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Journal of Pediatric Surgery 58 (2023) 1246–1251

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.sciencedirect.com/journal/journal-of-pediatric-surgery

The Factors Associated with the Selection of Early Excision Surgery for Congenital Biliary Dilatation with a Prenatal Diagnosis

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ARTICLE INFO

Article history:
Received 19 January 2023
Accepted 20 January 2023

Keywords:
Congenital biliary dilatation
Choledochal cyst
Liver fibrosis
Prenatal diagnosis
Gamma glutamyl transpeptidase
Cyst size

ABSTRACT

Purpose: The aim of this study was to clarify the appropriate management after birth for congenital biliary dilatation (CBD, choledochal cyst) patients with a prenatal diagnosis.
Method: Thirteen patients with a prenatal diagnosis of CBD who underwent liver biopsy during excision surgery were divided into two groups and retrospectively analyzed: group A, with liver fibrosis above F1 and group B, without liver fibrosis.
Results: Excision surgery was performed earlier in group A (F1–F2), at a median of 106 days old ($p = 0.04$). There were significant differences between the two groups in the presence symptoms and sludge, the cyst size, and the level of serum bilirubin and gamma glutamyl transpeptidase (GGT) before excision surgery ($p < 0.05$). Especially, in group A, prolonged serum GGT elevation and larger cysts were consistently observed from birth. The cut-off values of predictions for the presence of liver fibrosis in serum GGT and cyst size were 319 U/l and 45 mm. No significant differences were observed in the postoperative liver function or complications during the follow-up period.
Conclusion: In patients with prenatally diagnosed CBD, the postnatal serial changes of serum GGT values and cyst size, in addition to symptoms, could help to prevent progressive liver fibrosis.
Level of Evidence: III.
Type of Study: Treatment Study.

1. Introduction

Congenital biliary dilatation (CBD, choledochal cyst) is a congenital malformation involving dilatation of the extrahepatic bile duct with/without the intrahepatic bile duct. Most CBD patients have pancreaticobiliary maljunction (PBM), which causes pancreatic juice reflux to the bile duct [1]. With the development of prenatal diagnostics using ultrasonography (US), CBD patients with a prenatal diagnosis have been reported since the 1980s [2]. King's College Hospital group reported the first case series of prenatal diagnosis in CBD and cystic biliary atresia (BA). They provided that an algorithm for prenatally diagnosed cystic lesions in the hepatobiliary system that primarily distinguishes obstructive CBD with intrahepatic bile duct dilatation by US, and secondly distinguishes CBD from cystic BA by radionuclide scanning [3].

Subsequently, it was reported that the degree of liver fibrosis in CBD patients diagnosed in the neonatal period was more severe than patients diagnosed during infancy [4]. In recent years, it has been reported that progressive liver fibrosis may be observed even in asymptomatic CBD patients with a prenatal diagnosis who underwent excision surgery under 80 days old [5]. However, the changes in the condition of liver tissue according to the postnatal

Abbreviations: CBD, congenital biliary dilatation; PBM, pancreaticobiliary maljunction; BA, biliary atresia; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; HE, Hematoxylin–Eosin; CK19, cytokeratin-19; IQR, interquartile range; IRB, institutional review board; TB, total bilirubin; DB, direct bilirubin; AST, aspartate aminotransferase; GGT, gamma glutamyl transpeptidase; FIB-4, fibrosis-4 index; APRI, AST to platelet ratio index; ROC, receiver operating characteristic; AUC, area under the curve.

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https://doi.org/10.1016/j.jpedsurg.2023.01.050
0022-3468/

course in prenatally diagnosed CBD patients are unclear, and there have been few recent reports which evaluating liver tissue only in prenatally diagnosed CBD.

The postnatal clinical course of CBD patients with a prenatal diagnosis is the natural history of general pediatric CBD patients without a prenatal diagnosis who are diagnosed by symptoms. Therefore, we hypothesized that a detailed examination of the postnatal course up to excision surgery in prenatally diagnosed CBD patients would clarify the relationship between the postnatal course and the condition of liver tissue. In this study, to clarify the appropriate management after birth in pediatric CBD patients with a prenatal diagnosis, we retrospectively investigated the postnatal clinical course and pathological findings of liver wedge biopsy at excision surgery only in prenatally diagnosed CBD patients.

2. Patients and methods

We investigated 15 pediatric CBD patients with a prenatal diagnosis who underwent excision surgery of the extrahepatic bile duct with Roux-en-Y hepaticojejunostomy by laparotomy in Kyushu University between January 1991 and December 2020. Two patients were excluded due to a lack of pathological data. Finally, the postnatal clinical course after birth and the pathological findings of liver wedge biopsy at the time of excision surgery in 13 patients were analyzed in this study.

After birth, the horizontal diameter of cysts in the common bile duct was measured by US, computed tomography (CT), or magnetic resonance imaging (MRI). The longitudinal diameter was not measured in some cases (data not shown). The cyst size immediately after birth was measured on day 0 or 1, while the cyst size before surgery was measured within 1 week before excision surgery. Sludge in the cyst was followed by US or MRI from birth until before excision surgery. A blood test was performed within 1 week before excision surgery. The timing of excision surgery was determined by our team. The bile juice components (amylase and lipase) were examined when the catheter was inserted in the gallbladder before performing cholangiography at the time of excision surgery. The morphological type of CBD in each case was classified by Todani classification, according to the diagnostic criteria [1]. The postoperative follow-up was performed with blood tests using fibrosis-4 index (FIB-4) [6] and aspartate aminotransferase (AST) to platelet ratio index (APRI) [7], and imaging studies using US, CT, and MRI.

Three pathologists jointly analyzed the liver specimens in all cases by Hematoxylin–Eosin (HE), Azan, and Cytokeratin-19 (CK19) staining. The stage of liver fibrosis was classified according to New Inuyama classification as follows: F0, no fibrosis; F1, fibrous portal expansion; F2, bridging fibrosis; F3, bridging fibrosis with lobular distortion; F4, cirrhosis [8]. The grade of ductular reaction was divided into three degrees according to the circumference of the portal tract: mild, less than half; moderate, more than half, severe; more than three-quarters [9]. Thirteen patients with a prenatal diagnosis of CBD were divided into two groups as follows: group A, (patients with liver fibrosis above F1) and group B, (patients without liver fibrosis). The clinical and pathological data are shown in the Supplementary table.

All statistical analyses were performed with JMP ® Pro 15.2.1 (SAS Institute Inc.). Continuous variables were expressed as the median values (interquartile range [IQR]) and analyzed using Wilcoxon's rank sum test for two groups and Wilcoxon's signed rank test for identical entries. Nominal variables were analyzed using Fisher's exact test. The receiver operating characteristic (ROC) and area under the curve (AUC) were analyzed using logistic regression analyses. p values of <0.05 were considered to indicate statistical significance. These data retrospectively were collected from clinical records. This study was approved by the Institutional Review Board (IRB) of Kyushu University (no. 2021-90).

3. Results

The clinical characteristics of 13 pediatric patients with a prenatal diagnosis of CBD are shown in Table 1. Liver fibrosis with mild to moderate ductular reaction was found in 6 patients (46%). Group

Table 1
Comparison of the prenatally diagnosed CBD patients with and without liver fibrosis.

	Total, N = 13	Group A, n = 6	Group B, n = 7	*p*-value
Clinical findings				
Female (%)	77	83	71	1.00
Prenatal diagnosis (weeks)	26 (21–32)	23 (19–32)	28 (24–32)	0.43
Birth (weeks)	39 (38–40)	38 (38–39)	39 (39–40)	0.13
Birth weight (g)	3008 (2764–3190)	2993 (2834–3140)	3008 (2604–3315)	1.00
Symptoms present (%)	38	83	0	*<0.01*
Sludge present (%)	62	100	29	*0.02*
Blood test before surgery				
TB (mg/dl)	0.5 (0.4–2.7)	2.7 (0.6–7.8)	0.4 (0.4–0.5)	*0.02*
DB (mg/dl)	0.1 (0.1–0.8)	0.8 (0.3–3.0)	0.1 (0.0–0.1)	*0.01*
AST (U/l)	45 (35–98)	98 (55–138)	42 (33–45)	0.05
GGT (U/l)	319 (15–1017)	1017 (580–1566)	15 (10–31)	*<0.01*
Amylase (U/l)	27 (17–63)	23 (12–35)	36 (20–150)	0.12
Cyst size (mm) before surgery	38 (31–56)	56 (42–73)	32 (29–38)	*0.02*
Date of excision surgery (days)	122 (106–271)	106 (67–144)	133 (121–443)	*0.04*
Bile juice component				
Amylase (U/l)	325 (4–2549)	4 (2–11)	2482 (1103–7540)	*0.02*
Lipase (U/l)	60 (4–44,985), N = 7	24 (1–56), n = 4	44,985 (44,147–54,600), n = 3	0.05
Todani classification (Ia) (%)	62	50	71	0.59
Pathological findings				
Liver fibrosis (number of F0/F1/F2)	7/2/4	0/2/4	7/0/0	–
Ductular reaction present (%) [number of none/mild/moderate]	77 [3/6/4]	100 [0/2/4]	57 [3/4/0]	0.19
Bile plugs present (%)	31	67	0	*0.02*

The values indicate the median (interquartile range) or %.
Group A (patients with liver fibrosis above F1); Group B (patients without liver fibrosis [F0]).
TB, total bilirubin; DB, direct bilirubin; AST, aspartate aminotransferase; GGT, gamma glutamyl transpeptidase.
Normal upper limits of blood test results: TB < 1.6 mg/dl, DB < 0.4 mg/dl, AST < 31 U/l, GGT < 65 U/l, Amylase < 133 U/l.

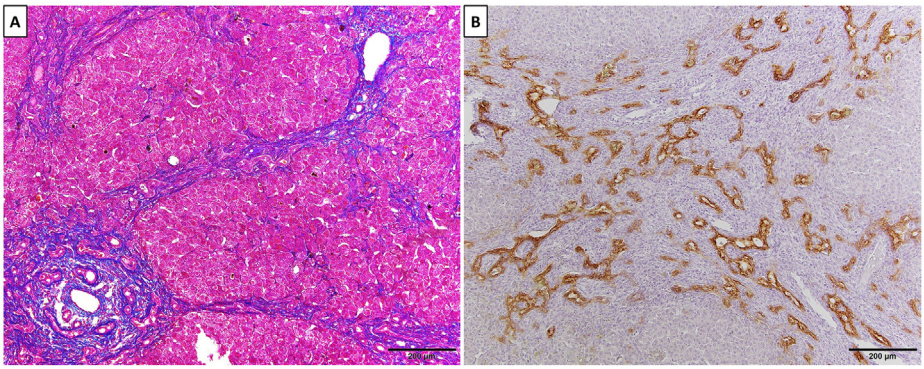

Fig. 1. The pathological findings of liver wedge biopsy specimens at the time of excision surgery in one patient with F2 fibrosis. (**A**) Bridging fibrosis and fibrous portal expansion was seen on Azan staining. (**B**) A moderate ductular reaction was observed at the limiting plate of the portal tracts by CK19 staining.

A included 4 patients with F2 fibrosis (67%) (Fig. 1) and 2 patients with F1 fibrosis (33%). Bile plugs in the intrahepatic bile ducts were seen in 4 patients in group A (67%).

In the present study, there were no differences in sex, gestational weeks at birth, birth weight, or Todani classification between groups A and B. The patients had no other medical history including phototherapy at birth other than CBD. Regarding the family history, a brother of one patient was diagnosed with BA. Symptomatic patients were observed in only group A, showing a significant difference ($p < 0.01$). There were 5 symptomatic patients (38%) and only 1 patient with liver fibrosis among 8 asymptomatic patients (13%). Initial symptoms were occasional acholic stool in 4 patients and abdominal distention in 1 patient. Three patients underwent biliary scintigraphy before excision surgery because of occasional acholic stool and high serum direct bilirubin (DB) values. The flow of bile juice into the intestine was also detected. Sludge in the cyst was detected by US or MRI from birth to before excision surgery in 8 patients (62%) and the presence of sludge was 100% in group A ($p = 0.02$). All patients with F2 fibrosis had symptoms of occasional acholic stool and sludge in the bile duct from birth to excision surgery. An analysis of sludge of the component ratio at the excision surgery in a patient with F2 fibrosis was revealed that it was 94% bilirubin calcium and 6% fatty acid calcium.

In the laboratory data between groups A and B, significant differences were observed in the preoperative serum total bilirubin ($p = 0.02$), DB ($p = 0.01$), and especially gamma glutamyl transpeptidase (GGT) levels ($p < 0.01$) (Table 1). The serial changes in serum GGT between two groups are shown in Fig. 2A. The serum GGT values of patients with liver fibrosis remained very high throughout all periods from birth to excision surgery. The serum GGT level was increased to over 300 U/l at 2 months old in group A, except for 1 patient who underwent excision surgery during the neonatal period, and a significant difference was observed in the median serum GGT levels at 2 months old between groups A and B (695 U/l [IQR, 432–1071, n = 5] vs. 46 U/l [IQR, 32–57, n = 7], $p < 0.01$). In group B, these serum GGT levels in identical patients decreased ($p < 0.05$) from birth to excision surgery, except for in 1 patient who showed a serum GGT level of 573 U/l at 468 days old after the detection of sludge in the cyst at 258 days old. As a prediction of liver fibrosis above F1 in the present study, the AUC of the preoperative serum GGT level was 0.976 (model: $p < 0.01$), and the cut-off point was 319 U/l (sensitivity: 100%, specificity: 85.7%) (Fig. 2B). In group A, the elevated serum GGT value after excision surgery improved to the normal range within 60 days (data not shown).

There were significant differences in the cyst size both at birth and before excision surgery between two groups (Fig. 3A). No difference was found in the rate of change of cyst size from birth to excision surgery. However, in most patients (92%), the cyst size of the horizontal diameter increased to 1.5 times in a median (IQR, 1.3–1.8). In group B, the cyst size increased in identical patients due to the extended observation period, showing a significant difference. In the clinical analysis, the preoperative cyst size of symptomatic patients was larger in comparison to asymptomatic patients (symptomatic; 60 mm [IQR, 43–82, n = 5] vs. asymptomatic; 33 mm [IQR, 29–43, n = 8], $p = 0.03$). Although no correlation was found between the preoperative cyst size and the timing of excision surgery, a negative correlation was confirmed

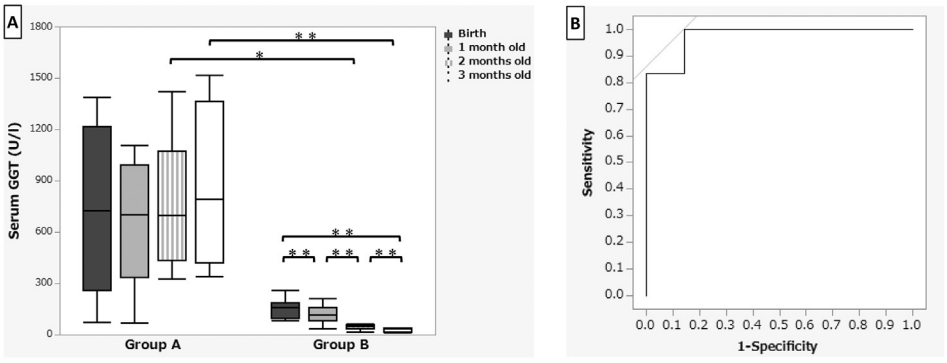

Fig. 2. The analysis of serial changes in the serum GGT level after birth (**A**) and ROC curve for the presence of liver fibrosis in preoperative serum GGT (**B**). (**A**) Significant differences were observed in the level of serum GGT at 2 and 3 months old between groups A and B. In group A, no marked differences were found in those values consistently. In group B, these values of in identical patients decreased from birth to 3 months old, showing significant differences. *$p < 0.01$, **$p < 0.05$. (**B**) The AUC was 0.976, and the best cut-off value was 319 U/l according to the ROC curve.

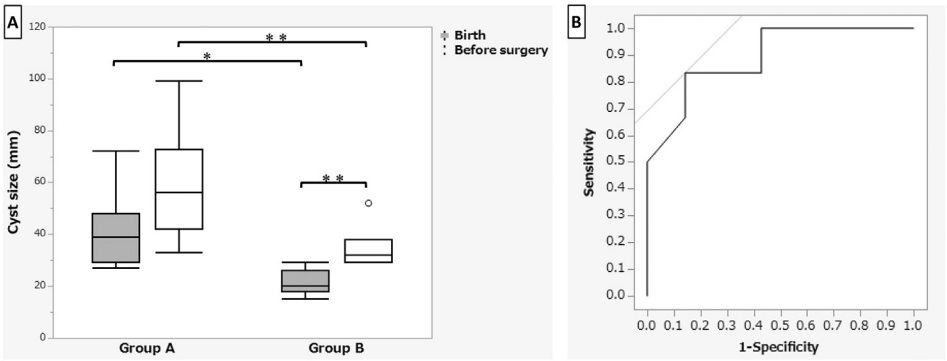

Fig. 3. The analysis of serial changes in the cyst size (**A**) and ROC curve for the presence of liver fibrosis by cyst size (**B**). (**A**) Significant differences were observed in the cyst size between groups A and B at birth and before surgery. There was a significant difference in the cyst size of group B between birth and before surgery but no marked difference in that of group A. *$p < 0.01$, **$p < 0.05$. (**B**) The AUC was 0.893, and the best cut-off value was 45 mm according to the ROC curve.

between cyst size at birth and the timing of excision surgery ($r = -0.6$, 95% CI $= -0.86$ to 0.06, $p = 0.03$). As a prediction of liver fibrosis above F1, the AUC of the preoperative cyst size was 0.893 (model: $p < 0.01$), and the cut-off point was 45 mm (sensitivity: 83.3%, specificity: 85.7%) (Fig. 3B).

Excision surgery was performed at a median of 122 days old. Excision surgery was performed earlier in group A in comparison to group B (106 days vs. 133 days, $p = 0.04$). One patient underwent excision surgery in the neonatal period due to the abdominal distention with a giant cyst. Drainage surgery was not performed before excision surgery in any of patients. In contrast to higher levels of the serum GGT and cyst size in group A, the median bile amylase concentration in the gallbladder at excision surgery in group A was much lower in comparison to group B and bile lipase concentration had the same trend but was only measured in a small number of patients (Table 1). Fig. 4 shows the levels of preoperative serum GGT and bile amylase between group A and B. In group A, the preoperative serum GGT level was higher and the bile amylase level lower than in group B, but no correlation was observed between these entries in this study ($r = -0.3$, 95% CI $= -0.74$ to 0.28, $p = 0.30$).

During the 15.3 (IQR, 9.3–22.8) years of follow-up after excision surgery, cholangitis and adhesive ileus occurred as postoperative complications in two patients of group B, respectively (Table 2). Cholangitis was treated conservatively. Adhesive ileus was treated by laparotomy at 15.3 and 13.1 years after excision surgery, respectively. However, no significant differences were observed in the postoperative liver function or complications during the follow-up period. In addition, the values of FIB-4 and APRI as liver fibrosis markers were comparable between two groups. At the time of writing this report, there are no patients with liver cirrhosis after excision surgery.

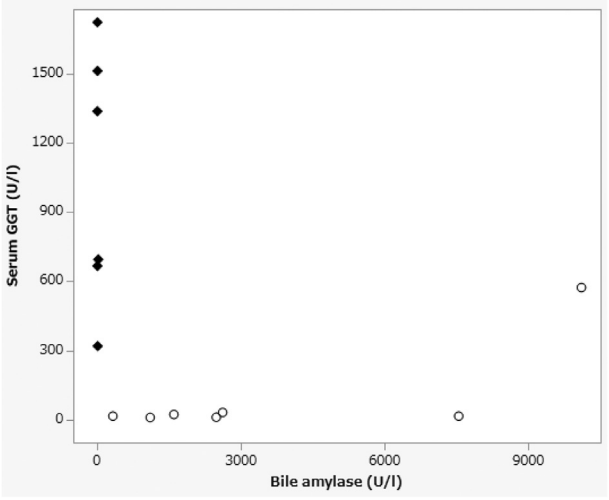

Fig. 4. The levels of preoperative serum GGT and bile amylase at the time of excision surgery in groups A and B. The levels of serum GGT were very high (range: 319–1724 U/l), while those of bile amylase were low (range: 1–20 U/l) in group A (◆). The levels of bile amylase were high (range: 325–10,100 U/l), while those of serum GGT were low (range: 10–573 U/l) except for 1 patient who underwent excision surgery at 471 days old in group B (○).

4. Discussion

We described the postnatal clinical course and liver stage at the time of excision surgery only in patients with a prenatally diagnosed CBD (choledochal cyst). In our study, liver fibrosis was observed in patients with some cholestatic changes (symptoms, sludge, large cyst, prolonged elevation of serum GGT). Especially, all patients with liver fibrosis above F1 had sludge in the large cyst and except for 1 neonatal surgery patient had prolonged elevation of serum GGT over 300 U/l at 2 months old after birth. On the other hand, there was no patient with simultaneous occurrence of sludge and elevated serum GGT after birth in patients without liver fibrosis. In short, it was thought that the appropriate management for a prenatally diagnosed CBD patients after birth in the present study is to follow a serial serum GGT and cyst size as well as the presence of symptom and sludge. The postnatal course of serum GGT and cyst size were associated with the condition of the liver tissue. Based on our results of the predictors for liver fibrosis, early excision surgery should be planned for patients with prolonged elevation of serum GGT over 319 U/l and cyst size over 45 mm, even if they have no or only mild elevation of serum DB, to avoid progressive liver fibrosis in patients with prenatally diagnosed CBD.

There have been few reports investigating liver specimens only in patients prenatally diagnosed with CBD, including our study, in the past 10 years [5,10]. Diao et al. reported 36 asymptomatic cases with high serum GGT values who underwent excision surgery before 80 days old among prenatally diagnosed CBD patients with a liver biopsy [5]. They noted a higher incidence of liver fibrosis above F1 in not only the late operation group (≥32 days old, 85%) but also the early operation group (≤28 days old, 63%) [5] than in our asymptomatic patients (13%). Although excision surgery was performed at an older age in our patients than in their population, continuous follow-up after birth might have aided in the detection of some cholestatic changes and prevented the progression of liver fibrosis, similar to a recent report [10]. Tanaka et al. also suggested that early surgery should be performed if serum GGT increased persistently, as they observed liver fibrosis of F1 in 33% (2 out of 6 patients) of prenatally diagnosed CBD patients with serum GGT

Table 2
Comparison of the postoperative liver function and complications in prenatally diagnosed CBD patients.

	Total, N = 13	Group A, n = 6	Group B, n = 7	*p*-value
Observation period (years)	15.3 (9.3–22.8)	17.3 (7.7–25.7)	12.1 (9.2–21.6)	0.62
Last followed blood test				
TB (mg/dl)	0.6 (0.5–0.9)	0.8 (0.5–1.0)	0.6 (0.4–0.8)	0.31
DB (mg/dl)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	1.00
AST (U/l)	27 (19–33)	20 (18–34)	27 (19–34)	0.47
GGT (U/l)	10 (9–15)	10 (9.8–12)	10 (9–16)	1.00
FIB-4	0.27 (0.14–0.38)	0.33 (0.17–0.43)	0.17 (0.12–0.32)	0.32
APRI	0.32 (0.28–0.36)	0.33 (0.28–0.39)	0.32 (0.27–0.36)	0.67
Postoperative complications				
Cholangitis, n	2	0	2	0.46
Ileus, n	2	0	2	0.46

FIB-4, fibrosis-4 index; APRI, AST to platelet ratio index.

levels that were over 100 U/l for 1 month [10]. If we prevent liver fibrosis above F1, their suggestion would be also helpful for the planning of early excision surgery.

In the present study, we suspected that the cyst size in prenatally diagnosed CBD patients might also be associated with liver fibrosis not just an elevated serum GGT level. Guan et al. reported that a preoperative cyst size at the horizontal line >4.1 cm might cause clinical symptoms based on their analysis of 125 CBD patients with a prenatal diagnosis [11]. The cyst size in the present study that predicted the presence of liver fibrosis above F1 was 4.5 cm. Since all symptomatic patients had liver fibrosis in our study, the cyst size, presence of symptoms, and presence of liver fibrosis were considered correlative factors. Therefore, a cyst size over 4 cm might be a condition for planning excision surgery for CBD patients with a prenatal diagnosis.

Our results showed that the factors such as serum GGT level and cyst size were strongly correlated with histologically proven liver fibrosis at a median of 106 days old. Based on these results, the timing of excision surgery, especially in cases with these risk factors of liver fibrosis, should be performed within 3 months old to prevent progressive liver fibrosis, regardless of any presence of symptom. On the other hand, considering the assumed risks of early surgery such as postoperative anastomotic stricture [3] or increase of intraoperative blood loss [11], in asymptomatic patients or patients without risk factors for liver fibrosis, it would be acceptable to delay excision surgery a little longer in order to allow time for decision-making about when to operate and to allow the patient to grow, and this may be accomplished by referring to the serum GGT value and cyst size. We should take care of the balance between the surgical risk associated with early excision surgery and the risks associated with early liver fibrosis. Our patients with liver fibrosis who underwent early excision surgery had as good postoperative liver function as patients without fibrosis. In the previous reports on markers of liver fibrosis, the values of FIB-4 over 3.25 and APRI over 1.5 were positive prediction for significant fibrosis in 82% [6] and 88% [7], respectively. Because the postoperative values of FIB-4 and APRI in the present study were very low, no progressive liver fibrosis was predicted at this time. However, it was reported that some CBD patients required liver transplantation at 4 months old [12] and 0.4 years old [13]. With reference to these previous reports [3–5,11–13], it was suggested that we should select early excision to prevent progressive liver fibrosis for patients with prenatally diagnosed CBD who show cholestatic changes.

Overall, the liver fibrosis in our patients with prenatally diagnosed CBD was thought to be caused by cholestasis. Because sludge in the cyst was confirmed with high probability (100%), the level of bile amylase was very low, and bile plugs in liver tissue were seen in these 4 patients with liver fibrosis. In neonatal condition, Kato et al. reported that calcium bilirubin sludge, which is induced by neonatal hemolysis, causes the early onset of CBD, as was observed in our patient [14]. On the other hand, the mixture of pancreatic and bile juice might have no effects on liver fibrosis in this study because the bile juice component levels were low in group A. Even though the pancreatic exocrine production may be age-dependent, it was predicted that a large cyst with high pressure of the biliary tract and a severe angle of the bile duct to pancreatic duct at PBM might inhibit the flux of pancreatic juice to the biliary tract and increase the level of serum GGT values as like our fibrosis group (Fig. 4). As a condition of the postnatal course in prenatally diagnosed CBD patients, these morphological features may lead to the formation of sludge, which would then cause liver damage following cholestasis as a result of further elevated biliary tract pressure [15].

The present study was associated with some limitations. The study population was relatively small, and the patients were managed at a single institution. Further studies from multiple centers using a consistent database are desired to determine the optimal management of patients with a prenatal diagnosis of CBD.

5. Conclusion

We investigated the postnatal clinical course and liver biopsy findings in patients with prenatally diagnosed CBD. Postnatal serial values of serum GGT and cyst size, in addition to symptoms, could help to prevent progressive liver fibrosis. The postoperative liver function was preserved in patients with F1/2 fibrosis at the time of surgery and who underwent early excision surgery.

Conflicts of interest

The authors declare no conflicts of interest in association with the present study.

Acknowledgments

We thank Brian Quinn, Editor-in-chief of Japan Medical Communication, (https://www.japan-mc.co.jp) for editing the English language of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2023.01.050.

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