The Different Clinical and Liver Pathological Characteristics between the Newborns and Infants with Choledochal Cysts

Man-Chin Hua[1,5], MD; Hsun-Chin Chao[2], MD; Reyin Lien[3], MD; Jin-Yao Lai[4], MD; Ming-Wei Lai[2,5], MD; Man-Shan Kong[2], MD

Background: This study was undertaken to investigate the different clinical presentations of newborns and older infants with choledochal cysts, and their liver pathological changes.

Methods: The medical records of patients who were diagnosed with choledochal cysts younger than 1 year old at our hospital from March 1991 through November 2006 were reviewed. Patients were divided into two groups: the newborn group, who presented before 1 month old including those antenatally diagnosed patients; and the infant group, who presented at 1 month to 12 months old. All of the patients' clinical data, including the operative, pathological reports and outcomes were studied and analyzed using the Chi-square and student-t tests.

Results: There were 35 patients included in the study. According to the Todani's classification, 74.2% of choledochal cysts were type I. Using Chi-square and student-t tests, the infant group had significantly higher pre-operative morbidity, abnormal levels of serum transaminase, gamma trans-peptide (γ-GT), and grade of liver fibrosis (≧ grade 2) ($p < 0.05$). The post operative complications were not statistically significant between newborn and infant groups.

Conclusion: Both groups had favorable outcomes after surgical intervention. We suggest that surgical treatment in infants should be performed as early as possible to prevent the progression of liver fibrosis.

(Chang Gung Med J 2009;32:198-203)

Key words: infant, choledochal cyst, liver pathology, surgery

Choledochal cyst is not a rare anomaly of congenital dilation of the biliary tract in Asia and occurs more commonly in the female patients. The age at diagnosis is getting younger due to the increased use of ultrasonography. In addition, prenatal diagnosis allows identification of biliary tree anomalies before birth and the onset of classical symptoms.[1,2] Choledochal cysts may present clinically with two distinct constellations determined primarily by the patient's age.[3] In infants, the clinical presentations may be indistinguishable from biliary atresia, and these patients have more cirrhosis and portal hypertension as compared with older children. There are a few reports in the literature discussing the different clinical presentations between the newborns and older infants with choledochal cysts and

From the [1]Department of Pediatrics, Chang Gung Memorial Hospital, Keelung; [2]Division of Pediatric Gastroenterology; [3]Division of Neonatology, Department of Pediatrics; [4]Division of Pediatric Surgery, Chang Gung Children's Hospital; Chang Gung Memorial Hospital, Taipei, Chang Gung University College of Medicine, Taoyuan, Taiwan; [5]Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan.

Received: Feb. 21, 2008; Accepted: May 6, 2008

Correspondence to: Dr. Man-Shan Kong, Division of Pediatric Gastroenterology, Chang Gung Children's Hospital. No. 5, Fusing St., Gueishan Township, Taoyuan County 333, Taiwan (R.O.C.) Tel.: 886-3-3281200 ext. 8969; Fax: 886-3-3288957; E-mail: kongchi@adm.cgmh.org.tw

the issue of liver pathologic changes. Therefore, our current study was undertaken to investigate these issues.

METHODS

During the past 15 years from March 1991 through November 2006, we retrospectively reviewed the medical records of patients who were diagnosed with choledochal cysts younger than 12 months old in our hospital. The patients who had biliary atresia associated with biliary cysts were excluded using results of intra-operative cholangiograms and the pathological reports of blind biliary trees. We analyzed the age at diagnosis, sex, clinical features, imaging findings, laboratory data, age at operation, operative findings and methods, liver pathological reports, and outcome of each patient. The patients were divided into two age groups: the newborn group consisted of those who presented within 1 month of birth and the antenatally diagnosed patients; and the infant group consisted of those who presented between 1 month and 12 months old. The post-operative early and late complications were defined as complications within 3 months of surgery and at more than 3 months after surgical intervention, respectively.

Liver fibrosis was assessed based on Ohkuma's classification, grade 0, no fibrosis; grade 1, mild fibrosis confined to portal area; grade 2, moderate fibrosis with portal- portal area (P-P) bridging fibrosis; grade 3, severe expansive fibrosis with P-P bridging; and grade 4, liver cirrhosis with a reconstruction of hepatic lobules.[4] Follow-up of the patients was carried out by review of the clinical records.

The Chi-square and student-t tests were used to evaluate the patients between these two age groups; a p value < 0.05 was considered as significant.

RESULTS

There were 14 male infants (40%) and 21 female infants (60%) aged from 0 to 12 months (mean, 3 months) available in the study. Sixteen patients (45.7%) were categorized into the newborn group including 12 patients in whom the cysts were detected using antenatal ultrasound. Nineteen patients (54.3%) were in the infant group. Table 1 shows the demographic data and clinical features of these patients. Jaundice (45.7%) excluding those physiologically related was the most common symptom followed by clay color stool (40%). These two features and hepatomegly had higher incidence in the infant group ($p < 0.05$). Eight of the newborn patients were asymptomatic ($p = 0.003$) after birth. Thirty-four of 35 patients were diagnosed using ultrasonography. There was one patient whose cyst was not detected using ultrasonography and that patients was mis-diagnosed as biliary atresia before surgery. The patent biliary tract was confirmed using results of intra-operative cholangiogram. According to the Todani's classification,[5] type I cyst (74.3%) was the predominant type in our study. There were 12 patients who had pre-operative morbidities including pseudopancreatitis, hypoalbuminemia, gallstone, poor body weight gain, cholangitis, cyst perforation with peritonitis, and inferior vena cava

Table 1. Demographic Data and Clinical Features of 35 Infant Choledochal Cysts

	Newborn group ≦ 1 m/o (n = 16)	Infant group 1 m/o (n = 19)	Total (n)	p value
Male: Female	7:9	7:12	14:21	0.739
Prematurity	1	2	3	0.653
Asymptomatic	8	1	9	0.003*
Jaundice (Direct)	3	13	16	0.003*
Clay color stool	2	12	14	0.009*
Hepatomegaly	1	8	9	0.007*
Abdominal mass	0	3	3	0.269
Cyst size				
8 mm~1 cm	0	3	3	0.269
> 1 cm	16	16	32	0.269
Pre-operative morbidities	1	11	12	0.004*
Pseudopancreatitis	0	3	3	0.269
Hypoalbuminemia	0	2	2	0.519
Gall stone	0	2	2	0.519
Poor body weight gain	0	2	2	0.519
Cholangitis	0	1	1	1.000
Cyst perforation with peritonitis	0	1	1	1.000
IVC thrombus	1	0	1	0.952

Abbreviations: n: number; IVC: inferior vena cava; *: statistically significant.

thrombus formation (Table 1). These morbidities were more common in the infant group than in the newborn group.

Thirty-one patients underwent surgical intervention. Thirty patients were treated using cyst excision with Roux-en-Y hepaticojejunostomy; one patient had cyst excision with Kasai hepatico-portoenterostomy. For the remaining four patients who did not have surgery during our study period, one underwent surgery after the study period and three were lost to follow up. There were seven post-operative early complications in six patients, two complications in the newborn group and five complications in the infant group (Table 2); the complication rate was 18.7%. Among them, biliary tract infection was the most common. A liver biopsy specimen was obtained during the operations in 12 patients of the newborn group and 17 patients in the infant group. The results of liver fibrosis based on the Ohkuma's classification were as follow. In the newborn group, grade 0, seven cases; grade 1, five cases. In the infant group, grade 0, seven cases; grade 1, three cases; grade 2, two cases; grade 3, two cases; grade 4, three cases.

The long-term outcomes of our patients after surgery were generally favorable. The late post-operative complications occurred in three and six patients in the newborn and infant groups, respectively (Table 2). Persisted elevation of the serum transaminase levels was the most common complication (4 patients).

Table 3 shows the various parameter differences between these two age groups. We found that pre-operative morbidities (p = 0.004), abnormal serum levels of transaminase (p = 0.001), gamma trans-peptide (γ-GT) (p = 0.013), and the grade of liver fibrosis (≧ grade 2) (p = 0.035) were statistically significant. However, the differences in post-operative early and late complications (Table 3) were not statistically significant between the 2 groups.

Table 2. Post Operative Early and Late Complications

Post operative early complications (≦ 3 months)	Newborn group (Number)	Infant group (Number)
Biliary tract infection/ cholangitis	1	2
Bile leak	0	2
Wound infection	1	0
Upper GI bleeding	0	1
Total	2	5
Post operative late complications (> 3 months)	**Newborn group (Number)**	**Infant group (Number)**
ALT > 40 U/L	1	3
Failure to thrive	1	0
Biliary stone formation	1	0
Pseudopancreatitis	0	1
Adhesion ileus with volvulus	0	1
Portal hypertension	0	1
Total	3	6

Table 3. Statistical Analysis between Two Groups of Infants with Choledochal Cysts

	Newborn group ≤ 1 m/o (N = 16)	Infant group > 1 m/o (N = 19)	p value
Male: Female	7:9	7:12	0.739
† Type I: IV cyst	13:3	13:6	0.460
Cyst size (cm)	4.86 ± 2.27	4.36 ± 3.18	0.605
Pre OP morbidity (N:P)	15:1	9:10	0.004*
ALT (U/L)	25.38 ± 15.51	132.74 ± 102.14	0.001*
Total bilirubin (mg/dl)	5.2 ± 4.638	5.363 ± 3.580	0.910
rGT	104.22 ± 74.79	310.50 ± 286.99	0.013*
operative age (day)	75.54 ± 76.20; ‡ 13	206.72 ± 133.67; ‡ 18	0.012*
Liver fibrosis (≧ grade 2)	0	7	0.035*
Post OP early complications (≦ 3 mo)	2 ; ‡ 13 (15.4%)	5; ‡ 18 (27.8%)	0.705
Post OP late complications (> 3 mo)	3; ‡ 13 (23%)	6; ‡ 18 (33.3%)	0.826

Abbreviations: N: negative; P: positive; OP: operative; *: statistically significant; †: according to the Todani's classification; ‡: indicate the number of patients who underwent surgical intervention.

After surgical intervention, our patients underwent regular follow-up examinations including liver function tests and abdominal ultrasounds for a period of 1 month to 10 years (mean, 2.32 years). Eight patients were lost to follow up.

DISCUSSION

Ultrasound is the most useful imaging technique to establish the diagnosis of choledochal cyst.[6] However, it may be difficult to distinguish choledochal cysts from biliary atresia with biliary cysts.[7] A survey of the American Academy of Pediatric Surgery Section found that 13% of patients with cystic dilation of the common bile duct (CBD) had extrahepatic atresia.[8] There were reports in the literature stating that choldochal cysts were larger than biliary cysts associated with biliary atresia.[9-11] It has been suggested that there is a 97% confidence of choledochal cyst when the diameter of the common bile duct is greater than 1 cm.[9] Thirty-two of our 35 patients (91.4%) had cysts size larger than 1 cm (mean, 4.59 cm). For the three patients who had choledochal cysts smaller than 1 cm, biliary atresia were excluded carefully. The classic triad of abdominal pain, jaundice and abdominal mass were not common in newborns or infants with choledochal cysts. Prior reports in the literature showed that there was an age difference in the presentations of choledochal cysts.[3,6,12] Pediatric cases frequently exhibited cystic lesions with jaundice and abdominal pain which were more apparent than in newborn and infants.[6,12-14] Todani et al also characterized newborn and infantile cases as (1) cystic choledochal dilation (2) a huge abdominal mass and jaundice with acholic stool, and (3) no symptomatic association of acute pancreatitis.[15] However, our results were different. Although type I cysts remained predominant, acholic stool was significantly higher in patients older than 1 month than in the newborn group ($p < 0.05$). In addition, only three in 35 patients had cysts large enough to be palpated as a mass lesion. In comparing patients in the newborn and infant groups, patients in the infant group had significantly higher numbers of pre-operative morbidities, abnormal elevation of serum transaminase, higher serum level of rGT, and more liver fibrosis (≧ grade 2). This may suggest that choledochal cysts during infancy is a progressive disease.

Untreated choledochal cysts uniformly have poor prognoses.[2] Currently, complete cyst excision with Roux-en-Y hepaticojejunostomy is widely accepted as the standard method of treatment for most choledochal cysts.[6,12,16] Thirty of 31 patients (96.7%) in our study underwent this method of operation. Operation by internal drainage is no longer accepted for fear of later cholangiocarcinoma and increased risk of cholangitis, pancreatitis, and gallstones.[6,12,13] To prevent anastomotic strictures, investigators recommend very high anastomoses beyond the relative stenosis in the common bile duct, or a plastic operation at the junction of the intrahepatic duct with the common bile duct.[16,17] The reported procedures related early complications including wound infections, sub-hepatic abscesses, cholangitis, bile leaks, pancreatitis, ileus, gastro-intestinal bleeding, and bowel perforation ranging from 12 to 17%.[6,16] Our study showed a slightly higher early complication rate (18.7%). Fortunately, these complications were successfully managed. In the procedure related late complications, recurrent strictures, biliary tract infection, portal hypertension and intrahepatic stone formation have been reported.[13,16,18,19] In our study, except for two patients who developed intra-hepatic stones or portal hypertension after operation, there was no stricture or biliary tract infection, and most of our patients had favorable outcomes. This may be related to short-term follow up after surgical intervention. Therefore, long-term follow up is needed to clarify the nature of infantile choledochal cysts.

Recently, laparoscopic surgery has become a popular technique in numerous surgical conditions because it is minimally invasive and has a quick recovery process. In 1995, Farello et al first described the laparoscopic resection and Roux-en-Y hepaticojejunosotmy in a 6-year-old child with a choledochal cyst.[20] Subsequently, investigators have tried laparoscopic surgery in choledochal cysts and the youngest case was a 3-month-old female infant.[21,22] This method may be another option for surgery in children with choledochal cysts.[22] However, its application in infancy needs more studies.

A treatment plan for newborns and infants is important because of the potential for complications later in life including biliary cirrhosis and portal hypertension.[1] However, the optimal surgical timing

in infants especially in the asymptomatic newborns is unknown. Due to the technical difficulty of surgery at an early age and the possible anastomotic complications, early surgical intervention has been suggested in patients with cysts of rapid expanding size,[1,23] deterioration of liver functions, obstructive jaundice, and in antenatally diagnosed patients for distinguishing choledochal cysts from biliary atresia with biliary cyst.[1] However, there have also been reports in the literature showing that liver fibrosis progresses much faster in the newborn cases.[12] Our favorable results of early surgical intervention for infants with choledochal cysts and the evidence of liver fibrosis in the older infants, suggest that early surgery even in asymptomatic patients may be justified.

Acknowledgements

We would like to thank the hospital staff and care givers for their cooperation, and the hospital authorities for allowing this research to take place.

REFERENCES

1. Okada T, Sasaki F, Ueki S, Hirokata G, Okuyama K, Cho K, Todo S. Postnatal management for prenatally diagnosed choledochal cysts. J Pediatr Surg 2004;39:1055-8.
2. Mackenzie TC, Howell LJ, Flake Aw, Adzick NS. The management of prenatally diagnosed choledochal cysts. J Pediatr Surg 2001;36:1241-3.
3. Sherman P, Kolster E, Davies C, Stringer D, Weber J. Choledochal cysts: heterogeneity of clinical presentation. J Pediatr Gastroenterol Nutr 1986;5:867-72.
4. Okamoto E, Ohkuma Y. Pathological reappraisal of biliary atresia and a new aspect on its etiology. J Jpn Soc Pediatr Surg 1975;7:205-11.
5. Todani T, Watanabe Y, Narusue M, Tabuchi K, Okajima K. Congenital bile duct cysts: Classification, operative procedures, and review of thirty-seven cases including cancer arising from choledochal cyst. Am J Surg 1997;134:263-9.
6. de Vries JS, de Vries S, Aronson DC, Bosman DK, Rauws EA, Bosma A, Heij HA, Gouma DJ, van Gulik TM. Choledochal cysts: age of presentation, symptoms, and late complications related to Todani's classification. J Pediatr Surg 2002;37:1568-73.
7. Matsubara H, Oya N, Suzuki Y, Kajiura S, Suzumori K, Matsuo Y, Suzuki T, Hashimoto T. Is it possible to differentiate between choledochal cyst and congenital biliary atresia (type I cyst) by antenatal ultrasonography? Fetal Diagn Ther 1997;12:306-8.
8. Bancroft JD, Bucuvalas JC, Ryckman FC, Dudgeon DL, Saunders RC, Schwarz KB. Antenatal diagnosis of Choledochal cyst. J Pediatr Gastroenterol Nutr 1994;18:142-5.
9. Lee HC, Yeung CY, Chang PY, Sheu JC, Wang NL. Dilatation of the biliary tree in children: sonographic diagnosis and its clinical significance. J Ultrasound Med 2000;19:177-82.
10. Kim WS, Kim IO, Yeon KM, Park KW, Seo JK, Kim CJ . Choledochal cyst with or without biliary atresia in neonate and young infants: US differentiation. Radiology 1998;209:465-9.
11. Jiexiong F, Minju L, Hongfeng T, Weizhong G, Shaoyong Y. Clinical and pathological characteristics of cystic lesions of extrahepatic bile duct in neonates. Acta Paediatr 2003;92:1183-9.
12. Suita S, Shono K, Kinugasa Y, Kubota M, Matsuo S. Influence of age on the presentation and outcome of choledochal cyst. J Pediatr Surg 1999;34:1765-8.
13. Jordan PH Jr, Goss JA Jr, Rosenberg WR, Woods KL. Some considerations for management of choledochal cyst. Am J Surg 2004;187:790-5.
14. Chaudhary A, Dhar P, Sachdev A, Kumar N, Vij JC, Sarin SK, Broor SL, Sharma SS. Choledochal cysts-Differences in children and adults. Br J Surg 1996;83:186-8.
15. Todani T, Urushihara N, Morotomi Y, Watanabe Y, Uemura S, Noda T, Sasaki K, Yoshikawa M. Characteristics of choledochal cysts in neonates and early infants. Eur J Pediatr Surg 1995;5:143-5.
16. Saing H, Han H, Chan KL, Chan FL, Cheng W, Tam PK. Early and late results of excision of choledochal cysts. J Pediatr Surg 1997;32:1563-6.
17. Ohi R, Yaoita S, Kamiyama T, Ibrahim M, Hayashi Y, Chiba T. Surgical treatment of congenital dilation of the bile duct with special reference to late complications after total excisional operation. J Pediatr Surg 1990;25:613-7.
18. Lee HC, Yeung CY, Fang SB, Jiang CB, Sheu JC, Wang NL. Biliary cysts in children-Long term follow up in Taiwan. J Formos Med Assoc 2006;105:118-24.
19. Bismuth H, Krissat J. Choledochal cystic malignancies. Ann Oncol 1999;10 Suppl 4:94-8.
20. Farello GA, Cerofolini A, Rebonato M, Bergamaschi G, Ferrari C, Chiappetta A. Congenital choledochal cyst video-guided laparoscopic treatment. Surg Laparosc Endosc 1995;5:354-8.
21. Ure BM, Nustede R, Becker H. Laparoscopic resection of congenital choledochal cyst, hepaticojejunostomy, and externally made Roux-en-Y anastomosis. J Pediatr Surg 2005;40:728-30.
22. Li L, Feng W, Jing-Bo F, Qi-Zhi Y, Gang L, Liu-Ming H, Yu L, Jun J, Ping W. Laparoscopic-assisted total cyst excision of choledochal cyst and Roux-en-Y hepatoenterostomy. J Pediatr Surg2004;39:1663-6.
23. Ando K, Miyano T, Kohno S, Takamizawa S, Lane G. Spontaneous perforation of choledochal cyst: a study of 13 cases. Eur J Pediatr Surg 1998;8:23-5.

新生兒與嬰兒膽道囊腫在臨床及肝臟病理表徵之差異

花曼津[1,5] 趙舜卿[2] 林瑞瑩[3] 賴勁堯[4] 賴明瑋[2,5] 江文山[2]

背 景： 本研究目的在探討新生兒與嬰兒膽道囊腫在臨床上之不同表現，及肝臟病理表徵之差異。

方 法： 收集從 1991 年 3 月至 2006 年 11 月於一歲以下診斷爲膽道囊腫之病例，將病人分爲兩組：新生兒組爲產前或於出生 1 個月內被診斷出膽道囊腫之病例；嬰兒組則爲出生 1 個月後至 12 個月內被診斷出膽道囊腫之病例。將病人臨床表徵、開刀發現、病理報告及預後加以整理，並以卡方式檢定和 t 檢定統計分析。

結 果： 此研究共包含 35 個病例。依據 Todani 分類，74.2% 病例屬於第一型。依據卡方式檢定和 t 檢定，我們發現嬰兒組之臨床表徵在開刀前有較多的膽道囊腫合併症，肝指數異常，γ-GT 上升，且開刀病理組織顯示有較嚴重之肝纖維化 (大於第二級)，以上均達到統計學意義 ($p < 0.05$)。開刀後遺症方面兩組則無顯著差異。

結 論： 兩組病人開刀預後都不錯。依此研究我們建議嬰兒膽道囊腫可以早一點開刀以減少肝纖維化之產生。

(長庚醫誌 2009;32:198-203)

關鍵詞：嬰兒，膽道囊腫，肝臟病理，開刀

[1]長庚紀念醫院 基隆院區 小兒科；長庚兒童醫院；長庚紀念醫院 台北院區 [2]兒童腸胃科，[3]新生兒科，[4]小兒外科；長庚大學 醫學院 [5]臨床醫學研究所

受文日期：民國97年2月21日；接受刊載：民國97年5月6日

通訊作者：江文山醫師，長庚兒童醫院 兒童腸胃科。桃園縣333龜山鄉復興街5號。Tel.: (03)3281200轉8969; Fax: (03)3288957; E-mail: kongchi@adm.cgmh.org.tw