Pediatric Surgery International (2023) 39:201
https://doi.org/10.1007/s00383-023-05486-y

ORIGINAL ARTICLE

Correlation of ectopic distal location of papilla of Vater and clinical characteristics in pediatric choledochal cysts

Suyun Chen[1,2] · Tong Yin[1,2] · Long Li[1,2,3] · Mei Diao[1,2] · Ting Huang[1,4]

Accepted: 10 May 2023 / Published online: 16 May 2023

Abstract

Purpose Ectopic distal location of papilla of Vater (EDLPV) is an obvious pathological feature of choledochal cyst (CDC). This study aimed to investigate the correlation between EDLPV and clinical characteristics of CDCs.

Methods Three groups were studied: Group 1 (G1), papilla in the middle third of second part of duodenum (n = 38); Group 2 (G2), papilla from the distal third of second part to the beginning of third part of duodenum (n = 168); Group 3 (G3), papilla from the middle of third part to fourth part of duodenum (n = 121). Relative variables among three groups were compared.

Results Compared with G1 and G2, G3 patients had the largest cysts (relative diameter: 1.18 *vs.* 1.60 *vs.* 2.62, $p < 0.001$), the youngest age (20.52 *vs.* 19.47 *vs.* -3.40 months, $p < 0.001$), the highest rate of prenatal diagnosis (26.32% *vs.* 36.31% *vs.* 62.81%, $p < 0.001$), the lowest occurrence of protein plugs in common channel (44.74% *vs.* 38.69% *vs.* 16.53%, $p < 0.001$), and the most elevated total bilirubin level (7.35 *vs.* 9.95 vs. 28.70 μmol/L, $p < 0.001$). Prenatally diagnosed G3 patients had heavier liver fibrosis than G2 (13.16% *vs.* 1.67%, $p = 0.015$).

Conclusion The more distal papilla location, the more severe clinical characteristics of CDCs, suggesting a crucial role in its pathogenesis.

Keywords Choledochal cyst · Dislocation of papilla of Vater · Pediatric · Pathogenesis

Introduction

The pathogenesis of choledochal cyst (CDC) is still in controversy. Spitz [1] successfully established an experimental model of cystic dilatation by ligation of distal end of CBD in newborn lambs, indicating obstruction of distal CBD is one of the etiologies [2, 3]. PBMU is a common pathological change. It allows free regurgitation of pancreatic juice to CBD, which may cause inflammation, destroy biliary epithelium and underlying muscle, and result in weakness of cyst wall, and eventually CBD dilatation and/or distal stenosis [4]. Therefore, PBMU was considered as one of the etiologies. However, the hypothesis is challenged. First, fusiform or cylindrical dilatation was only constructed in animal models of PBMU [5, 6]. Second, more severe reflux merely induced milder dilatation, while bile amylase level was lower with more dilated cysts [7]. Additionally, CBD dilatation does not occur in some patients with PBMU [8]. And for neonates and infants, secretory response of pancreas to stimulation is extremely poor, and the concentrations of amylase and lipase in duodenal fluid are negligible [9, 10].

Papilla of Vater represents embryonic hepatic diverticulum, and occurs prior to the development of pancreaticobiliary ductal union [11]. Li and Yamataka [12] first reported in 2001 that ectopic distal location of papilla of Vater (EDLPV) was closely associated with PBMU and proposed that ectopic distal budding of hepatic diverticulum in early embryos was one of the pathogeneses of CDC [12–15]. In addition, there were some studies on correlation between PBMU and EDLPV [16, 17]. Kim [18] also reported a 30-month-old CDC patient with EDLPV in 2011. The purpose of this study was to investigate the

✉ Long Li
lilong_pediatric20@163.com

1 Department of Pediatric Surgery, Capital Institute of Pediatrics, Beijing, China

2 Capital Institute of Pediatrics-Peking University Teaching Hospital, Beijing, China

3 Department of Pediatric Surgery, Tsinghua University Affiliated Beijing Tsinghua Changgung Hospital, Beijing, China

4 Children's Hospital Capital Institute of Pediatrics, Graduate School of Peking Union Medical College, Beijing, China

correlation between EDLPV and clinical characteristics of CDCs.

Patients and methods

Patients

In this retrospective study, CDC patients underwent definitive operation at Children's Hospital Capital Institute of Pediatrics between January 2020 and March 2022 were reviewed. The exclusion criteria were as follows: 1. Location of papilla of Vater was indistinguishable by intraoperative cholangiography (IOC), e.g., papilla location was obscured by a large cyst; and 2. External drainage or endoscopic retrograde cholangiopancreatography (ERCP) was performed before surgery. The study was approved by Ethical Committee of Capital Institute of Pediatrics.

Methods

Preoperative abdominal ultrasonography, computed tomography (CT), laboratory tests, and IOC were conducted routinely. Follow information was extracted from electronic medical record system: demographics, clinical manifestations, imaging examination results, and laboratory test results.

Papilla location was determined by the surgeon according to IOC during operation and reviewed by another researcher before analysis. For prenatally diagnosed patients, age at onset, expressed as a negative number, was defined as the period from the time of prenatal diagnosis to the date of birth, and duration of disease was defined as the period from the time of prenatal diagnosis to the date of surgery. Advanced fibrosis was defined as Ludwig stage of 3 or 4 [19]. The sizes of cyst, common hepatic duct (CHD), common channel (CC), and intrahepatic bile duct (IHD) were measured first according to IOC, secondly according to ultrasonography and CT. To eliminate the effect of age and magnification on parameters, a relative index was calculated as previously described [12]. Sludge and protein plugs were comprehensively detected by ultrasonography, CT, IOC, and intraoperative irrigation.

Patients were categorized into 3 groups based on location of major papilla (Fig. 1): Group 1 (G1): papilla in the middle third of second part of duodenum; Group 2 (G2): papilla in the distal third of second part, the junction between second and third part, and the beginning of third part of duodenum; and Group 3 (G3): papilla from the middle of third part to fourth part of duodenum.

Statistical analysis

Statistical analysis was carried out using SPSS version 24.0 (IBM, Armonk, NY, USA). Normally distributed continuous variables expressed as mean ± SD were compared by ANOVA, while non-normally distributed variables expressed as interquartile range were compared by nonparametric KruskalWallis test. Categorical variables described as proportions were compared by χ^2 test or Fisher's exact test. $p < 0.05$ was considered statistically significant.

Results

Demographic data

Between January 2020 and March 2022, a total of 380 CDCs underwent definitive surgery in our center, and 53 patients were dropped out in accordance with exclusion criteria (8 for nonvisible papilla location, 31 for external drainage, and 14 for ERCP), leaving 327 for the study.

Of 327 patients, 38 (11.62%) were allocated to G1, 168 (51.38%) to G2, and 121 (37.00%) to G3 (Table 1). EDLPV was observed in 289 (G2 and G3, 88.38%).

Age

Median age at onset was − 3.50 (1.63, 30.80) months. At onset, G3 patients were much younger than both G1 ($p < 0.001$) and G2 ($p < 0.001$) patients (G1 *vs.* G2 *vs.* G3, 20.52 *vs.* 19.47 *vs.* − 3.40 months, $p < 0.001$) (Table 1). Median age at surgery was 20.23 (1.87, 44.93) months. G3 patients were markedly younger at surgery than both G1 ($p < 0.001$) and G2 ($p < 0.001$) patients (G1 *vs.* G2 *vs.* G3, 31.18 *vs.* 27.75 *vs.* 3.43 months, $p < 0.001$) (Table 1). There were no significant differences between G1 and G2 patients (age at onset, $p = 1.000$; and age at surgery, $p = 0.967$).

Prenatal diagnosis

One hundred and forty-seven patients (44.95%) were diagnosed prenatally (G1 *vs.* G2 *vs.* G3, 26.32% *vs.* 36.31% *vs.* 62.81%, $p < 0.001$) (Table 1). A significantly greater proportion of prenatal diagnosis was demonstrated in G3 compared with both G1 ($p < 0.001$) and G2 ($p < 0.001$). However, a significant difference was not displayed between G1 and G2 ($p = 0.242$).

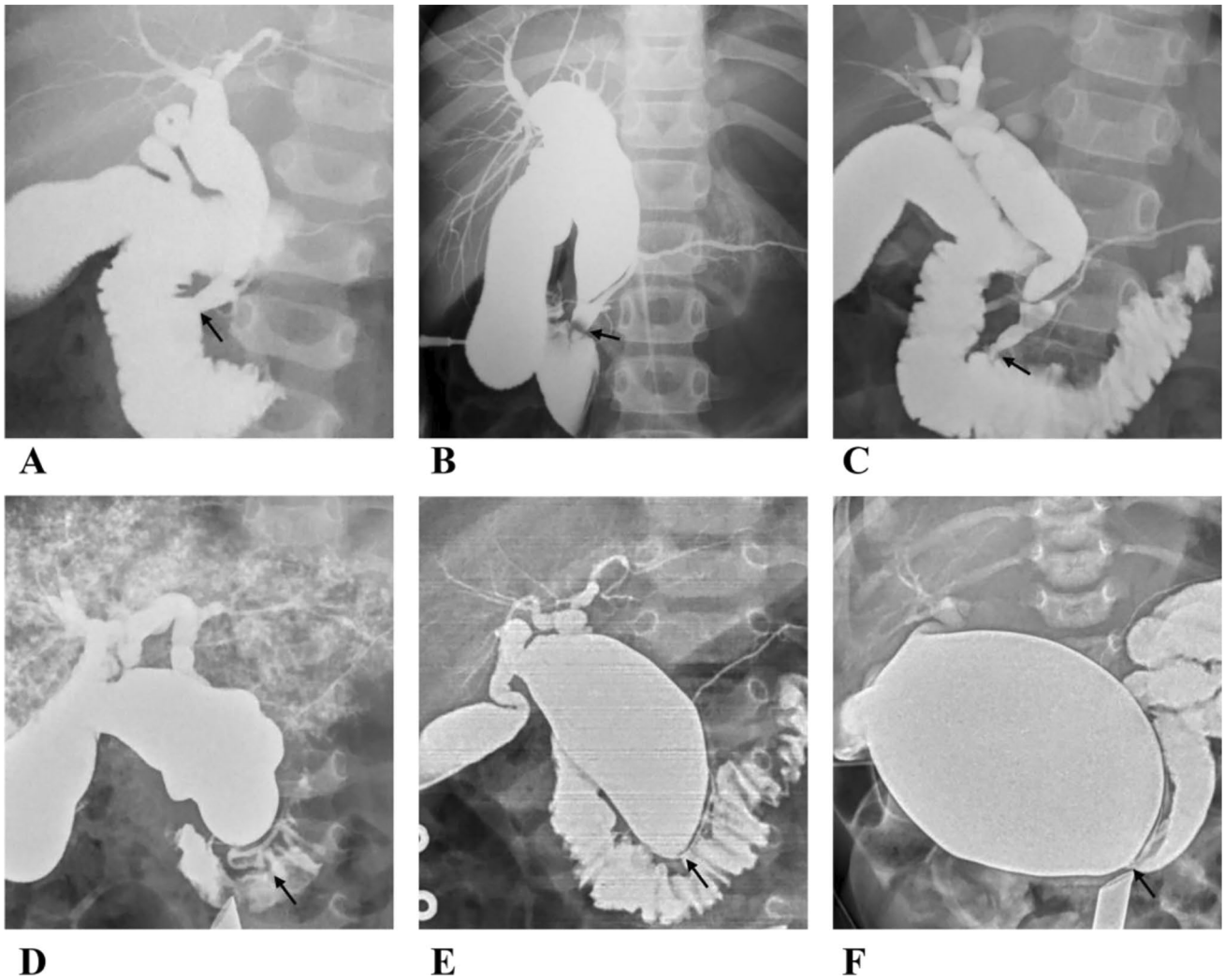

Fig. 1 Location of papilla of Vater by cholangiography: **A** papilla in the middle of second part of duodenum (Group 1); **B** papilla in the junction between second and third part of duodenum (Group 2); **C** papilla in the beginning of third part of duodenum (Group 2); **D** papilla in the middle of third part of duodenum (Group 3); **E** papilla in the junction between third and fourth part of duodenum (Group 3); **F** papilla in the fourth part of duodenum (Group 3). Arrows indicated the location of papilla

Cyst size

Mean relative cyst length was 3.35 ± 1.61 (G1 *vs.* G2 *vs.* G3, 2.38 *vs.* 2.93 *vs.* 4.25, $p < 0.001$) (Table 1). G3 patients had approximately 1.79-fold longer cysts than G1 patients ($p < 0.001$) and 1.45-fold longer than G2 patients ($p < 0.001$), and G2 patients had approximately 1.23-fold longer cysts than G1 patients ($p = 0.035$).

Mean relative cyst diameter was 1.93 ± 1.25 (G1 *vs.* G2 *vs.* G3, 1.18 *vs.* 1.60 *vs.* 2.62, $p < 0.001$) (Table 1), which was largest in G3 patients ($p < 0.001$ *vs.* G2), second in G2 patients ($p = 0.041$ *vs.* G1), and smallest in G1 patients ($p < 0.001$ *vs.* G3).

Two hundred and sixty-seven patients (81.65%) had cystic dilatation (G1 *vs.* G2 *vs.* G3, 65.79% *vs.* 78.57% *vs.* 90.91%, $p = 0.001$) (Table 1). G3 patients more frequently had cystic dilatation compared with both G1 ($p < 0.001$) and G2 ($p = 0.005$), while there was no statistical discrepancy between G1 and G2 ($p = 0.095$).

Size of common channel

Mean relative CC length was 0.65 ± 0.34 (G1 *vs.* G2 *vs.* G3, 0.52 *vs.* 0.69 *vs.* 0.64, $p = 0.022$) (Table 1). Compared with G1 patients, G2 patients had a longer CC ($p = 0.007$) and G3 patients tended to have a longer CC ($p = 0.099$), while G3 and G2 patients had comparable lengths ($p = 0.225$). No significant differences were noted in relative CC diameter among three groups ($p = 0.191$).

Table 1 Comparison among three groups in clinical data

	Group 1 (n = 38)	Group 2 (n = 168)	Group 3 (n = 121)	*p*
Age at surgery (month)	31.18 (8.87, 48.84)[a]	27.75 (3.28, 50.04)[a]	3.43 (0.82, 28.73)[b]	< 0.001
Duration of disease (month)	7.95 (3.18, 12.37)[a]	4.80 (1.81, 12.28)[a]	4.70 (2.40, 7.43)[a]	0.115
Age at onset (month)	20.52 (− 0.65, 37.08)[a]	19.47 (− 3.26, 37.56)[a]	− 3.40 (− 3.95, 16.85)[b]	< 0.001
Prenatal diagnosis, n (%)	10 (26.32)[b]	61 (36.31)[b]	76 (62.81)[a]	< 0.001
Relative cyst length (38/165/119)*	2.38 ± 0.87[c]	2.93 ± 1.04[b]	4.25 ± 1.98[a]	< 0.001
Relative cyst diameter (38/165/119)*	1.18 ± 0.63[c]	1.60 ± 0.93[b]	2.62 ± 1.46[a]	< 0.001
Cystic dilatation, n (%)	25 (65.79)[b]	132 (78.57)[b]	110 (90.91)[a]	0.001
Relative CC length (34/143/72)*	0.52 ± 0.24[b]	0.69 ± 0.34[a]	0.64 ± 0.38[ab]	0.022
Relative CC diameter (35/145/73)*	0.19 ± 0.07[a]	0.20 ± 0.11[a]	0.18 ± 0.08[a]	0.191
Relative CHD diameter (38/155/109)*	0.36 ± 0.24[b]	0.42 ± 0.28[b]	0.52 ± 0.36[a]	0.012
Relative IHD diameter (35/117/85)*	0.39 ± 0.25[a]	0.43 ± 0.28[a]	0.49 ± 0.32[a]	0.194
Height of the second lumbar vertebra (mm) (38/165/119)*	19.21 ± 5.43[a]	18.51 ± 5.66[a]	15.03 ± 5.64[b]	< 0.001
IHD diameter				
> 3 mm (36/130/92)*	33 (91.67)[a]	110 (84.62)[a]	78 (84.78)[a]	0.541
≥ 8 mm (35/139/94)*	11 (31.43)[ab]	53 (38.13)[a]	19 (20.21)[b]	0.015
≥ 10 mm (35/139/94)*	8 (22.86)[ab]	43 (30.94)[a]	13 (13.83)[b]	0.011
Sludge in CBD, n (%)	27 (71.05)[a]	126 (75.00)[a]	102 (84.30)[a]	0.093
Intrahepatic sludge, n (%)	3 (7.89)[ab]	13 (7.74)[b]	22 (18.18)[a]	0.018
Protein plugs in CC, n (%)	17 (44.74)[a]	65 (38.69)[a]	20 (16.53)[b]	< 0.001
Perforation, n (%)	1 (2.63)[a]	16 (9.52)[a]	19 (15.70)[a]	0.055
Pancreatitis, n (%)	11 (28.95)[a]	47 (27.98)[a]	12 (9.92)[b]	0.001
Vomiting, n (%)	24 (63.16)[a]	110 (65.48)[a]	47 (38.84)[b]	< 0.001
Abdominal pain, n (%)	26 (68.42)[a]	98 (58.33)[a]	36 (29.75)[b]	< 0.001

Quantitative variables were expressed as mean ± SD for normal distribution, and median (P25, P75) for abnormal distribution; categorical variables were expressed as frequency (percentages)

CC common channel, *CHD* common hepatic duct, *IHD* intrahepatic bile duct, *CBD* common bile duct

*The three numbers in brackets separated by backslash represented the number of patients in Group 1, Group 2, and Group 3, respectively. Different superscript letters ([a,b,c]) in the same row indicated statistical differences among three groups ($p < 0.05$)

Diameter of common hepatic duct

Mean relative CHD diameter was 0.45 ± 0.31 (G1 *vs.* G2 *vs.* G3, 0.36 *vs.* 0.42 *vs.* 0.52, $p = 0.012$) (Table 1). There was marked dilatation in G3 patients compared to G1 patients ($p = 0.014$) and to G2 patients ($p = 0.015$), while there was no significant difference between G1 and G2 patients ($p = 0.281$).

Diameter of intrahepatic bile duct

Of 327 patients, whether IHD diameter is > 3 mm can be determined in 258 (> 3 mm, 85.66%, 221/258; G1 *vs.* G2 *vs.* G3, 91.96% *vs.* 84.62% *vs.* 84.78%, $p = 0.541$), and whether ≥ 8 and 10 mm in 268 (≥ 8 mm, 30.97%, 83/268, G1 *vs.* G2 *vs.* G3, 31.43% *vs.* 38.13% *vs.* 20.21%, $p = 0.015$; ≥ 10 mm, 23.88%, 64/268, G1 *vs.* G2 *vs.* G3, 22.86% *vs.* 30.94% *vs.* 13.83%, $p = 0.011$).

Compared with G3, G2 patients were inclined to have dilatation of IHD (≥ 8 mm, $p = 0.004$; and ≥ 10 mm, $p = 0.003$, respectively) (Table 1). The rates of diameter ≥ 8 mm and ≥ 10 mm in G1 had tendency to be higher compared with G3 (≥ 8 mm, $p = 0.180$; and ≥ 10 mm, $p = 0.217$, respectively) and be lower compared with G2 (≥ 8 mm, $p = 0.462$; and ≥ 10 mm, $p = 0.348$, respectively), but the differences were not significant. However, a comparison of relative IHD diameter among three groups did not reveal significant differences (G1 *vs.* G2 *vs.* G3, 0.39 *vs.* 0.44 *vs.* 0.49, $p = 0.194$).

Sludge and protein plugs

Sludge was detected in 255 patients in CBD (77.98%). The incidence tended to be higher in G3, although no significant differences were noted among three groups (G1 *vs.* G2 *vs.* G3, 71.05% *vs.* 75.00% *vs.* 84.30%, $p = 0.093$) (Table 1). G3 patients had a higher incidence than G2 and G1 (G3 *vs.* G1 + G2, 84.30% *vs.* 74.27%, $p = 0.035$).

Intrahepatic sludge was found in 38 patients (11.62%) (G1 *vs.* G2 *vs.* G3, 7.89% *vs.* 7.74% *vs.* 18.18%, $p = 0.018$) (Table 1). G3 patients had a higher incidence compared with

G2 ($p=0.007$), and no significant differences between G1 and either G2 ($p=1.000$) or G3 ($p=0.129$) were observed.

Protein plugs in CC were observed in 102 patients (31.19%). The occurrence in G3 was distinctly lower compared with both G2 (16.53% *vs.* 38.69%, $p<0.001$) and G1 (16.53% *vs.* 44.74%, $p<0.001$) (Table 1), with no significant difference between G1 and G2 ($p=0.492$).

Perforation

Prevalence of perforation was 11.01% (36/327) (G1 *vs.* G2 *vs.* G3, 2.63% *vs.* 9.52% *vs.* 15.70%, $p=0.055$). Compared with G2 and G1, G3 patients had a higher risk (G3 *vs.* G1 + G2, 15.70% *vs.* 8.25%, $p=0.035$). G3 patients tended to have a higher risk than both G2 and G1, although there were no significant differences among three groups (Table 1).

Clinical manifestations

Fewer G3 patients complained of pancreatitis, vomiting, and abdominal pain compared with both G1(9.92% *vs.* 28.95%, $p=0.004$; 38.84% *vs.* 63.16%, $p=0.009$; and 29.75% *vs.* 68.42%, $p<0.001$, respectively) and G2 (9.92% *vs.* 27.98%, $p<0.001$; 38.84% *vs.* 65.48%, $p<0.001$; and 29.75% *vs.* 58.33%, $p<0.001$, respectively) (Table 1), and differences between G1 and G2 did not reach significance ($p=0.904$, $p=0.787$, and $p=0.251$, respectively).

Liver function

Detailed data were demonstrated in Table 2. The levels of total bilirubin and directed bilirubin increased progressively from G1 to G2 patients (G1 *vs.* G2, $p=0.013$, $p=0.007$, respectively), reaching the highest values in G3 patients (G2 *vs.* G3, $p<0.001$, $p<0.001$, respectively). The levels of γ-glutamyl transferase (GGT) and total bile acid (TBA) were significantly elevated in G3 patients compared with both G1 ($p=0.001$, $p=0.025$, respectively) and G2 ($p<0.001$, $p=0.040$, respectively) patients; and the levels of albumin, amylase, and prealbumin were markedly lower in G3 patients compared with both G1 ($p=0.002$, $p<0.001$, and $p<0.001$, respectively) and G2 ($p<0.001$, $p<0.001$, and $p=0.003$, respectively) patients; however, there were no significant differences when G1 patients were compared with G2 patients (GGT, $p=1.000$; TBA, $p=0.830$; albumin, $p=1.000$; amylase, $p=1.000$; and prealbumin, $p=0.386$, respectively). Cholinesterase level was significantly lower in G3 patients compared with G2 patients ($p=0.046$), while no significant differences were noted between G1 and either G2 ($p=1.000$) or G3 ($p=0.214$) patients. There were no significant differences in the levels of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase among three groups ($p=0.708$, $p=0.386$, and $p=0.449$, respectively).

Prevalence of advanced fibrosis was 10.19% (33/327). Advanced fibrosis had a tendency to be associated with a more distal location of papilla. Especially for prenatally detected patients (n = 147), G3 patients had a higher risk

Table 2 Comparison among three groups in biological and pathological data

	Group 1 (n = 38)	Group 2 (n = 168)	Group 3 (n = 121)	*p*
Biological data				
Alanine aminotransferase (U/L)	23.75 (14.50, 50.20)^{a}	24.35 (13.23, 44.88)^{a}	25.00 (13.90, 59.70)^{a}	0.708
Aspartate aminotransferase (U/L)	34.15 (27.88, 46.70)^{a}	35.05 (27.40, 49.05)^{a}	37.20 (28.90, 58.55)^{a}	0.386
Total bilirubin (μmol/L)	7.35 (6.18, 11.50)^{c}	9.95 (7.33, 30.63)^{b}	28.70 (8.50, 131.65)^{a}	< 0.001
Directed bilirubin (μmol/L)	2.10 (1.60, 3.30)^{c}	3.10 (1.83, 7.55)^{b}	9.80 (2.35, 18.45)^{a}	< 0.001
Alkaline phosphatase (U/L)	238.50 (192.25, 319.00)^{a}	252.50 (193.25, 319.15)^{a}	255.00 (198.50, 349.00)^{a}	0.449
γ-glutamyl transferase (U/L)	48.10 (19.18, 193.75)^{b}	63.85 (20.93, 206.00)^{b}	214.00 (61.45, 402.00)^{a}	< 0.001
Albumin (g/L)	43.58 ± 3.74^{a}	43.18 ± 4.23^{a}	41.05 ± 4.54^{b}	< 0.001
Total bile acid (μmol/L)	4.20 (2.25, 6.30)^{b}	4.50 (2.30, 9.28)^{b}	6.60 (2.65, 19.85)^{a}	0.008
Amylase (U/L)	59.00 (24.00, 86.25)^{a}	51.00 (14.00, 95.00)^{a}	18.00 (7.00, 50.00)^{b}	< 0.001
Cholinesterase (KU/L)	7.74 (6.71, 9.48)^{ab}	7.82 (6.75, 8.92)^{a}	7.26 (6.41, 8.52)^{b}	0.033
Prealbumin (mg/L)	173.06 ± 49.66^{a}	158.18 ± 39.94^{a}	142.54 ± 45.80^{b}	< 0.001
Advanced fibrosis, n (%)				
Total cohort (36/167/121)*	5 (13.89)^{a}	11 (6.59)^{a}	17 (14.05)^{a}	0.087
Prenatal detected patients (10/60/76)*	1 (10.00)^{ab}	1 (1.67)^{b}	10 (13.16)^{a}	0.035
Postnatal detected patients (26/107/45)*	4 (15.38)^{a}	10 (9.35)^{a}	7 (15.56)^{a}	0.461

*The three numbers in brackets separated by backslash represented the number of patients in Group 1, Group 2, and Group 3, respectively. Different superscript letters (^{a,b,c}) in the same row indicated statistical differences among three groups ($p<0.05$)

compared with G2 (13.16% *vs.* 1.67%, $p=0.015$) (Table 2). The same trend was observed for postnatally detected patients, but the values did not reach significance ($p=0.267$).

Discussion

Current study discovered that the more distal location of papilla, the larger cysts, echoing our previous report [12]. In addition, EDLPV was associated with the morphology of cyst, corresponding to our previous report [15]. The more distal location of papilla, the more elongated CBD, as result of which CBD wall might get weaker and distal end narrower. Longer cysts possibly mechanically increased resistance to bile flow. Distal obstruction might eventually become heavier anatomically and mechanically, giving rise to more dilatation of CBD.

A longer CC was also correlated with EDLPV. In our study, relative CC length was longer in G3 and G2 compared with G1 (G1 *vs.* G2 + G3, 0.52 ± 0.24 *vs.* 0.67 ± 0.3512, $p=0.008$), consistent with our previous investigation [12]. PBMU issues from a long CC, indicating PBMU correlated with EDLPV. Based on our current data, with the exception of no significant difference between patients with papilla in the junction between third and fourth part of duodenum and G1 patients (0.32 ± 0.17 *vs.* 0.52 ± 0.24, $p=0.111$), others with EDLPV had longer CC (0.69 ± 0.35 *vs.* 0.52 ± 0.24, $p=0.006$). For some patients with a large cyst, CC might be obscured, especially for those with papilla in the junction between third and fourth part and the fourth part of duodenum. Missing data may lead to bias.

Critically, given that patients with more distal location of papilla were most frequently detected prenatally, CBD dilatation occurred during fetal life, and cysts were large enough that they were most diagnosed prenatally. While patients with more proximal location were most frequently diagnosed postnatally due to relatively smaller cysts. Furthermore, patients with more distal location were much younger, for location of papilla determined at 22 days of gestation [11]. Both abnormal embryonic development and relatively larger cysts contribute to younger age at onset and surgery.

Despite the fact that both G3 and G2 patients had EDLPV, there were plenty of intriguing disparities between them. The heavier distal obstruction might give rise to less reflux of bile into pancreatic duct, thereby decreasing the occurrences of pancreatitis, abdominal pain, and vomiting. Meanwhile, the composition ratio of bile to pancreatic juice mixed in CC might be relatively lower, probably contributing to a lower incidence of protein plugs in CC. More severe distal obstruction and younger age, when patients tend to be more pliable, might be responsible for higher rates of cystic dilatation, intrahepatic sludge, and advanced fibrosis, more elevated biliary obstructive indicators, and lower levels of cholinesterase [20], albumin, and prealbumin.

Surprisingly, with a larger CBD and CHD, G3 patients had a lower occurrence of IHD dilatation compared with G2, but IHD diameter was not smaller. More severe distal obstruction might result in a more dilated cyst and CHD, which, in the meantime, might serve as a cushion and relieve pressure on IHD. Weakness of CBD wall might be associated with younger age [1]. In the experimental study by Miyano [2], fusiform dilatation with IHD dilatation was induced by ligation of distal CBD in mature animals (10 dogs, 5 rabbits, and 10 rats), while cystic dilatation without IHD dilatation in 10 immature rats. In our study, IHD dilatation was less common in G3 patients, but the diameter of dilated IHD was larger when the pressure in cyst was sufficiently high. Relatively slighter obstruction and buffering, and older age in G1 patients might be the reason why there was no significant difference compared to G3.

Hepatic diverticulum, arising from ventral primitive foregut, develops into bile duct, ventral pancreas, and liver, while dorsal pancreas originates from the opposite during embryonic development [11]. Location of papilla of Vater depicts the budding of hepatic diverticulum in early embryonic life. As duodenum rotates and becomes C-shaped, ventral pancreas fuses with dorsal pancreas [21]. Meanwhile, superior branch of ventral pancreas joining dorsal pancreatic duct forms main pancreatic duct [22]. Major papilla generally enters the left-lateral-posterior middle wall of descending portion of duodenum.

Ectopic distal budding of hepatic diverticulum, resulting in a longer distance from ventral pancreas to hepatic plate and to dorsal pancreas, might be responsible for the stretch and weakness of CBD and CC, giving rise to distal stenosis and a longer CC, ultimately, dilatation and PBMU [12, 13]. Therefore, we postulated that EDLPV might be one of the pathogeneses of CDC. Further research is required to validate and explore the underlying molecular mechanism.

In conclusion, EDLPV was closely correlated with clinical characteristics of CDCs. Patients with a more distal location of papilla had longer cysts and common channels, more severe clinical features, considerably younger age, and a higher proportion of prenatal diagnosis.

Author contributions Mrs. Suyun Chen had primary responsibility for protocol development, enrollment, preliminary data analysis and writing the manuscript.Mr. Tong Yin participated in the development of the protocol and contributed to the writing of the manuscript.Mr. Ting Huang participated in the collection of data.Dr. Long Li and Dr. Mei Diao supervised the design and execution of the study, performed the final data analyses and contributed to the writing of the manuscript.All authors reviewed the manuscript.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations

Conflict of interest All authors declare that they have no conflict of interest.

References

1. Spitz L (1977) Experimental production of cystic dilatation of the common bile duct in neonatal lambs. J Pediatr Surg 12(1):39–42. https://doi.org/10.1016/0022-3468(77)90293-7
2. Miyano T, Suruga K, Suda K (1979) Abnormal choledocho-pancreatico ductal junction related to the etiology of infantile obstructive jaundice diseases. J Pediatr Surg 14(1):16–26. https://doi.org/10.1016/s0022-3468(79)80570-9
3. Davenport M, Basu R (2005) Under pressure: choledochal malformation manometry. J Pediatr Surg 40(2):331–335. https://doi.org/10.1016/j.jpedsurg.2004.10.015
4. Babbitt DP (1969) Congenital choledochal cysts: new etiological concept based on anomalous relationships of the common bile duct and pancreatic bulb. Ann Radiol 12(3):231–240
5. Kato T, Hebiguchi T, Matsuda K, Yoshino H (1981) Action of pancreatic juice on the bile duct: pathogenesis of congenital choledochal cyst. J Pediatr Surg 16(2):146–151. https://doi.org/10.1016/s0022-3468(81)80341-7
6. Ohkawa H, Sawaguchi S, Yamazaki Y, Ishikawa A, Kikuchi M (1982) Experimental analysis of the ill effect of anomalous pancreaticobiliary ductal union. J Pediatr Surg 17(1):7–13. https://doi.org/10.1016/s0022-3468(82)80316-3
7. Diao M, Li L, Cheng W (2011) Congenital biliary dilatation may consist of 2 disease entities. J Pediatr Surg 46(8):1503–1509. https://doi.org/10.1016/j.jpedsurg.2010.12.022
8. Morine Y, Shimada M, Takamatsu H, Araida T, Endo I, Kubota M, Toki A, Noda T, Matsumura T, Miyakawa S, Ishibashi H, Kamisawa T, Shimada H (2013) Clinical features of pancreaticobiliary maljunction: update analysis of 2nd Japan-nationwide survey. J Hepato-Biliary-Pancreat Sci. 20(5):472–480. https://doi.org/10.1007/s00534-013-0606-2
9. Fumino S, Ono S, Shimadera S, Kimura O, Iwai N (2010) Impact of age at diagnosis on clinical features in children with anomalous arrangement of the pancreaticobiliary duct. Eur J Pediatr Surg 20(5):325–329. https://doi.org/10.1055/s-0030-1255097
10. Lebenthal E, Lee PC (1980) Development of functional responses in human exocrine pancreas. Pediatrics 66(4):556–560
11. Roskams T, Desmet V (2008) Embryology of extra- and intrahepatic bile ducts, the ductal plate. Anat Rec 291(6):628–635. https://doi.org/10.1002/ar.20710
12. Li L, Yamataka A, Yian-Xia W, Da-Yong W, Segawa O, Lane GJ, Kun W, Jin-Zhe Z, Miyano T (2001) Ectopic distal location of the papilla of vater in congenital biliary dilatation: implications for pathogenesis. J Pediatr Surg 36(11):1617–1622. https://doi.org/10.1053/jpsu.2001.27932
13. Li L, Yamataka A, Wang YX, Wang DY, Wang K, Li ZX, Shimizu T, Yamashiro Y, Zhang JZ, Lane GJ, Miyano T (2003) Anomalous pancreatic duct anatomy, ectopic distal location of the papilla of Vater and congenital biliary dilatation: a new developmental triad? Pediatr Surg Int 19(3):180–185. https://doi.org/10.1007/s00383-002-0914-0
14. Li L, Liu XL, Fu JB, Yamataka A, Miyano T (2005) Pancreatic duct anomalies associated with ectopic papilla of vater in choledochal cyst. Chin J Pediatr Surg. 26(6):293–296. https://doi.org/10.3760/cma.j.issn.0253-3006.2005.06.004. (**Chinese**)
15. Li L, Wang YX, Wang DY, Fang T, Xing MQ, Zhang JZ (2002) The significance of ectopic pancreaticobiliary communication of choledochal cyst in children. Chin J Pediatr Surg. 23(2):122–123. https://doi.org/10.3760/cma.j.issn.0253-3006.2002.02.008. (**Chinese**)
16. Gong ZH, Xiao XM, Zhou YM, Zheng S, Hu B, Gong B (2004) Location of duodenal papilla and pancreaticobiliary maljunction. J Clin Pediatr 22(8):540–542. https://doi.org/10.3969/j.issn.1000-3606.2004.08.019. (**Chinese**)
17. Han XW, Li Z, Zhang W, Wu G (2008) The relative analysis between duodenal papilla ectope and pancreaticobiliary maljunction. J Clin Radiol 27(8):1050–1052. https://doi.org/10.3969/j.issn.1001-9324.2008.08.014. (**Chinese**)
18. Kim SK, Jeong YJ, Kim JC (2011) Choledochal cyst with ectopic distal location of the papilla of Vater. J Korean Surg Soc 81(1):85–88. https://doi.org/10.4174/jkss.2011.81.Suppl1.S85
19. Batts KP, Ludwig J (1995) Chronic hepatitis. An update on terminology and reporting. Am J Surg Pathol 19(12):1409–1417. https://doi.org/10.1097/00000478-199512000-00007
20. Montagnese C, Scalfi L, Signorini A, De Filippo E, Pasanisi F, Contaldo F (2007) Cholinesterase and other serum liver enzymes in underweight outpatients with eating disorders. Int J Eating Disord. 40(8):746–750. https://doi.org/10.1002/eat.20432
21. Kanagasuntheram R (1960) Some observations on the development of the human duodenum. J Anat 94(Pt 2):231–240
22. Dawson W, Langman J (1961) An anatomical-radiological study on the pancreatic duct pattern in man. Anat Rec 139:59–68. https://doi.org/10.1002/ar.1091390109