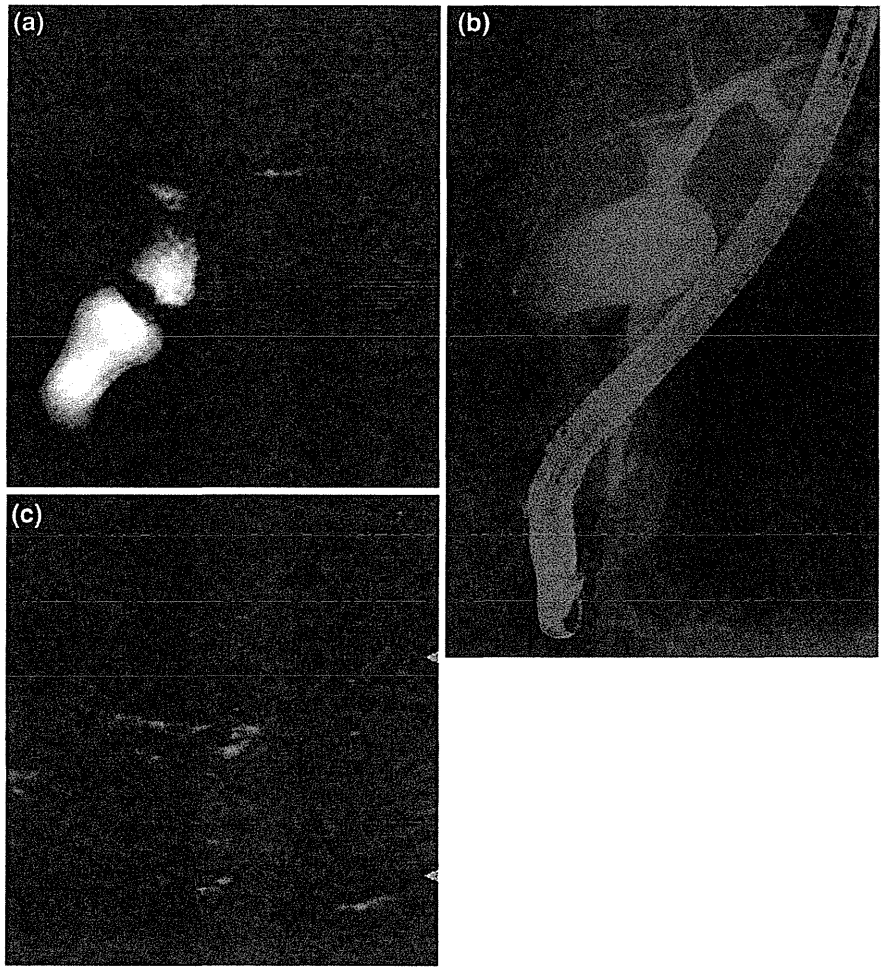

Fig. 2 Pancreaticobiliary maljunction without biliary dilatation was suspected by magnetic resonance cholangiopancreatography (MRCP) (**a**) and confirmed on endoscopic retrograde cholangiopancreatography (ERCP) (**b**). Ultrasonography in this patient showed gallbladder wall thickening (**c**)

Treatment of PBM

Once a diagnosis of PBM has been established, immediate prophylactic surgery is recommended before the onset of malignant changes. Cholecystectomy and resection of the extrahepatic bile duct (flow-diversion surgery) is an established standard for the surgical treatment of congenital biliary dilatation [3, 22]. Internal drainage operations have been abandoned because of the high risk of postoperative carcinogenesis.

On the other hand, treatment of PBM without biliary dilatation and without cancer is controversial. Prophylactic cholecystectomy is performed in many institutes, as most biliary cancers that develop in PBM patients without biliary dilatation are gallbladder cancers [38, 39]. However, some surgeons propose excision of the extrahepatic bile duct together with the gallbladder for PBM patients without biliary dilatation [23], because the frequency of bile duct cancer in PBM patients without biliary dilatation is higher compared to that in the general population [2], and K-ras and/or p53 gene mutations are also reportedly seen in the bile duct of PBM patients without biliary dilatation [23, 40].

Strategy for early diagnosis of PBM

Compared to congenital biliary dilatation, PBM cases without biliary dilatation rarely evoke symptoms, and most patients are not diagnosed until the onset of advanced stage gallbladder cancer [1, 38]. Detecting PBM before the development of biliary cancer is important in order to allow for prophylactic surgery. Epithelial hyperplasia of the gallbladder induced by longstanding continuous stasis of the bile intermingled with refluxed pancreatic juice is a characteristic pathological change in PBM patients [41–43]. To achieve early detection of PBM without biliary dilatation, MRCP is warranted in patients showing thickening of the gallbladder wall on screening US under suspicion of PBM (Fig. 2c) [44].

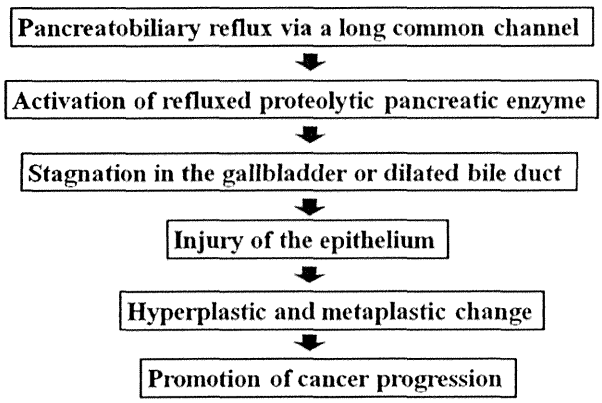

Fig. 3 Mechanism of biliary carcinogenesis in pancreaticobiliary maljunction [1]

High confluence of pancreaticobiliary ducts

The frequency of common channel formation ranges from 55 % to 91 % [17], and the mean length of the common channel has been reported as 4.5 mm [45]. To investigate the clinical significance of a relatively long common channel, we defined high confluence of pancreaticobiliary ducts (HCPBD) as a disease state in which the common channel length is ≥6 mm and communication is occluded when the sphincter of Oddi is contracted (Fig. 4a, b) [17].

In our series of 95 HCPBD patients, reflux of contrast medium into the pancreatic duct was detected in 86 % of patients who underwent postoperative T-tube cholangiography. Elevated amylase levels in bile were observed in all patients, although the mean levels were significantly lower than those in PBM patients. Gallbladder cancer was identified in 11 HCPBD patients (12 %). Similar to PBM patients, hyperplastic changes with increases in both the proliferative activity of epithelial cells and K-ras mutations were also detected in the noncancerous epithelium of the gallbladder in HCPBD patients [1, 18, 19]. A relatively long common channel also appears to represent an important risk factor for the development of gallbladder cancer. However, several differences exist between HCPBD and PBM without biliary dilatation in terms of other features, such as gender predilections, age at diagnosis, incidence of concomitant gallbladder cancer, and biliary amylase levels. HCPBD appears to represent an intermediate clinical condition that is both morphologically and functionally difficult to differentiate clearly from PBM. We consider that HCPBD should currently be managed as a disease entity independent of PBM in terms of the appropriate therapeutic strategies [1, 22].

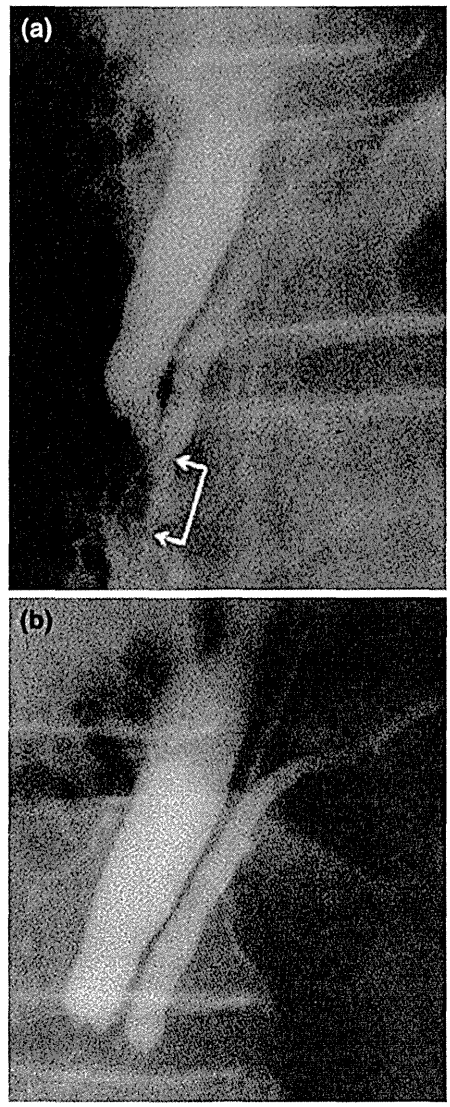

Fig. 4 Images from endoscopic retrograde cholangiopancreatography of high confluence of pancreaticobiliary ducts (HCPBD) [3]. The bile and pancreatic ducts form a common channel (*arrows*) 8 mm long during sphincter relaxation (**a**). Communication between these two ducts is interrupted during contraction of the sphincter of Oddi (**b**)

Conclusions

Biliary cancers occur frequently through proliferative processes provoked by chronic inflammation resulting from the persistence of pancreatic juice refluxed through a long common channel. Once PBM is diagnosed, immediate prophylactic surgery is recommended before malignant changes develop. It is important to diagnose PBM before the onset of biliary carcinogenesis. To achieve early detection of PBM without biliary dilatation, MRCP is recommended for patients showing gallbladder wall thickening on screening US under suspicion of PBM. Further investigations and surveillance studies are also needed to clarify appropriate surgical strategies for PBM without biliary dilatation.

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ORIGINAL ARTICLE

Exploring the length of the common channel of pancreaticobiliary maljunction on magnetic resonance cholangiopancreatography

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Abstract
Background In the revised diagnostic criteria for pancreaticobiliary maljunction (PBM), PBM can be diagnosed from a long common channel by magnetic resonance cholangiopancreatography (MRCP). However, it is necessary to differentiate from high confluence of pancreaticobiliary ducts (HCPBD) with a relatively long common channel (≥6 mm) and effect of the sphincter in the pancreaticobiliary junction. This multicenter study aimed to explore definite value of the length of an abnormally long common channel, which enables to distinguish PBM from HCPBD on MRCP.
Methods In 184 PBM patients and 22 HCPBD patients who were diagnosed by direct cholangiography and underwent MRCP, the length of the common channel was measured.
Results The length of the common channel was 16.2 ± 6.9 mm on direct cholangiography and 13.9 ± 6.2 mm on MRCP in PBM patients, and 7.7 ± 1.5 mm and 6.6 ± 1.4 mm in HCPBD patients. The optimal cut off value of the length of the common channel to distinguish PBM from HCPBD was identified to be 9 mm.
Conclusions Pancreaticobiliary maljunction can be diagnosed from an abnormally long common channel on MRCP, but in cases of the common channel ≤9 mm on MRCP, direct cholangiography is needed to confirm PBM.

Keywords Common channel · Magnetic resonance cholangiopancreatography · Pancreaticobiliary maljunction

Introduction

Pancreaticobiliary maljunction (PBM) is a congenital malformation in which the pancreatic and bile ducts join anatomically outside the duodenal wall, usually forming a markedly long common channel [1–4]. The action of the sphincter of Oddi does not affect the pancreaticobiliary junction, reflux of pancreatic juice into the bile duct can easily occur, resulting in injury to the biliary epithelium, which develops to carcinogenesis in the biliary tract [2–4]. As PBM is a high-risk factor for biliary cancer, prophylactic surgical procedure is performed once PBM is diagnosed. Early and accurate diagnosis of PBM is necessary before biliary cancer develops [3].

In the initial diagnostic criteria for PBM [2], the pancreatic and bile ducts connect with an obviously long common channel showing the lack of effect of the sphincter muscle on the pancreaticobiliary junction should be confirmed by direct cholangiography such as endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), or intraoperative cholangiography for the diagnosis of PBM. The criteria for PBM were revised in 2013, 23 years to the day since the initial version, taking the recently advanced diagnostic imaging modalities [4]. In the criteria [4], PBM can be diagnosed from an abnormally long common channel and/or an abnormal union between the pancreatic and bile ducts by magnetic resonance cholangiopancreatography (MRCP) or three dimensional drip infusion cholangiography computed tomography (3D-DIC-CT) by direct cholangiography.

Endoscopic retrograde cholangiopancreatography can visualize pancreatic and biliary anatomy in detail, and is a gold standard for diagnosis of PBM. However, due to complications such as pancreatitis in ERCP, MRCP is currently becoming one of the first choices for examining pancreaticobiliary diseases in a noninvasive manner. In typical cases with an abnormally long common channel, PBM can be diagnosed only by MRCP. However, in cases with a relatively long common channel, it is necessary to confirm that the effect of the papillary sphincter does not extend to the junction by direct cholangiography and differentiate from high confluence of pancreaticobiliary ducts (HCPBD) [3–5], which has a relatively long common channel (≥6 mm) and the effect of the sphincter reaches the pancreaticobiliary junction. In contrast to ERCP, MRCP cannot determine the action of sphincter to pancreaticobiliary junction. In which cases can we diagnose PBM only by MRCP? What is the minimum length of an abnormally long common channel specific to PBM on MRCP?

This multicenter study aimed to explore the definite value of the length of an abnormally long common channel, which enables us to distinguish PBM from HCPBD on MRCP.

Patients and methods

Patients

A retrospective, multicenter study was carried out during the period from 1996 to 2012 in 21 institutions in Japan. The study subjects included 184 patients with PBM (M/F: 48/136; age 41.2 ± 26.2, range 0–89 years) and 22 patients with HCPBD (M/F: 9/13; age 61.7 ± 10.9, range 42–79 years) diagnosed by direct cholangiography (ERCP, PTC, intraoperative cholangiography, and T- or C-tube cholangiography). All patients also underwent MRCP. PBM was diagnosed by an abnormal long common channel and/or confirmation that the effect of the papillary sphincter does not extend to the junction. HCPBD was defined as a common channel ≥6 mm in length in which the communication between the pancreatic and bile ducts occluded while the sphincter contracted. The longest length of the common channel was measured on ERCP and MRCP. The length was measured manually using a goniometer or ruler on the films

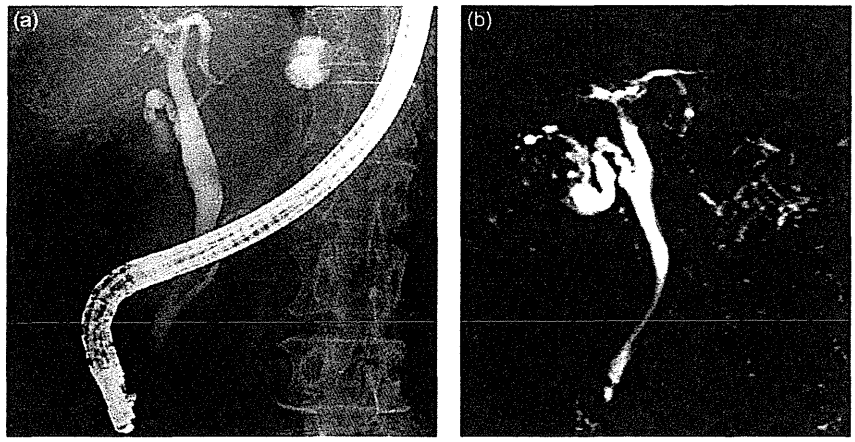

Fig. 1 (**a**) Endoscopic retrograde cholangiopancreatography (ERCP) and (**b**) magnetic resonance cholangiopancreatography (MRCP) imaging showing an abnormally long common channel in a pancreaticobiliary maljunction (PBM) patient

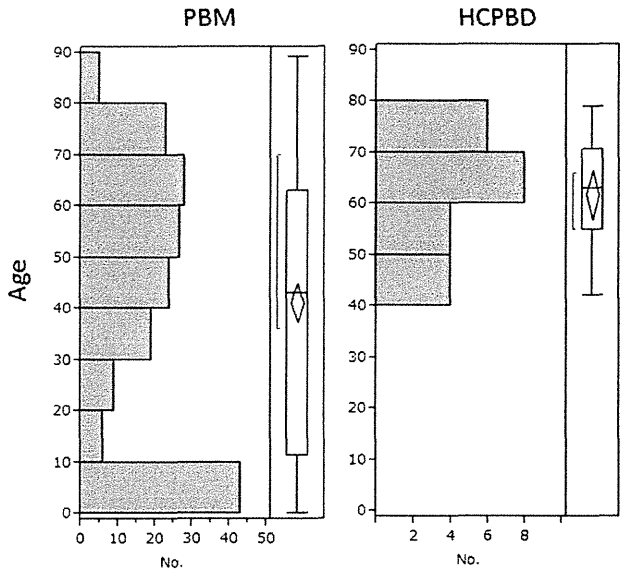

Fig. 2 The age distribution of pancreaticobiliary maljunction (PBM) and high confluence of pancreaticobiliary ducts (HCPBD)

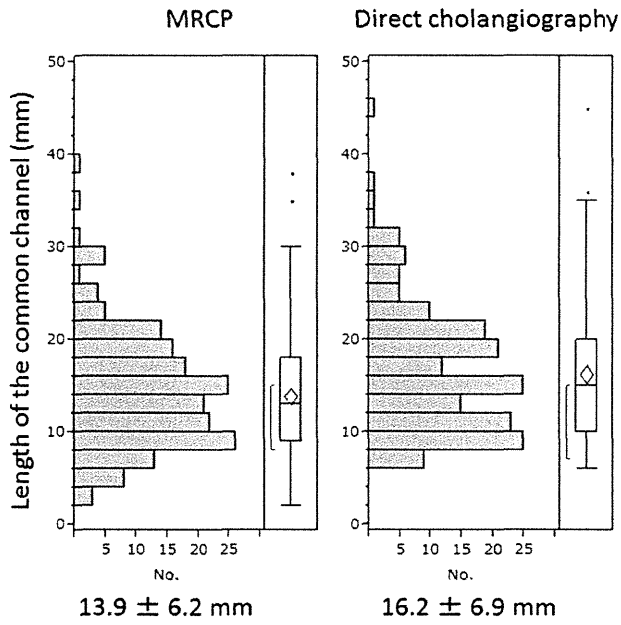

Fig. 3 The length of common channel of pancreaticobiliary maljunction (PBM) measured by direct cholangiography and magnetic resonance cholangiopancreatography (MRCP)

or by counting the pixels in digital images by a practician in each institute (Fig. 1). Length of the common channel could not be measured in 49 PBM patients on MRCP.

The age distribution of PBM and HCPBD is shown in Figure 2.

Statistical analysis

All analyses were performed with SAS software, JMP 9.0 (SAS Institute, Cary, NC, USA). The Wilcoxon rank sum test was used as a non-parametric statistic to compare the length of common channel in each MRCP and direct cholangiography. The Spearman's rank correlation coefficient (ρ) was used for correlation analysis of both length of common channel. Logistic regression and receiver operator characteristic (ROC) curves were used to determine the optimal cut-off value of the length of the common channel to distinguish PBM from HCPBD. A P-value of less than 0.05 was regarded to indicate a statistically significant difference.

Results

Length of the common channel of PBM on direct cholangiography and MRCP

In PBM patients, the length of the common channel was 16.2 ± 6.9 mm (mean ± SD) on direct cholangiography and 13.9 ± 6.2 mm on MRCP, respectively (Fig. 3), and it was

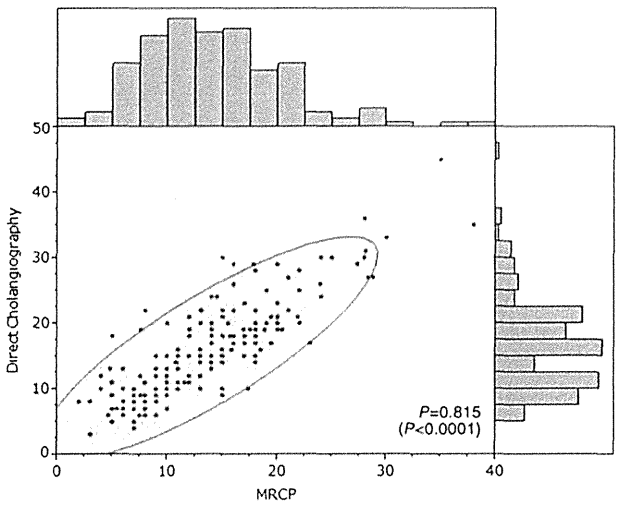

Fig. 4 The correlation between the length of common channel measured by direct cholangiography and magnetic resonance cholangiopancreatography (MRCP) in pancreaticobiliary maljunction (PBM) patients

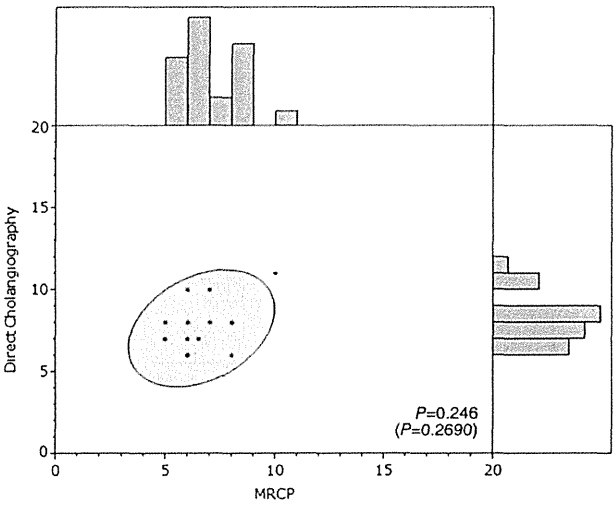

Fig. 5 The correlation between the length of common channel measured by direct cholangiography and magnetic resonance cholangiopancreatography (MRCP) in high confluence of pancreaticobiliary ducts (HCPBD) patients

significantly shorter on MRCP ($P < 0.0001$). In PBM patients, there is a correlation between the length of the common channel measured by direct cholangiography and on MRCP (Fig. 4).

On the other hand in HCPBD patients, the length of the common channel was 7.7 ± 1.5 mm on the direct cholangiography and 6.6 ± 1.4 mm on MRCP, and there were no significant correlations between them (Fig. 5). The length of the common channel showed a significant difference between PBM patients and HCPBD patients ($P < 0.0001$).

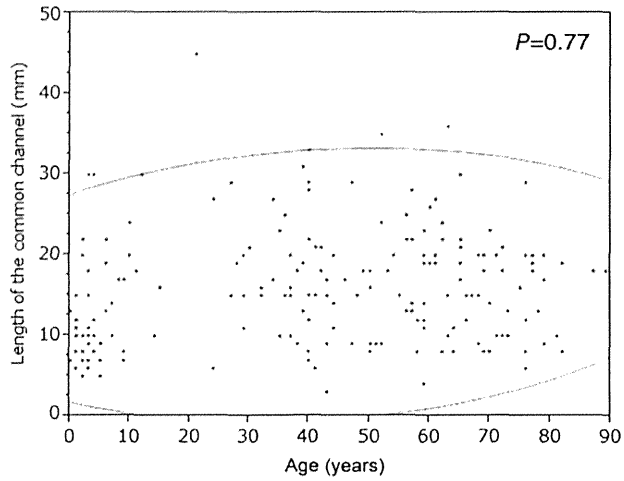

Fig. 6 The correlation between age and length of common channel measured by direct cholangiography in pancreaticobiliary maljunction (PBM) patients

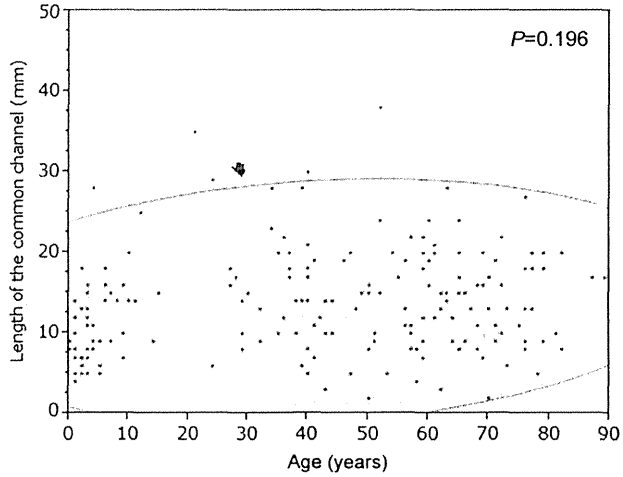

Fig. 7 The correlation between age and length of common channel measured by magnetic resonance cholangiopancreatography (MRCP) in pancreaticobiliary maljunction (PBM) patients

Age and length of the common channel of PBM

There was no relationship between age and length of the common channel in PBM patients on direct cholangiography (Fig. 6) or on MRCP (Fig. 7).

Exploring the definite value of the length of the common channel to distinguish PBM from HCPBD on MRCP

On the basis of the logistic regression and ROC curve data, the optimal cut-off value of the length of the common channel to distinguish PBM from HCPBD was 9 mm. Using this cutoff value, sensitivity was 79.3%, specificity was 95.4%, and the area under the curve was 0.89 (Figs 8,9).

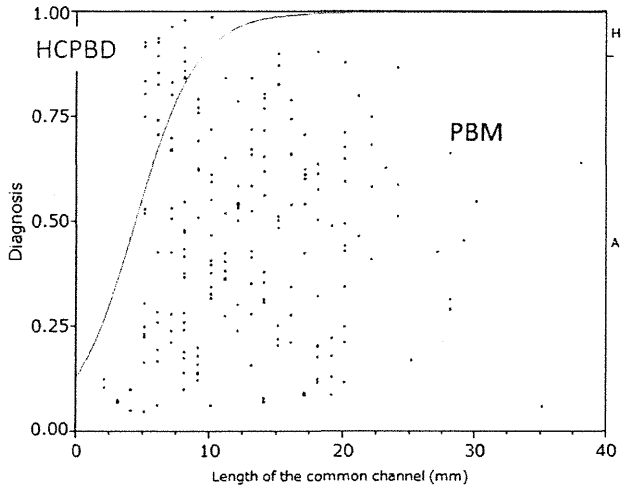

Fig. 8 The logistic regression analysis of pancreaticobiliary maljunction (PBM) and high confluence of pancreaticobiliary ducts (HCPBD)

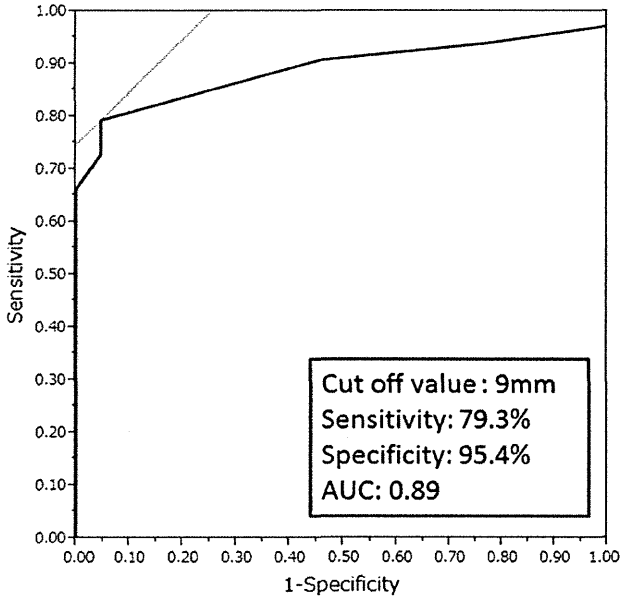

Fig. 9 The receiver operating characteristic curve evaluating the optimal cutoff value of the common channel to distinguish pancreaticobiliary maljunction (PBM) from high confluence of pancreaticobiliary ducts (HCPBD) on magnetic resonance cholangiopancreatography (MRCP)

Diagnostic rate of PBM on MRCP

Of the 184 patients with PBM, 124 (67%) were diagnosed on MRCP as having PBM based on findings of an abnormally long common channel (Fig. 1). Reasons unable to diagnose as PBM on MRCP were poor visualization of the main pancreatic duct (n = 16), poor MRCP image status (n = 14), short common channel (n = 12), obscure by large choledochal cyst (n = 9), suboptimal depiction of pancreaticobiliary junction (n = 8), complex union (n = 3), and others (n = 5).

Discussion

In PBM, pancreatic juice continuously refluxes into the biliary tract via a long common channel, and this pancreatobiliary reflux provokes high rates of biliary tract cancer [2–5]. According to the nationwide survey in Japan, biliary tract cancers occurred in 433 (28.6%) of 1511 adult patients with PBM [6]. Therefore, a prophylactic operation is recommended, once a patient is confirmed to suffer from PBM [3]. Early and accurate diagnosis of PBM is necessary. On the other hand, pathophysiological conditions similar to PBM including pancreatobiliary reflux can occur also in cases with a relatively long common channel [5, 7]. To clarify clinical significance of a relatively long common channel, HCPBD was defined as a common channel ≥6 mm in length in which the communication between the pancreatic and bile ducts occluded while the sphincter contracted [3–5]. Bile amylase levels (average 47774 IU/L) were elevated in all HCPBD cases, and gallbladder cancer was associated with 8% HCPBD cases [8]. Lower bile amylase levels in HCPBD cases compared to average 255,950 IU/L in PBM cases and lower incidence of associated gallbladder cancers than PBM appear to be attributed to intermittent pancreatobiliary reflux in HCPBD [8]. A relatively long common channel also appears to be an important risk factor for the development of gallbladder cancer, but currently most HCPBD cases do not undergo prophylactic operation but are vigilantly followed up with or without endoscopic sphincterotomy for the purpose of diversion of the pancreatic and bile ducts [3, 8].

In the diagnostic criteria for PBM revised in 2013 [4], PBM can be diagnosed only from an abnormally long common channel by MRCP. However, cases with a relatively long common channel should be distinguished from HCPBD by confirming that the effect of the papillary sphincter does not extend to the junction by direct cholangiography. To explore the definite value of the length of an abnormally long common channel, which enables differentiation of PBM and HCPBD only on MRCP, we compared the length of common channel of HCPBD and PBM by the direct cholangiography and MRCP.

In PBM patients, there is a correlation between the length of common channel measured by direct imaging and MRCP, and the length of common channel as measured by MRCP was significantly shorter that measured by direct cholangiography. This phenomenon is also reported in the literature [9–11]. As reasons for these facts, it is suspected the longest length of common channel at the

relaxed phase of the papillary sphincter can be measured dynamically on direct cholangiography, but the length of the common channel depicted on MRCP is not always the longest due to the static nature of MRCP. Another reason might be lower spatial resolution to visualize the narrow distal segment created by the sphincter of Oddi on MRCP.

In the study, the optimal cut-off value of the length of the common channel to distinguish PBM from HCPBD on MRCP was 9 mm. The length of the common channel is not included in the diagnostic criteria for PBM because various factors such as age, stature, and taking position in examination should be considered [2]. However, the length of the common channel on MRCP was not different in ages in this study and MRCP is routinely taken on a prone position, the length of the common channel on MRCP may be used as a diagnostic tool for PBM.

In this study, PBM could be diagnosed in 67% of 184 PBM patients on MRCP. Major reasons unable to diagnose as PBM on MRCP were poor visualization of the main pancreatic duct, poor quality image, short common channel, obscure by large choledochal cyst, and suboptimal depiction of pancreaticobiliary junction. Detection rates for PBM on MRCP reportedly were 40% (4/10) [12], 44% (12/27) [13], 57% (41/72) [14], 60% (12/20) [15], and 82% (9/11) [9]. As additional reported reasons, MRCP is limited by small-caliber ducts and patient motion creating artifacts in pediatrics. A small-caliber duct is not easily-delineated on MRCP compared with direct cholangiography, which dilates caliber of duct by injection of contrast material [12, 13, 15]. Although secretin is not available in Japan currently, secretin stimulation appears to be useful for the improvement of depiction of duct confluence [16, 17].

Overall, about half of PBM cases can be diagnosed only on MRCP. However, in the cases of the common channel of less than 9 mm on MRCP, direct cholangiography is needed to confirm PBM.

Our study has a number of limitations. First, the number of HCPBD cases is small. HCPBD is a recently proposed concept and direct cholangiography is essentially necessary for diagnosis of PBM. Many HCPBD cases are diagnosed as a by-product by ERCP performed for examination of biliary stones or malignancy. It is necessary to improve the accuracy by increasing the number of samples of HCPBD in the future. Second is the nature of a retrospective and multicenter study over 16 years. The MRCP imaging protocols are different in centers and the period. However, as PBM and HCPBD are rare diseases, multicenter study during a long period is necessary.

In conclusion, PBM can be diagnosed from an abnormally long common channel on MRCP, but in the cases of the common channel ≤9 mm on MRCP, direct cholangiography is needed to confirm PBM.

Conflict of interest None declared.

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総　説

膵・胆管合流異常とその診断基準の改訂

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千葉和朗　岩崎　将[1)]

要旨：膵・胆管合流異常は，解剖学的に膵管と胆管が十二指腸壁外で合流する先天性の形成異常である．合流異常には，胆管に拡張を認める例（先天性胆道拡張症）と拡張を認めない例がある．合流異常は，乳頭部括約筋の作用が膵胆管の合流部に及ばないため膵液と胆汁の相互逆流がおこり，胆道癌や膵炎などを引きおこすので，胆道の発癌予防の手術が推奨される．診断基準2013では，MRCP，3D-DIC-CT，EUSやMD-CTのMPR像などにより合流異常の診断が可能となったが，非典型例ではERCPによる確定診断が必要である．比較的長い共通管を有する症例（膵胆管高位合流）では，合流異常と類似する病態を呈することがある．

索引用語：膵・胆管合流異常，先天性胆道拡張症，膵胆管高位合流，胆嚢癌，胆管癌

はじめに

膵・胆管合流異常（以下合流異常）の概念は，先天性胆道拡張症（以下胆道拡張症）の研究から生まれた．木積らは，1916年に総胆管嚢胞の剖検例で，膵管と胆道系が長い共通管で合流しており，この合流形式の異常が胆道拡張の病因であろうと推察した[1)]．Milwaukee Children's Hospitalの放射線医であるBabbittは，1969年に3例の胆道拡張症の術中造影所見から，膵管と胆道系との異常な合流形態がその病因であると論じた[2)]．その後，ERCPの普及とともに合流異常の報告が増加し，合流異常は世界的に認識されるようになった．その後の研究にて合流異常が胆道拡張症の原因のすべてではないことがわかり，さらに胆管拡張のない合流異常の存在が明らかになった．

合流異常の診断基準は，日本膵・胆管合流異常研究会の診断基準検討委員会が中心となって1986年に案が作成され[3)]，1990年に改訂[4)]，そして2013年9月に23年ぶりに改訂された[5)6)]．また2012年5月には，日本膵・胆管合流異常研究会と日本胆道学会により膵・胆管合流異常の診療ガイドラインが，世界で初めて発刊された[7)8)]．本稿では，われわれの経験をもとに，ガイドラインに沿って合流異常に関して概説し，さらに改訂された診断基準を紹介する．

I　膵・胆管合流異常とは

1．疾患概念

合流異常は，解剖学的に膵管と胆管が十二指腸壁外で合流する先天性の形成異常と定義される[5)6)]．合流異常には人種差があり東洋人種で頻度が高く，また性差があり女性は男性の約3倍の頻度である[7)8)]．合流異常には，胆管に拡張を認める

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Pancreaticobiliary maljunction and the revised diagnostic criteria
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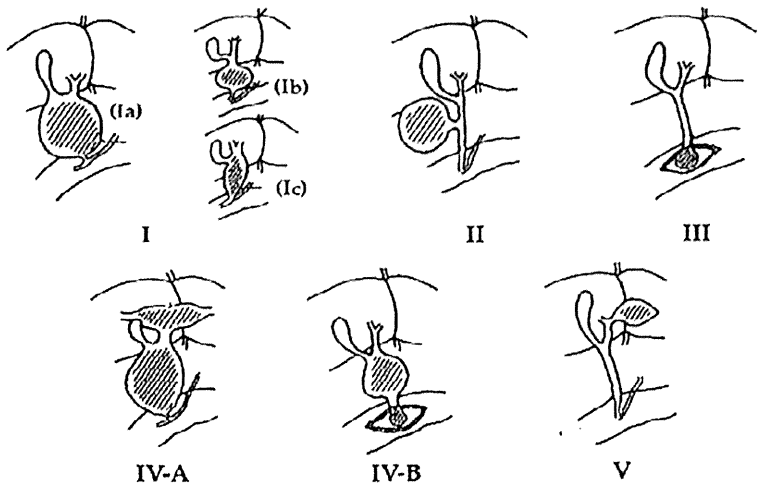

Figure 1. 先天性胆道拡張症の戸谷分類[10].

例と胆管に拡張を認めない例（胆管非拡張型）がある.

2. 合流異常と先天性胆道拡張症

胆道拡張症は，胆道系が限局性に拡張した先天性の胆道形成異常で，従来は先天性総胆管嚢腫（congenital choledochal cyst）と呼ばれていた．胆道拡張症の分類は，1959年にAlonso-Lejにより3型に分けられ[9]，現在は合流異常の概念を取り入れ5型に分けた戸谷分類（Figure 1）[10]が広く使われている．戸谷I型は肝外胆管の拡張を呈し，Ia型（嚢腫状拡張），Ib型（分節型），Ic型（円筒状拡張）に亜分類される．II型は憩室型で極めてまれであり，III型は胆管瘤（choledochocele）とも呼ばれ，十二指腸壁内の総胆管末端部の嚢状拡張である．IV型は多発型で，肝内・肝外とも拡張を認めるIV-A型と，肝外だけに2カ所以上の拡張を認めるIV-B型に分けられる．V型は肝内胆管のみが拡張したもので，Caroli病が含まれる．I型とIV-A型の頻度が非常に高く，またIa型，Ic型とIV-A型はほぼ全例に合流異常を合併するが，他のIb，II，III，IV-B，V型では合流異常の合併はほとんどみられない．現在わが国では，いわゆる狭義の先天性胆道拡張症は，戸谷I型（Ibは除く）とIV-A型を意味することが多い[7][8].

3. 発生論

1）膵臓と胆道の発生過程

膵臓と胆道の発生は，胎生4週頃にその先端が肝臓となる肝憩室と背側膵原基が相対して発生し，その後肝憩室から腹側膵原基が突出する．腹側膵原基は左・右の二葉に分かれて発生し，その後左葉は早期に消退して右葉が残り腹側膵になると考えられている．腹側膵原基は，胎生6週から始まる内臓回転にともない，肝憩室から生ずる原始総胆管とともに時計方向に回転し，背側膵原基の下方に接触して癒合する．胆管は，6週から内腔形成が下部から肝側に向かって進み，10週頃に完成する．腹側膵原基の主導管と，その上行枝と癒合した部位より上流の背側膵原基の主導管が，主膵管（Wirsung管）を形成する（Figure 2）[11][12]．この複雑な発生過程のために，膵臓や胆道では種々の形成異常が生じる.

2）合流異常の発生論

合流異常では，胆管系と背側膵管は直接合流することはなく，また背側膵管系は正常であることから，その発生には，腹側膵原基と背側膵原基が癒合する以前の胎生早期における胆管下部と腹側膵の導管系の異常が大きな影響を及ぼすと考えられている[7][8][13][14]．また，長い共通管から分枝が出ていることより，共通管は膵管由来とする考えがある[14][15].

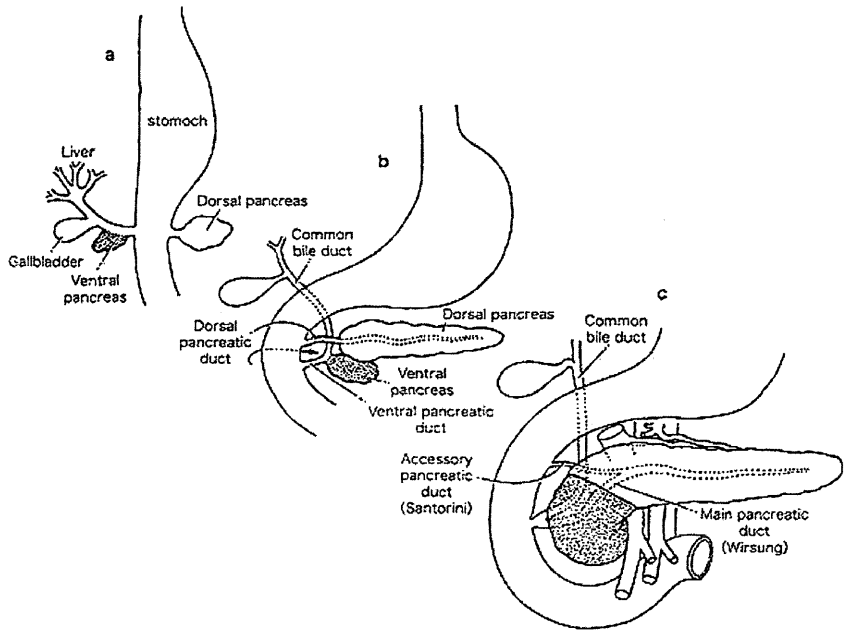

Figure 2. 膵胆道の発生[11)12)] **a**：胎生6週，**b**：腹側膵原基の回転，**c**：腹側膵管と背側膵管の癒合.

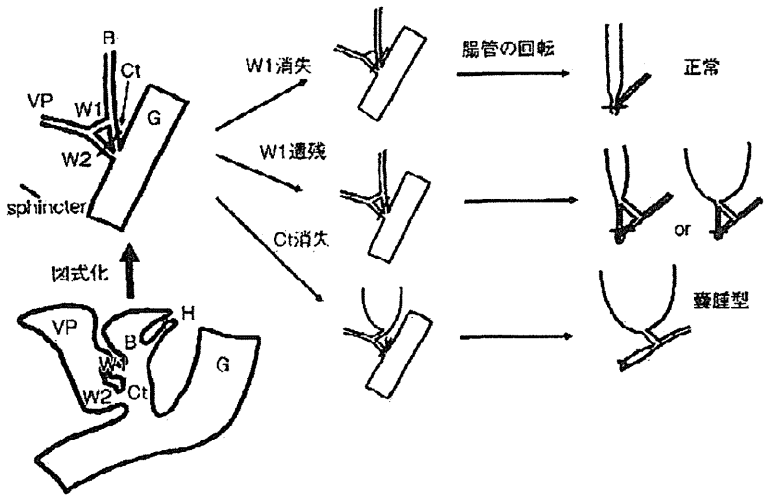

Figure 3. 大井の嚢胞型膵・胆管合流異常の発生に関する説[13)]．W1：腹側膵原基左葉の導管，W2：腹側膵原基右葉の導管，VP：腹側膵，B：胆管，Ct：胆管末端部，G：消化管，H：肝臓.

Odgersは，11.4mmの胎芽で，前膵原基に由来する2本の膵管を認め，これは左・右両葉の癒合が遅れたためと説明した[16)]．大井は，胆管が嚢胞状を呈する合流異常の発生をOdgersの説より以下のごとく説明した．左葉の導管（W1）が消退すれば，右葉の導管（W2）が胆管と通常の様式で合流し，腹側膵管と総胆管で主乳頭が形成される．何らかの原因で左葉の導管（W1）が残存すれば，これに由来する異常な結合枝（Co）をもつ合流異常が形成される．また，総胆管末端部（Ct）が閉塞すると，通常の合流異常が形成され胆汁は左葉の導管（W1）を介し右葉の導管（W2）

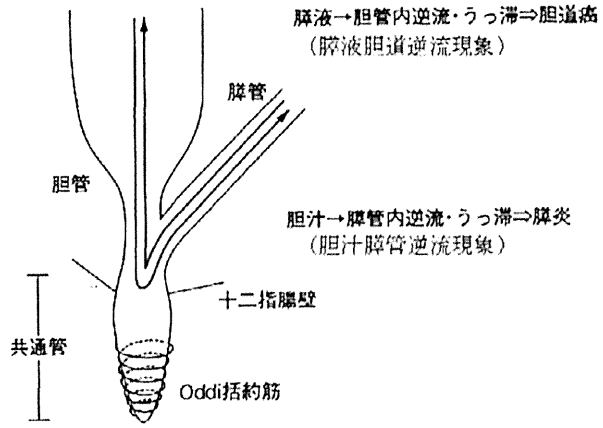

Figure 4. 膵・胆管合流異常の病態[7)23)].

を通って，十二指腸に流出する（Figure 3）[13)].

しかし，合流異常の発生機序に関しては，他にもさまざまな説があり合意は得られていない[14)17)~19)].

4. 病態のメカニズム

正常の十二指腸主乳頭部には，乳頭部括約筋（Oddi括約筋）が存在し，胆管末端部から膵胆管の合流部を取り囲んで胆汁の流れを調節し，同時に膵液の逆流を防止している．これに対し合流異常では，長い共通管を有するのでその括約筋が膵管と胆管合流後の共通管を取り囲むため，括約筋の作用が合流部に及ばないことより，膵液と胆汁の相互混入（逆流）がおこる[3)~7)]．通常，膵管内圧は胆管内圧より高いので，合流異常では膵液が胆道系に容易に逆流する（膵液胆道逆流現象）．ただし，ある状況下では，胆汁の膵管内への逆流もおこり得る（胆汁膵管逆流現象）．この膵液と胆汁の混和液が，胆嚢や拡張胆管内，および拡張した共通管や膵管内にうっ滞し，胆道ないし膵にいろいろな病態を引きおこす[7)8)20)~23)]（Figure 4）．

5. 症状と合併症

合流異常では，合併する膵胆道病変により黄疸，腹痛，発熱などの症状を呈することが多い．

1）胆道癌

合流異常では高率に胆道癌を合併する．癌発生の機序としては，圧勾配により長い共通管を介して胆道内に逆流した膵液と胆汁のうっ滞が重要な因子と考えられている．合流異常では，膵液中のホスホリパーゼA2が胆汁と混和すると強力な細胞毒性をもつリゾレシチンなどが産生される[24)]．その結果，慢性炎症にともなう胆道の粘膜上皮障害と修復が繰り返され，過形成を主体とする粘膜上皮の変化やDNAの突然変異などを介して最終的に癌化するというhyperplasia-dysplasia-carcinoma sequenceの説が有力であり，通常の胆道癌のadenoma-carcinoma sequenceや*de novo*発癌とは異なると考えられる[7)8)]．

合流異常の全国集計では，成人の胆道拡張症で22%，胆管非拡張型合流異常で42%に胆道癌の合併が認められた．その局在の割合は胆道拡張症において胆嚢癌62%，胆管癌32%で，胆管非拡張型においては胆嚢癌が88%と高率であった[25)26)]．胆管非拡張型では，肝外胆管に胆汁うっ滞がないため，肝外胆管は傷害作用を受けにくいと考えられている．合流異常に合併した胆道癌は，好発年齢が50~65歳で通常の癌発症年齢よりも15~20歳ほど若年であり，同時性・異時性重複癌例が多い．また胆嚢癌における結石合併率は低い[7)8)27)]．

2）膵炎

合流異常，特に胆道拡張症では，高率に急性膵炎を合併する．その頻度は成人では約9%であるのに対し，小児では約28%から43.6%とさらに高い[7)8)]．合流異常に合併する急性膵炎の発生要因として，共通管の拡張，膵管の拡張，膵頭部膵管の複雑な走行異常，蛋白栓などが考えられている．また，臨床的に一過性のものや，軽症で再発性のものが多い．合流異常では，何らかの原因で長い共通管が一時的に閉塞した場合，胆管内圧の異常上昇と同時に胆汁が膵管内に逆流し膵管内圧が高まり膵炎が惹起され，さらに拡張した胆管内にうっ滞した感染胆汁が膵管内に逆流した場合，特に膵に傷害を与えると考えられている．一方，共通管での一時的な閉塞が解除され，胆汁や膵液の十二指腸排泄が速やかに行われるようになれば，膵炎は消退するものと考えられる[28)~32)]．

合流異常の慢性膵炎合併率は，全国集計では3%であった[33)]．合流異常に合併する慢性膵炎の平均年齢は30~36歳と，若年症例が多い．画像

上，結石は多くの例で拡張した共通管や共通管近傍の主膵管内のみに認められ，分枝膵管内にまでび漫性にみられることは少ない．また，アルコール性膵炎などの一般的な慢性膵炎に合併するカルシウムを主成分とする膵石とは異なり，X線透過性の蛋白質を主成分とする非陽性結石を認めることが多い．合流異常における慢性膵炎の発症機序として，胆汁と混和した膵液が拡張した共通管や主膵管内にうっ滞することで非陽性結石が形成され，慢性膵炎へ発展する可能性が推察されている[7)8)29)30)]．

6．治療と予後

合流異常と診断されれば，胆道発癌を予防するために早期の手術が推奨される．胆道拡張症では，拡張胆管内に癌発生が高率におこるので，肝外胆管切除術と胆道再建の分流手術が基本術式である．一方，胆管非拡張型では合併する胆道癌のほとんどが胆嚢癌であることより，予防的胆嚢摘出のみで経過を観察することが多い．しかし，胆管癌の発生を危惧して肝外胆管切除も行う施設もあり，現在のところ統一された見解がない[7)8)34)]．

術後の晩期合併症としては，吻合部や肝内胆管狭窄による胆管炎や肝内結石および胆管癌の出現などがあり，術後の経過観察は生涯必要である[7)8)]．

II 膵・胆管合流異常の診断基準2013

日本膵・胆管合流異常研究会の診断基準検討委員会では，最近の合流異常における病態の解明や画像診断の進歩を踏まえて，2011年から診断基準の改訂作業を始めた．そして，第36回日本膵・胆管合流異常研究会（2013年9月）での案を最終案とし，膵・胆管合流異常診断基準2013(Table 1)[5)6)]が作成された．以下に解説を加える．

1．定義

膵管と胆管の十二指腸壁外合流という解剖学的な観点からの定義であり，機能的な側面は含まれていない．従来の定義では“先天性の奇形”が用いられていたが，今回“先天性の形成異常”に変更した．

2．画像診断

画像上，膵管と胆管が異常に長い共通管をもって合流することにより診断される例が多い．膵管と胆管が異常な形で合流する例は，複雑な形態を呈することが多い[13)]．

近年，画像診断の進歩により，直接胆道造影以外の検査法でも合流異常の診断が可能となった．MRCPや3D-DIC-CT像などでは，異常に長い共通管の所見より合流異常と診断できる．しかし，MRCPではOddi括約筋作用が膵胆管合流部に及んでいるかいないかを確認できないので，共通管の短い例や複雑な合流様式を示す例では直接胆道造影による確定診断が必要となる[7)8)35)]．

EUS，IDUSまたはMD-CTのMPR像により膵管と胆管の壁外合流が確認できた場合，合流異常と診断できる．しかし，非典型例ではやはりERCPによる確定診断が必要である[7)8)36)]．

3．高アミラーゼ胆汁

膵管内圧は通常胆管内圧より高いので，合流異常では膵液が胆管内へ容易に逆流する．したがって胆汁中の膵酵素であるアミラーゼ値の上昇は，膵液胆道逆流現象の有力な診断証拠となる．合流異常では胆汁中アミラーゼ値が10000IU/*l*以上の異常高値を示すことが多い[25)]．しかし，合流異常でも胆汁中アミラーゼ値が異常高値を示さない例もある[37)~39)]．

一方，乳頭部括約筋作用が膵胆管合流部まで及んでいても，比較的長い共通管を有する症例では，胆汁中膵酵素が異常高値を呈し，合流異常と類似する病態を呈することがある．われわれは，ERCP施行時共通管の長さが6mm以上であり，膵胆管合流部に括約筋作用が及ぶ例を，膵胆管高位合流（以下高位合流）と定義した[40)]．高位合流例では，高率にTチューブ造影による膵管の描出や胆汁中のアミラーゼ値の上昇を認め，10%程度の例で胆嚢癌の合併がみられた．また，高位合流例の胆嚢粘膜では，合流異常例の胆嚢と同様に，粘膜の過形成変化，細胞増殖能の亢進や*K-ras*遺伝子変異が高率に認められた．しかし，高位合流では性差がなく，診断時の年齢は合流異常より高齢であり，合流異常に比べて胆嚢癌の合併率や胆汁中アミラーゼ値は低い．この差違の要因として，合流異常では常に膵管と胆管の交通が保たれ

Table 1. 膵・胆管合流異常の診断基準 2013

日本膵・胆管合流異常研究会
日本膵・胆管合流異常研究会診断基準検討委員会

(定義)

膵・胆管合流異常とは，解剖学的に膵管と胆管が十二指腸壁外で合流する先天性の形成異常をいう．

(病態)

膵・胆管合流異常では，機能的に十二指腸乳頭部括約筋（Oddi 筋）の作用が膵胆管合流部に及ばないため，膵液と胆汁の相互逆流が起こり，胆汁や膵液の流出障害や胆道癌など胆道ないし膵にいろいろな病態を引き起こす．

(診断基準)

膵・胆管合流異常の診断は，画像または解剖学的検索によって行われ，以下のいずれかを満たせばよい．

1. 画像診断

1) 直接胆道造影（ERCP，経皮経肝胆道造影，術中胆道造影など）または MRCP や 3D-DIC-CT 像などで，膵管と胆管が異常に長い共通管をもって合流するか，異常な形で合流することを確認する．
ただし，共通管が比較的短い例では，直接胆道造影で乳頭部括約筋作用が膵胆管合流部に及ばないことを確認する必要がある．

2) EUS または multidetector-row CT（MD-CT）の multi-planar reconstruction（MPR）像などで，膵管と胆管が十二指腸壁外で合流することを確認する．

2. 解剖学的診断

手術または剖検などで，膵胆管合流部が十二指腸壁外に存在するか，または膵管と胆管が異常な形で合流することを確認する．

(補助診断)

つぎのような所見は，膵・胆管合流異常の存在を強く示唆しており，有力な補助診断となる．

1. 高アミラーゼ胆汁

開腹直後または内視鏡的あるいは経皮的に採取した胆管内または胆嚢内の胆汁中膵酵素が異常高値を示す．
しかし，膵・胆管合流異常例でも血清濃度に近い例や，それ以下の低値例も少なからずある．また，膵胆管合流部に乳頭部括約筋作用が及ぶ例でも，胆汁中膵酵素が異常高値を呈し，膵・胆管合流異常と類似する病態を呈する例もある．

2. 肝外胆管拡張

膵・胆管合流異常には，胆管に拡張を認める例（先天性胆道拡張症）と胆管に拡張を認めない例（胆管非拡張型）がある．
肝外胆管に嚢胞状，紡錘状，円筒状などの拡張がみられるときには，膵・胆管合流異常の詳細な検索が必要である．
なお，胆管拡張の診断は，年齢に相当する総胆管径の基準値を参考にする．

日本膵・胆管合流異常研究会診断基準検討委員会
神澤 輝実（東京都立駒込病院内科，委員長），安藤 久實（愛知県心身障害者コロニー），濵田 吉則（関西医科大学附属枚方病院小児外科），藤井 秀樹（山梨大学第一外科），越永 従道（日本大学小児外科），漆原 直人（静岡県立こども病院小児外科），糸井 隆夫（東京医科大学消化器内科）

ていて恒常的に膵液と胆汁の逆流が生じているが，高位合流では括約筋収縮時には膵胆管の交通が遮断されることより膵液の胆道内逆流は一過性であり，両者間で膵胆管の逆流現象の生じる状況や逆流量などが異なることが推察される．また高位合流では，合流異常例でしばしばみられる乳頭部機能の異常，共通管の拡張，複雑な膵胆管合流様式などは認められない．したがって高位合流は，形態と機能の両面において合流異常とはっきりと鑑別しがたい中間の病態であるが，現段階では高位合流は normal variant として，合流異常とは異なる範疇として扱うべきと考える[7)8)40)~45)]．

胆汁中アミラーゼ値の上昇だけで合流異常とは診断できないが，その異常高値は合流異常を強く示唆する所見である．

4. 肝外胆管拡張

従来胆管拡張の診断は，総胆管径の基準値を 15 歳以上で 10mm にすることが多かった．しかし，腹部 US による総胆管径の基準値の策定では，小児・成人とも胆管径は年齢とともに大きくなるので，年齢に相当する総胆管径の基準値を参考にすることが推奨される[34)46)47)]．

5. 合流形式の分類

合流異常の合流形式の分類は，3 型に分ける分

類[5)7)8)]や新古味分類[48)]などが用いられてきたが，今後統一する必要がある．

III 今後解決すべき問題点

1. 胆管非拡張型合流異常の診断

胆管非拡張型と診断して胆嚢摘出のみを行った術後に胆管癌が生じた報告[7)49)]があり，胆管非拡張型の診断を再考する必要がある．肝外胆管の拡張基準として，年齢別の総胆管径の基準値の策定が行われたが[34)46)47)]，単に総胆管径のみでなく形態も考慮するべきだとの意見も少なくない．

2. 胆管非拡張型合流異常の早期診断

胆管非拡張型は臨床症状に乏しく，合併した胆嚢癌による黄疸などの症状を契機に診断されることが多い．合流異常では胆嚢粘膜の過形成を呈することが多いので，検診のUSで胆嚢粘膜（胆嚢壁内側の低エコー層）の肥厚を認めた場合にMRCPなどを行って，発癌前に胆管非拡張型を拾い上げることができる[7)8)50)51)]．胆管非拡張型の早期診断の体系を確立し，普及させる必要がある．

3. 胆管非拡張型合流異常の治療法の確立

胆管非拡張型では，予防的胆嚢摘出のみで経過を観察するのか，肝外胆管切除も行うべきなのか，長期経過を調べて明らかにする必要がある．

4. 長期予後の解明

分流術後の長期経過において重篤な合併症が出現する例の存在が明らかになってきた．症例ごとの長期予後を明らかにして，その治療法の妥当性について検証する必要がある．

本論文内容に関連する著者の利益相反
：なし

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膵・胆管合流異常

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索引用語：膵・胆管合流異常，先天性胆道拡張症，診断基準，膵胆管高位合流

1 はじめに

膵・胆管合流異常(合流異常)は，解剖学的に膵管と胆管が十二指腸壁外で合流する先天性の形成異常であり，胆管に拡張を認める例(先天性胆道拡張症)と拡張を認めない例がある．合流異常は，乳頭部括約筋の作用が膵胆管の合流部に及ばないため膵液と胆汁の相互逆流が起こり，胆汁や膵液の流出障害や胆道癌などを引き起こす[1]．

合流異常の診断基準が，最近の合流異常における病態の解明や画像診断の進歩をふまえて，2013年に改訂された[2,3]．また，合流異常の診療ガイドラインが2012年5月に世界で初めて発刊された[4,5]．

本稿では，改訂された合流異常の新しい診断基準の説明と，合流異常の診療ガイドラインの中で知っておくべきClinical Question (CQ)を紹介する．

2 膵・胆管合流異常診断基準2013

合流異常の診断基準は，日本膵・胆管合流異常研究会の診断基準検討委員会が中心となって1986年に案が作成され[6]，1990年に改訂され[7]，1994年に英文報告された[8]．この診断基準が長年使用されてきたが，2013年に23年ぶりに改訂され(表1)[2]，英文化された(表2)[3]．

今回改訂された診断基準の主な変更点は，①定義の奇形という用語を変更した，②病態を詳しく述べた，③診断基準の画像診断を大きく変更した，④胆管拡張の診断に言及した，である．

1．定義

従来と同様に，膵管と胆管の十二指腸壁外合流という解剖学的な観点からの定義であり，機能的な側面は含まれていない．

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[*2] 同 肝胆膵外科