.

Of all hepatobiliary cancers, cholangiocarcinoma (CCC) is the most frequent histological type encountered. CCs are highly prevalent in Asia, especially in China. Once CCC develops, it is highly malignant with poor outcome. There-}

pancreatobiliary reflux). Occult pancreatobiliary reflux appears to be caused by either APBJ or sphincter of Oddi dysfunction (occult pancreatobiliary reflux). Occult pancreatobiliary reflux appears responsible for the majority of our adult cases of CC. Thus, our findings suggest that the formation of adult CC is primarily due to sphincter of Oddi dysfunction.

REFERENCES

1. Bhavsar MS, Vora HB, Giriyappa VH. Cholecadal cysts: a review of literature. Saudi J Gastroenterol. 2012;18:230–236.
2. Babbitt DP. Congenital choledochal cyst: new etiological concept based on anomalous relationships of the common bile duct and pancreatic bulb. Ann Radiol. 1969;12:231–240.
3. Babbitt DP, Starshak RJ, Clemett AR. Choledochal cyst: a concept of etiology. Am J Roentgenol Radium Ther Nucl Med. 1973;119:57–62.
4. Imazu M, Iwai N, Tokiwa K, et al. Factors of biliary carcinogenesis in choledochal cysts. Eur J Pediatr Surg. 2001;11:24–27.
5. Sai JK, Ariyama J, Suyama M, et al. A case of occult regeneration of pancreatic juice into the biliary tract: diagnosis with secret in injection magnetic resonance cholangiopancreatography. Gastrointest Endosc. 2002;56:929–932.
6. Sai JK, Suyama M, Kubokawa Y, et al. Occult pancreatobiliary reflux in patients with a normal pancreatobiliary junction. Gastrointest Endosc. 2003;57:364–368.
7. Beltrán MA, Vracko J, Cummsile MA, et al. Occult pancreatobiliary reflux in gallbladder cancer and benign gallbladder diseases. J Surg Oncol. 2007;96:26–31.
8. Beltrán MA, Contreras MA, Crues KS. Pancreatobiliary reflux in patients with and without cholecithiasis: is it a normal phenomenon? World J Surg. 2010;34:2915–2921.
9. Kamisawa T, Anjiki H, Egawa N, et al. Diagnosis and clinical implications of pancreatobiliary reflux. World J Gastroenterol. 2008;14:6622–6626.
10. Vracko J, Wiechel KL. Increased gallbladder trypsin in acute cholecystitis indicates functional disorder in the sphincter of Oddi and could make EPT a logical procedure. Surg Laparosc Endosc Percutan Tech. 2003;13:308–313.
11. Touoli J, Craig A. Clinical aspects of sphincter of Oddi function and dysfunction. Curr Gastroenterol Rep. 1999;1:116–122.
12. Craig AG, Chen LD, Saccone GT, et al. Sphincter of Oddi dysfunction associated with choledochal cyst. J Gastroenterol Hepatol. 2001;16:230–234.
13. Ponce J, Garrigues V, Sala T, et al. Endoscopic biliary manometry in patients with suspected sphincter of Oddi dysfunction and in patients with cystic dilatation of the bile ducts. Dig Dis Sci. 1989;34:367–371.
14. Seetharam P, Rodrigues G. Sphincter of Oddi and its dysfunction. Sandi J Gastroenterol. 2008;14:1–6.
15. Polido WT, Lorenz JC, Tayag WY. Choledochal cyst in an adult: congenital or an acquired clinical entity? WebmedCentral HEPATO-BILIARY. 2012;3:WMC002920.
16. Edil BH, Cameron JL, Reddy S, et al. Choledochal cyst disease in children and adults: a 30-year single-institution experience. J Am Coll Surg. 2008;206:1000–1005.
17. Nicholl M, Pitt HA, Wolf P, et al. Choledochal cysts in western adults: complexities compared to children. J Gastrointest Surg. 2004;8:245–252.
18. Yeom SK, Lee SW, Cha SH, et al. Biliary reflux detection in anomalous union of the pancreatobiliary duct patients. World J Gastroenterol. 2012;18:952–959.
19. Motosugi U, Ichikawa T, Araki T, et al. Radiological Society of North America 2005 Scientific Assembly and Annual Meeting, November 27 to December 2, 2005, Chicago IL. Available at: http://archive.rsna.org/2005/4410029.html. Accessed January 18, 2015.
20. Park SM, Kim WS, Bae IH, et al. Common bile duct dilatation after cholecystectomy: a one-year prospective study. *J Korean Surg Soc.* 2012;83:97–101.

21. Dahnert W. Radiology Review Manual. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

22. Kamisawa T, Takuma K, Anjiki H, et al. Pancreaticobiliary maljunction. *Clin Gastroenterol Hepatol.* 2009;7:S84–S88.

23. mortaro KJ, Rocha TC, Streeter JL, et al. Multimodality imaging of pancreatic and biliary congenital anomalies. *Radiographics.* 2006;26:715–731.

24. Song HK, Kim MH, Myung SJ, et al. Choledochal cyst associated with anomalous union of pancreaticobiliary duct (AUPBD) has a more grave clinical course than choledochal cyst alone. *Korean J Intern Med.* 1999;14:1–8.

25. Sugiyama M, Atomi Y, Kuroda A. Pancreatic disorders associated with anomalous pancreaticobiliary junction. *Surgery.* 1999;126:492–497.

26. Yun SP, Lee JY, Jo HJ, et al. Long-term follow-up may be needed for pancreaticobiliary reflux in healthy adults. *J Korean Surg Soc.* 2013;84:101–106.

27. Beltrán MA. Pancreaticobiliary reflux in patients with a normal pancreaticobiliary junction: pathologic implications. *World J Gastroenterol.* 2011;17:953–962.

28. Beltrán MA. Current knowledge on pancreaticobiliary reflux in normal pancreaticobiliary junction. *Int J Surg.* 2012;10:190–193.

29. Snell RS. Clinical Anatomy for Medical Students. 5th ed. New York: Little, Brown & Co; 1995:257 pp.

30. Behar J. Physiology and pathophysiology of the biliary tract: the gallbladder and sphincter of Oddi: a review. *ISRN Physiol.* 2013 Article ID 837630, 15 pp.

31. Toouli J. What is sphincter of Oddi dysfunction? *Gut.* 1989;30:753–761.

32. Toouli J, Geenen JE, Hogan WJ, et al. Sphincter of Oddi motor activity: a comparison between patients with common bile stones and controls. *Gastroenterology.* 1982;82:111–117.

33. Worthley CS, Baker RA, Saccone GTP, et al. Interdigestive and post-prandial contractile activity of the human sphincter of Oddi. *Aust NZ J Med.* 1987;17:502.

34. Honda R, Toouli J, Dodds WJ, et al. Relationship of sphincter of Oddi spike bursts to gastrointestinal myoelectric activity in conscious opossums. *J Clin Invest.* 1982;69:770–778.

35. Anderson MC, Hamman RL, Suriyapa C, et al. Pancreatic enzyme level in bile of patients with extrahepatic biliary tract disease. *Am J Surg.* 1979;137:301–306.

36. Tanaka M. Advances in research and clinical practice in motor disorders of the sphincter of Oddi. *J Hepatobiliary Pancreat Surg.* 2002;9:564–568.

37. Sai JK, Suyama M, Nobukawa B, et al. Precancerous mucosal changes in the gallbladder of patients with occult pancreaticobiliary reflux. *Gastrointest Endosc.* 2005;61:264–268.

38. Benjamin IS. Biliary cystic disease: the risk of cancer. *J Hepatobiliary Pancreat Surg.* 2003;10:335–10339.

39. Kamisawa T, Okamoto A, Tsuruta K, et al. Carcinoma arising in congenital choledochal cysts. *Hepatogastroenterology.* 2008;55:329–332.

40. Todani T, Watanabe Y, Toki A, et al. Carcinoma related to choledochal cysts with internal drainage operations. *Surg Gynecol Obstet.* 1987;164:61–64.

41. Todani T, Watanabe Y, Narusue M, et al. Congenital bile duct cysts: classification, operative procedures, and review of thirty-seven cases including cancer arising from choledochal cyst. *Am J Surg.* 1977;134:263–269.

42. Mabrut JY, Bozio G, Hubert C, et al. Management of congenital bile duct cysts. *Dig Surg.* 2010;27:12–18.

43. Lee SE, Jang JY, Lee YJ, et al. Choledochal cyst and associated malignant tumors in adults: a multicenter survey in South Korea. *Arch Surg.* 2011;146:1178–1184.

44. Alonso-Lej F, Rever WB Jr, Pessagno DJ. Congenital choledochal cyst, with a report of 2, and an analysis of 94 cases. *Int Abstr Surg.* 1959;108:1–30.