A Study of Histopathological Profile of Liver in Paediatric Choledochal Cysts

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ABSTRACT

BACKGROUND

Choledochal cysts are rare congenital dilatations of the biliary tract with an incidence of approximately 1 in 1000 live births. Most cases present with jaundice or other obstructive symptoms and are treated by surgical resection of the cyst and re-anastomosis. A liver biopsy at the time of surgery is mandatory to study the histological changes including fibrosis and to grade these changes to determine prognosis. We wanted to study the histology of liver biopsies received along with choledochal cysts, grade the hepatocellular damage and fibrosis, and correlate these findings with clinical presentation of the patients.

METHODS

40 liver biopsies received along with choledochal cysts in paediatric patients were assessed for histological changes using 7 parameters including liver fibrosis and scored semi-quantitatively according to established scoring systems. These scores were correlated with the clinical data, age at surgery, sex of the patient, type of choledochal cyst, clinical features, and the results were analysed for their role in predicting patient prognosis.

RESULTS

We found that all the cases showed histological variations in the liver biopsy. Age of children showed an inverse relationship with histological scoring. Infants showed higher scores in comparison to older children. Fibrosis of the liver was also higher in Infants. Most of the cases presented with clinical jaundice. Patients with jaundice, pain abdomen, fever and acholic stools showed higher scores. We found that the sex of the patient and type of choledochal cysts were independent of the scores.

CONCLUSIONS

Younger age and more severe clinical presentation warrant an urgent surgical intervention in paediatric choledochal cyst. Histological assessment of the liver is mandatory to grade the hepatocellular changes including fibrosis and suggest prognosis and follow up of patients.

KEYWORDS

Liver Histology, Grading, Paediatric Choledochal Cyst

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BACKGROUND

Choledochal cyst is a cystic or fusiform dilatation of the biliary tree, intrahepatic or extrahepatic or both[1]. Choledochal Cysts (CCs) are rare medical conditions with an incidence of 1 in 100,000 to 1 in 150,000 individuals in Western countries to 1 in 13,000 individuals in Japan. High prevalence of choledochal cysts is seen in in East Asia. First case was reported by Douglas in 1852.[2,3] In 1959, Alonso-Lej et al reported 94 cases of choledochal cyst disease and suggested the initial three classes. This classification system has been modified by Todani et al to include two additional groups of patients, those with combined intrahepatic and extrahepatic disease, and those with isolated intrahepatic disease, Caroli's disease.[4] The aetiology of congenital dilatation of Common Bile Duct (CBD) in choledochal cysts is not well defined. Some studies indicate congenital causes while others acquired. Most widely accepted explanation is that it may be related to chronic reflux of the digestive and caustic pancreatic juice into the bile duct secondary to an abnormal connection between pancreatic duct (Wirsung's duct) and the CBD.[5] Congenital biliary dilatation is associated with pancreaticobiliary ductal malunion, distal CBD stenosis, intrahepatic duct dilatation and abnormal hepatic histology.[2,6] Histological changes in the liver in a case of choledochal cyst are seldom reported and a liver biopsy not performed. Liver changes and hepatic fibrosis associated with choledochal cyst have considerable association with patient characteristics and also determine prognosis of patients.

In this study we have used microscopic parameters to assess and grade the histological changes of the liver including fibrosis in a semi quantitative manner and correlated the scoring with clinical characteristics, type of choledochal cyst, the age of patients and clinical presentation.

METHODS

A cross sectional study of 5 years duration was taken up at a tertiary paediatric referral hospital, from September 2014 to August 2019 after obtaining ethical clearance from the Institutional Ethics Committee. All the histological specimens of choledochal cyst along with simultaneous liver biopsy received at the Department of Pathology were included in the study. Detailed recording of clinical history and radiological findings were done in every case. All cases underwent preoperative abdominal ultrasound. Contrast-Enhanced Computed Tomography (CECT) of abdomen was done to confirm the diagnosis and to classify the cyst into one of the subtypes according to Todanis classification. All cases later underwent cystectomy with Roux-en-Y hepaticojejunostomy or hepaticoduodenostomy.

Gross examination of the specimens was done and representative sections (2 - 3 per case) were submitted. Specimens were fixed in 10 % buffered formalin and processed by automatic tissue processor. Routine paraffin embedding was done and 4µ sections were stained with Haematoxylin and Eosin and the tissue sections were examined microscopically. Detailed histopathological examination of choledochal cysts and liver biopsies was performed.

The gross findings of the choledochal cysts were documented along with a histopathological examination of the H & E slides. All choledochal cysts were evaluated for the following histological findings, simple columnar epithelium, hyperplasia, metaplasia, dysplastic or neoplastic changes in the epithelial lining, mural ulceration, mural fibrosis, acute and chronic inflammation.

Liver biopsies were graded for specific histological changes and fibrosis in a semi-quantitative manner and cases were segregated based on the score. Each parameter was separately scored according to the changes observed.[7] Fibrosis was assessed separately according to Okhuma, classification.[8] The six histological parameters considered were, Cholestasis (CHS), Hepato-Cellular Damage (HCD), Parenchymal Inflammation (PI), Bile Duct Proliferation (BDP), Bile Duct Inflammation (BDI), and Central Venous Distention (CVD), were graded as grades 0 to 3, lowest score being 0, indicating absence of the feature and highest score being 3 [Table 1]

Ohkuma's classification was used to evaluate the fibrotic changes in the liver.[7] Fibrosis was graded as 0 to 4, the lowest score being 0 indicating no fibrosis and the highest score being 4 indicating cirrhosis of the liver. We chose Ohkuma classification for this study, due its wide use in all the research related to choledochal cyst associated liver histology. The score obtained for the histological parameters was correlated with clinical data which included age, sex, type of the choledochal cyst and symptoms at admission. Due to the small number of cases in each group no statistical correlation was done.

RESULTS

The total number of cases included in this study was 40 and age range of patients was 21 days to 12 years. 12 cases (30 %) belonged to the infantile group (age 1 year or less than a year), 28 cases (70 %) belonged to classic paediatric group (more than 1 year).13 cases (32.5 %) were seen in age group of 1 - 5 yr. most common age group was more than 5 years (37.5 %). 15 cases (37.5 %) were male patients, and 25 cases (62.5 %) were female, Male to female ratio being 1:1.6.

The commonest clinical presentation of choledochal cyst was jaundice, seen in 29 cases (72.5 %). Vomiting was seen in 25 cases (62.5.5 %), fever in 18 cases (45 %), pain abdomen in 17 cases (42.5 %), abdominal lump in 12 cases (30 %), and only 8 [20 %] in the study patients presented with pale stools (20 %) The classical triad of pain, lump and jaundice was seen in only 6 cases (15 %).

Most of the infants presented with jaundice and vomiting while older children presented most commonly with pain abdomen. On CT (Computed Tomography)-Scan abdomen, all cases showed dilated cystic lesion communicating with the bile duct and separate from the gall bladder. CT scan showed normal liver in 26 cases (65

%), altered echotexture in 7 (17.5 %) cases and hepatomegaly in 7 cases (17.5 %).

In 23 cases (57 %), Roux en Y hepaticojejunostomy was performed and 17 cases (43 %) were managed by hepaticoduodenostomy. 31 cases had type I choledochal cyst and 9 cases had type IV. Most of the cases belonged to type I. The specimen received in all the cases was an already cut open specimen of the choledochal cyst with gall bladder along with a wedge-shaped liver biopsy. Choledochal cysts showed cyst wall composed of dense fibrous tissue with a columnar or flattened lining epithelium, showing focal ulceration or denudation. Sub epithelial inflammatory infiltrate was seen. There was no evidence of dysplastic or malignant changes. Liver histology was graded according to the 6 parameters.[6,9] Most of the cases showed grade 1 and grade 2 changes. Cases showing grade 3 changes were mostly infants. Each parameter was graded separately, and results were tabulated and compared.

22 / 40 (55 %) cases showed cholestasis of which majority of cases 11 cases (27.5 %) showed intracanalicular cholestasis, 7 cases (17.5 %) showed intra hepatocytic cholestasis and 4 cases (10 %) showed centrilobular cholestasis with bile plug formation. Hepatocellular damage of varying degrees was seen in 36 / 40 cases (90 % cases). 15 cases (37.5 %) showed ballooning degeneration, 15 cases (37.5 %) showed feathery degeneration and 6 cases (15 %) showed hepatocellular necrosis. Cases showing hepatocellular necrosis were mostly infants (5 out of 6 cases were infants), while older children showed lower grades of hepatocellular damage. Parenchymal inflammation of varying degrees was seen in 36 cases (90 %). Most of the cases (17 cases - 42.5 %) showed moderate parenchymal inflammation. 11 cases (27.5 %) showed mild inflammation and 8 cases (20 %) showed severe parenchymal inflammation. Inflammatory cells were lymphocytes and neutrophils. Cases showing severe inflammation showed neutrophilic infiltration.

Bile duct proliferation was seen in 34 cases (85 %). 16 cases (40 %) showed moderate bile duct proliferation. 11 cases (27.5 %) showed mild and 7 cases (17.5 %) showed severe bile duct proliferation. Bile duct inflammation was seen in 35 cases (87.5 %). 16 cases (40 %) showed mild bile duct inflammation. 13 cases (32.5 %) showed moderate and 6 cases (15 %) showed severe bile duct inflammation. Central venous distension was seen in 33 cases (82.5 %). 20 cases (50 %) showed moderate central venous distension. 10 cases (25 %) showed mild and 3 cases (7.5 %) showed severe central venous distension.

Fibrosis was graded according to Okhuma's classification[6] as grade 0 to grade 4. Liver fibrosis was seen in 35 cases (87.5 %) Majority of cases showed grade 1 and grade 2 fibrosis. 11 cases (27.5 %) showed periportal fibrosis, 12 cases (30 %) showed moderate portal-portal bridging fibrosis, 8 cases (20 %) showed severe expansive bridging fibrosis with widened bridges and 4 cases (10 %) showed cirrhotic changes. Cases showing cirrhosis were all infants.

Correlation of Histological Findings with Clinical Data

We correlated liver histology with the age of the patient at the time of surgery.

Age	CHS			HCD			PI			BDP			BDI			CVD			PF			
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	4
Infants (10)	3	5	4	0	7	6	2	6	4	3	6	3	4	5	3	4	6	2	1	2	5	4
1 – S yrs. (11)	5	2	0	5	5	1	4	5	2	3	5	2	5	3	3	3	6	1	5	4	2	0
> S yrs. (12)	3	0	0	10	3	0	5	6	2	5	5	2	7	5	0	3	8	0	5	6	1	0

Table 1a.

Sex	CHS			HCD			PI			BDP			BDI			CVD			PF			
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	4
Male	3	2	3	4	4	5	4	6	4	4	6	2	6	4	2	4	7	2	6	2	2	2
Female	6	6	2	10	8	5	5	13	4	5	11	6	10	8	5	7	12	3	5	10	5	3

Table 1b.

Type of Cyst	CHS			HCD			PI			BDP			BDI			CVD			PF			
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	4
Type 1	8	5	4	13	9	4	9	12	6	7	12	6	12	10	6	7	17	4	7	9	5	4
Type 4	3	2	0	2	6	2	2	5	2	4	4	1	4	3	1	3	3	1	4	3	3	0

Table 1c.

Clinical Feature	CHS			HCD			PI			BDP			BDI			CVD			PF			
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	4
Jaundice	4	6	2	6	9	4	5	10	4	6	10	4	9	11	4	4	9	1	4	5	8	5
Vomitings (13)	6	4	3	6	7	2	4	3	1	4	5	1	1	2	2	2	3	1	2	4	4	3
Fever (14)	2	3	1	4	4	2	5	9	6	3	3	0	4	8	3	3	3	0	6	3	4	3
Pain Abdomen (15)	5	4	2	3	8	2	5	5	4	5	6	3	4	6	4	5	6	2	5	4	4	0
Abdominal Distension (10)	3	3	1	1	2	1	1	3	1	1	2	0	1	3	1	2	2	0	7	1	2	3
Acholic Stools (8)	2	4	2	3	3	2	1	3	3	2	4	3	2	4	2	1	2	0	0	1	3	2

Table 1a, 1b, 1c, 1d. Correlation of Histological Grading of Liver Changes with Age of the Patients, Sex of the Patients and Type of Choledochal Cyst, Changes and Clinical Symptoms of the Patients

CHS: Cholestasis, HCD: Hepatocellular Damage, PI: Portal Inflammation, BDP: Bile Duct Proliferation, BDI: Bile Duct Inflammation, CVD: Central Venus Distension, PF: Portal Fibrosis

Histological changes of higher grades were observed in infants < 1 yr. and of lower grades were observed in older children > 5 yr. Out of 12 infants, 7 showed grade 2 hepatocellular damage and 5 showed grade 3 hepatocellular damage. Most of the older children showed grade 1 hepatocellular damage. All cases showing grade 3 cholestasis were also infants.

All the infants showed liver fibrosis of varying degrees. Most of the infants showed grade 3 and grade 4 liver fibrosis. 5 of the 12 infants (42 %) showed severe expansive bridging fibrosis and 4 (33 %) showed cirrhotic changes. All cases showing cirrhotic changes were infants. Cirrhosis was not found in children over 1 yr. of age. Children over 1 yr. of age showed mostly grade 1 periportal and grade 2 moderate bridging fibrosis. Histological findings did not show any significant correlation with the sex of the patient or the type of cyst. [Table 1]

Patients with clinical symptomatology at admission showed more severe histological changes. Most of the cases presenting with jaundice showed features of ductular changes, bile duct proliferation and bile duct inflammation of moderate to high grade and also significant

hepatocellular damage. Cases presenting with fever showed moderate to severe parenchymal inflammation. Cases presenting with pain abdomen were all older children and showed significant hepatocellular damage and lower degree of fibrotic changes in the liver. Acholic stools suggesting biliary obstruction was seen in infants and they also manifested higher grades of hepatocellular damage and hepatic fibrosis. [Table 1]

Parameter	Features	Grading
1. Cholestasis	Canalicular	1
	Hepatocyte	2
	Centrilobular	3
2. Hepatocellular damage	Ballooning	1
	Feathery degeneration	2
	Necrosis	3
3. Parenchymal inflammation	Mild	1
	Moderate	2
	Severe	3
4. Bile duct proliferation	Mild	1
	Moderate	2
	Severe	3
5. Bile duct inflammation	Mild	1
	Moderate	2
	Severe	3
6. Central venous distention	Mild	1
	Moderate	2
	Severe	3

Table 2. Grading of Hepatocellular Changes in the Liver Biopsy of Choledochal Cyst

Ref: Nambirajan et al, 2000.

Clinical Features N = 40	HCD		PI		Fibrosis	
	% cases with low scores On grading [0/1]	% cases with high scores on grading [2/3]	% cases with low scores on grading [0/1]	% cases with high scores on grading [2/3]	% cases with low scores on grading [1/2]	% cases with high scores on grading [3/4]
Jaundice N = 29	20.6	44.8	17.2	48.2	31.8	44.8
Fever N = 18	22.2	33.3	27.1	50	50	38.0
Pain Abdomen N = 17	17.6	58.8	29.4	58.8	52.5	23.5
Acholic Stool N = 8	37.5	62.5	12.5	75	12.5	62.5

Table 3. Correlation of Liver Histological Changes in Choledochal Cyst with Clinical Symptoms

HCD - Hepatocellular Damage, PI - Parenchymal Inflammation, all comparisons are in percentage.

We correlated the major clinical symptoms- jaundice, fever, pain abdomen and acholic stools with the 3 most variable histological parameters among the 7 included in the study, i.e., Hepato-Cellular Damage [HCD], Parenchymal Inflammation [PI] and fibrosis. For, HCD and PI scores were grouped into 0 + 1 as low and 2 + 3 as high respectively and for fibrosis, 1 + 2 was taken as low and 3 + 4 as high. The percentage of cases coming under low and high category among the total number was calculated and it was found that clinical symptoms are associated with higher scores. Particularly notable are high scores with obstructive symptoms, jaundice and acholic stool. [Table 3]. Due to the low number of cases in each group statistical significance could not be assessed.

DISCUSSION

Variable liver changes associated with choledochal cysts were noted in all the 40 cases in the study (100 %). Age of the patients ranged between 5 months and 12 years. Early presentation in the infancy was seen in 28 % and commonest was the 1-to-5-year age group 32 %. We did not have any case of antenatally diagnosed choledochal cyst. About 25 % of choledochal cysts are diagnosed antenatally or within the first year of life, 60 % during the first decade of life, and about 20 % go undiagnosed into adulthood.[9]

Literature mentions an unexplained female preponderance, commonly reported as 4:1 or 3:1.[16,7] There was a significant female preponderance (62 %) in our study too. In a study conducted by N. Sugandhi et al, on 46 patients, only 4 were in infantile group. 29 were females and 17 were males.[7] In a study conducted by Chatura et al (2016), 5 / 16 were in infantile age group and 11 / 16 were in paediatric age group.[17]

Cysts were classified clinic-radiologically using Todani's classification.[10] Out of 40 patients, 31 (77 %) had type I and 9 (23 %) had type IV cysts. Higher number of cases belonged to type IV [77 %] which was comparable to other studies like Lein and Arah.[6,11,18]

Jaundice was the commonest clinical presentation seen in 30 cases, vomiting and pain abdomen were the other common symptoms and probable reason for the hospital admission in older children. Clay coloured or acholic stools suggesting biliary obstruction was seen in only 8 cases out of 40 and all of them were infants. Pain abdomen was complained by older children.

The grade of histological changes was inversely proportional to the age of the subjects in our study. More liver damage was noted in younger patients. Numerous other studies have also documented that younger patients and paediatric patients have more liver changes.[11,12]

All the 12 infants in our study had higher grades of hepatocellular damage. The degree of hepatocellular damage, inflammation, bile ductular proliferation and fibrosis was greater in patients with more severe clinical symptoms like, jaundice, fever and pain abdomen. Similar findings were noted by Sugandhi in their study. Liver changes did not show any variation with the type of choledochal cyst, akin to their study.

Choledochal cysts associated liver changes in the new-born and infants is different in comparison to those in children and adults and seems to have clinical and pathological features similar to correctable biliary atresia. Prompt surgical treatment is imperative because of the difficulty in differentiating this entity from cystic Biliary Atresia (BA) and early onset of liver fibrosis.[19] The pathogenesis of CC in infancy and older children is often debated. It appears that the pancreatic co-biliary reflux caused by anomalous junction of pancreatic and common bile ducts results in fusiform dilatation of CBD in children and adults.[15] This theory, however, does not explain the CC diagnosed prenatally or presenting early in infancy. Cholestatic jaundice with acholic stools in infantile CC is attributed to the stenosis or obliteration of lower CBD

during embryonic development of bile duct. The obstruction of CBD also leads to progressive hepatocellular damage ranging from fibrosis to cirrhosis. It appears that the clinical and pathological features of type-I cystic BA and infantile CC resemble each other pointing to a common pathogenesis. Some authors have classified it as the correctable form of BA.[14] Obstructive cholangiopathy is the main pathology in neonatal cases even though they may have APBJ (Anomalous Pancreatico-Biliary Junction) and the obstructive lesions in choledochus are too tight to allow free reflux of pancreatic juice into the choledochus, causing acute and chronic cholangitis with abdominal pain. Thus, the newborn group is a special population of patients with choledochal cysts who are at risk for liver fibrosis in the infantile period.[20]

The incidence of fibrosis and cirrhosis in choledochal cyst is known. Fuji Shioro in their study of liver fibrosis in patients with choledochal cysts in both paediatric and adult cases found other that besides younger age other clinical characteristics, jaundice without abdominal pain, lower pancreatic enzyme levels had a greater incidence of liver fibrosis.[21] Similar to children with EHBA (Extra-Hepatic Biliary Atresia) obstructive cholangiopathy is implicated in the pathophysiology of liver fibrosis, obstruction of the bile duct, refluxed pancreatic secretions into the bile duct, cholangitis, infection in the bile and an immature biliary system are thought to be involved in liver fibrosis.[22] Fuji Shioro felt that obstructive cholangiopathy is the main cause of liver fibrosis associated with choledochal cyst.[23,24] These findings suggest that younger age is associated with more severe symptoms and warrants early intervention. Due to the severity of clinical presentation and associated liver changes, a treatment plan for new-born's and infants is important. Optimal surgical timing in asymptomatic infants is necessary. Infantile choledochal cyst is also associated with thinner wall and potential complication of cyst rupture. Associated congenital anomalies of the biliary tract are also described.[25]

The study finds greater hepatocellular changes in younger patients and those with severe clinical features particularly with obstructive symptoms. Early intervention is suggested in antenatally detected cysts with increasing size. Many studies have documented that liver fibrosis progresses rapidly in the new-born. Therefore, early surgery even in asymptomatic paediatric patients is justified. Most of the hepatic changes of choledochal cysts are known to regress and normalisation of fibrosis occurs post cystectomy. We suggest an early intervention along with a simultaneous liver biopsy for HPE (Histo-Pathology Examination).

Poddar[16] in their series felt a delayed referral of median 2 months was responsible for a high incidence of secondary biliary cirrhosis and subsequent mortality in infants and also that choledochal cyst should be suspected strongly in children presenting with pain abdomen especially when combined with jaundice. Portal hypertension in patients with choledochal cysts may occur either because of secondary biliary cirrhosis,[13,26] or direct compression by the cyst.[27]

Gong ZH and Xia et al[25] did an immunohistochemical assessment of liver fibrosis to get an indicator for post-operative prognosis and concluded that liver fibrosis is more common and severe in infants than in children. Obstruction of bile ducts and proliferation of bile duct cells were the main pathogenic factors for fibrosis, while HLA-DR mediated immune injury may play a limited role. Fumino and Higuchi et al studied 15 patients of choledochal cyst and liver biopsy was studied microscopically for fibrosis and cirrhosis. They concluded that prompt surgical intervention is recommended for neonatal and infantile cases because irreversible liver cirrhosis can occur as early as in infancy.[28]

One particular patient in our study, a 10-year-old child showed grade 3 fibrosis suggesting that a late presentation might also be associated with fibrosis. Gong reported that hepatic fibrosis associated with choledochal cyst may occur in all ages if associated with recurrent cholangitis.[25] older children may present obstruction with gall stones secondary to biliary stasis and cholecystitis. We are unaware of any previous history of recurrent pain abdomen in this child which is a possibility.

All the choledochal cysts revealed histology on the expected lines. No metaplasia or dysplasia was noted in any of the cases. However, fibrotic cyst wall was seen in older children. This study included only 40 cases because liver biopsies were not performed in all the cases of choledochal cystectomies. The study could not include the hepatic changes in post-operative period due to and lack of consent for a repeat biopsy.

CONCLUSIONS

Paediatric choledochal cysts are invariably associated with histopathological changes of varying degrees in the liver. Both hepatocellular damage and fibrosis are much more common in infants and children with more severe clinical symptoms. Liver biopsy has to be a part of the surgical protocol for choledochal cysts. Pathological interpretation of liver tissue and assessment of fibrosis has an important role in the diagnosis and prognosis of patients with choledochal cysts.

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