

# Histopathological Changes of Liver Observed in Paediatric Patients Presenting with Choledochal Cyst: A Cross-sectional Study in a Tertiary Care Hospital, Kolkata, India

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## ABSTRACT

**Introduction:** Choledochal cyst is an uncommon congenital anomaly of the biliary tract, with a higher incidence seen in Asia. It is commonly associated with Pancreaticobiliary Malunion (PBMU). It is believed to be caused by two factors: weakness of the wall and obstruction distal to it. Choledochal cysts can be roughly classified into two types according to the shape of the common bile duct: cystic dilatation and fusiform dilatation. They may be intrahepatic, extrahepatic, or both. Recognition and management of choledochal cyst disease are important due to the risk of developing cholangiocarcinoma and various pathological changes in liver tissue.

**Aim:** To investigate hepatocellular changes, with particular attention to fibrosis, in paediatric patients with choledochal cyst.

**Materials and Methods:** A descriptive cross-sectional study was carried out in the Outpatient Department (OPD), Institute of Postgraduate Medical Education and Research, SSKM Hospital, Kolkata, West Bengal, India, from October 2017 to September 2019. A total of 48 cases from both sexes in the paediatric age group were collected over a period of one year and eleven months. After obtaining clinical histories, histopathological examinations were performed on all cases to diagnose choledochal cyst and to assess the associated hepatocellular abnormalities. Routine Haematoxylin and Eosin (H&E) stained slides were examined, and reticulin staining was

also conducted for a better assessment of fibrosis in hepatic tissues. All available information was meticulously documented in tables and charts. For data analysis, Microsoft Excel 2007 and Statistical Package for Social Sciences (SPSS) software version 16.0 for windows were used.

**Results:** Majority of the patients 23 (47.91%) were between 1 year and 6 years of age. There was variation in the histopathological findings, with age-wise distribution of different changes in liver tissue documented. Reticulin-stained slides showed prominent fibrosis in liver tissue, which is associated with poor prognosis. The data indicated that there were an equal number of patients (50%) with histologically proven liver cirrhosis in the <1 year and 1-6 years age group. There were no cases of cirrhosis in the >6-12 years age group. Eight cases of liver fibrosis were observed, ranging from mild to severe, while the remaining 40 cases presented with no fibrosis. Among those with fibrosis, 2 cases (25%) were in the <1 year category, 5 (62.5%) cases were in the 1-6 years category, and 1 (12.5%) case was in the >6-12 years category.

**Conclusion:** Fibrosis and cirrhosis were found to be more common in children aged 1-6 years compared to older children. Reticulin staining is an excellent method for confirming the presence of increased fibrosis in the liver, and these findings are very helpful for assessing prognosis and following-up with patients.

**Keywords:** Liver fibrosis, Paediatric population, Pancreaticobiliary malunion

## INTRODUCTION

Choledochal cyst is a dilatation of the biliary tree and is a congenital disease. Numerous chromosomal anomalies have been identified, such as chromosomal duplication of 17q12, which is associated with type 1 choledochal cyst, as well as, mutations in Hepatocyte Nuclear Factor 1-beta (HNF1B) [1,2]. Most reported cases worldwide come from Asia, with an incidence of approximately 1 in 1,000 [3]. This cyst is an uncommon anomaly of the biliary tract, first reported by Douglas in 1852 [4]. The incidence in newborns has been increasing in recent years due to advances in diagnostic imaging techniques [5].

Choledochal cysts are commonly associated with PBMU, which allows pancreatic fluid to reflux into the biliary system and bile to flow into the pancreatic duct. In recent years, combined anomalies of the common channel, pancreatic duct and intrahepatic duct have been recognised with increasing frequency [6,7]. The condition is believed to result from two factors, weakness of the ductal wall and an obstruction distal to it. Radiological and histological studies of patients with choledochal cysts clearly demonstrate that distal segmental stenosis closely correlates with cystic dilatation of the

common bile duct, and the site of stenosis is related to an abnormal choledochopancreatic ductal junction.

Choledochal cysts can be roughly classified into two types based on the shape of the common bile duct: cystic dilatation and fusiform dilatation [8]. They can be intrahepatic, extrahepatic, or both. Both Todani and Komi have described classifications for choledochal cysts based on the presence or absence of PBMU. Several varieties of type I cysts, accounting for 80-90% of cases, exhibit segmental or diffuse fusiform dilatation of the common bile duct: Type Ia is the common type; Type Ib represents segmental dilatation; and Type Ic indicates diffuse dilatation. Type II cysts consist of a true choledochal diverticulum. Type III cysts refer to the dilatation of the intraduodenal portion of the common bile duct (choledochocoele). Type IV cysts are further subdivided into type IVa, which involves multiple intrahepatic and extrahepatic cysts, and type IVb, which involves multiple extrahepatic cysts. Type V, or Caroli's disease, consists of a single or multiple dilatations of the intrahepatic ductal system [9].

In all reported series, there is a preponderance of female patients with choledochal cysts (F:M ratio of 4:1). There are two clinically distinct

groups of patients: the first group is younger than one year of age, with most infants presenting a clinical picture indistinguishable from that of biliary atresia, as they experience complete biliary obstruction and jaundice. The second group is usually older than one year, with the most common presentations being abdominal pain and jaundice; occasionally, a mass may be felt, often due to cholangitis. Patients presenting later may exhibit features of pancreatitis [10,11].

Recognition and management of choledochal cyst disease are crucial due to the risk of developing cholangiocarcinoma. Based on this risk, complete excision of the cyst followed by histopathological examination is considered the standardised intervention [12]. Choledochal cysts are also associated with pancreatobiliary ductal malunion, intrahepatic duct dilatation, and liver tissue fibrosis. In the present study, the authors assessed and graded the histopathological changes in the liver, including inflammation, bile duct proliferation, fibrosis, and cirrhosis, correlating these findings with clinical characteristics, the type of choledochal cyst, the age of patients and clinical presentation.

Therefore, the aim of the present was to study the different histopathological features of choledochal cysts using general and special stains. The objectives were to understand the profile of liver changes associated with choledochal cysts through histopathological examination and to detect the age-wise incidence of fibrosis and cirrhosis of the liver.

## MATERIALS AND METHODS

The present descriptive cross-sectional study was conducted in the OPD, Institute of Postgraduate Medical Education and Research, SSKM Hospital (leading hospital with a substantial volume of general and paediatric the OPD footfall), Kolkata, West Bengal, India, from October 2017 to September 2019. The study evaluates clinicopathological findings and correlates them with histopathology in the study population. Necessary permission from the Ethics Committee (Inst/IEC/1330 dated 07/01/12) was obtained prior to the commencement of the study.

**Sample size:** The paediatric population of both sexes diagnosed clinically and radiologically with choledochal cysts, who subsequently underwent surgical resection of the cyst, were included in the study. Cases were collected over a period of two years (October 2017 to September 2019). In the present study, 50 cases were selected after applying appropriate inclusion and exclusion criteria.

**Inclusion criteria:** Paediatric population of both sexes, preoperatively diagnosed (clinically and radiologically) as cases of choledochal cyst, patients undergoing surgical resection of the cyst and patients whose detailed history findings available were included in the study.

**Exclusion criteria:** All adult patients with choledochal cyst, critically ill patients with choledochal cyst, patients from whom proper consent and cooperation not obtained and inadequate biopsy samples deemed not suitable for evaluation were excluded from the study.

However, in two cases, liver biopsy material was inadequate because at least 1.5 cm length biopsies and 11 portal tracts are needed for better interpretation [13]. Consequently, these two cases were excluded from the study. Therefore, 48 cases formed the final study sample.

## Study Procedure

Specimens received in the Department of Pathology were fixed in 10% buffered formal saline solution. The gross description of individual biopsy samples was noted in a register, with special reference to size, number of tissue bits, colour, etc. Biopsy samples were placed on filter paper and submitted entirely for thorough processing. The sections were processed and stained with H&E stains, as well as, reticulin stains. Reporting of the slides was conducted using specific histopathological criteria.

## STATISTICAL ANALYSIS

All available information was meticulously documented in tables and charts. For data analysis, Microsoft Excel 2007 and SPSS version 16.0 for Windows were used.

## RESULTS

In [Table/Fig-1], age and gender-wise distribution of cases is presented, showing that the majority of the patients (47.91%) in the present study were between 1 year and 6 years of age. The minimum age of the patient was one month, while the maximum age was 12 years. The mean age of patients in the present study was 5.4 years. It also indicates that the majority of the patients (75%) were females.

Age (years)	Male patients, n (%)	Female patients, n (%)
<1	2 (4.2)	4 (8.3)
1-6	5 (10.4)	18 (37.5)
>6-12	5 (10.4)	14 (29.2)
Total	12 (25)	36 (75)

[Table/Fig-1]: Age and gender-wise distribution of cases.

The present study found that children presented with various clinical features, including abdominal pain, jaundice, palpable lumps, nausea, vomiting and acholic stools. A few children exhibited symptoms of pancreatitis, with abdominal pain being the most common clinical feature, followed by jaundice. The clinical profile of the study population has been shown in [Table/Fig-2]. It reveals that all cases of pancreatitis (5 cases) occurred in patients older than 1 year (100%), and no cases of pancreatitis were reported in children under 1 year of age. The maximum cases of jaundice and acholic stools (66.7%) were seen in children under 1 year, while 85.7% of the cases with Abdominal Pain (ABP) and palpable lumps were in the age group over 1 year.

Age (years)	Nausea and vomiting (n=19), n (%)	Pancreatitis (n=5), n (%)	Jaundice and acholic stool (n=10), n (%)	ABP and lump (n=14), n (%)
<1	0	0	6 (60)	2 (14.3)
>1-12	19 (100)	5 (100)	4 (40)	12 (85.7)
Total	19 (100)	5 (100)	10 (100)	14 (100)

[Table/Fig-2]: Clinical profile of study populations.

The distribution of cases according to the type of choledochal cyst has been shown in [Table/Fig-3]. The maximum number of cases of cirrhosis and fibrosis occurred in the 1-6 year age group has been shown in [Table/Fig-4]. The histopathological examination of all cases has been shown in [Table/Fig-5,6]. It shows that the majority of patients (62.5%) with histologically proven liver fibrosis were from the 1-6 years age group, with the minimum age of a patient being one month and the maximum age being eight years.

Type of choledochal cyst	No. of cases, n (%)
Type-1	31 (64.6)
Type-2	12 (25)
Others (Type-3,4)	5 (11.04)
Total	48 (100)

[Table/Fig-3]: Distribution of cases according to types of choledochal cyst.

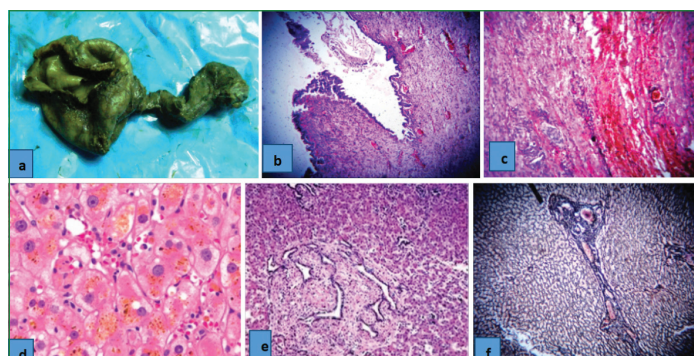
Grade of liver fibrosis	<1 year (n)	1-6 years (n)	>6-12 years (n)
Grade-1 (mild fibrosis confined to portal area)	0	0	0
Grade-2 (moderate fibrosis with Portal-portal area (P-P) bridging fibrosis)	0	1	1
Grade-3 (severe expansive fibrosis with P-P bridging)	0	2	0
Grade-4 (liver cirrhosis with a reconstruction of hepatic lobules)	2	2	0
Total 8 cases, n (%)	2 (25)	5 (62.5)	1 (12.5)

[Table/Fig-4]: Grade of liver fibrosis according to age group.

Age (years)	Cholestasis (n=29)	Bile duct proliferation (n=14)	Inflammation in gall bladder (n=36)	Giant cell reaction (n=8)	Necrosis in liver (n=4)	Fibrosis in liver (n=8)	Cirrhosis in liver (n=4)
<1	5 (17.2)	4 (28.6)	4 (11.1)	1 (12.5)	1 (25)	2 (25)	2 (50)
1-6	18 (62.1)	6 (42.8)	15 (41.7)	5 (62.5)	3 (75)	5 (62.5)	2 (50)
>6-12	6 (20.7)	4 (28.6)	17 (47.2)	2 (25)	0	1 (12.5)	0
Total	29 (100)	14 (100)	36 (100)	8 (100)	4 (100)	8 (100)	4 (100)

**[Table/Fig-5]:** Histopathological examination details of all cases.

Values presented as n (%)



**[Table/Fig-6]:** a) Gross features of choledochal cyst; b) Columnar cell lining and fibro-collagenous wall of choledochal cyst on histopathology (H&E, 10X); c) Congestion of the choledochal cyst wall (H&E, 40X); d) Cholestasis in liver biopsy (H&E, 40X); e) Bile duct proliferation of liver (H&E, 40X); f) Bridging fibrosis (Reticulin stain, 10X).

The findings also reveal that there was an equal number of patients (50%) with histologically proven liver cirrhosis in both the <1 year and 1-6 years age groups, and number cases of cirrhosis were reported in the >6-12 years age group. The maximum number of liver biopsy samples exhibited features of cholestasis, with 29 (60.4%) cases, while the majority of cases presented without bile duct proliferation in the liver, 34 (70.8%) cases. Only 18 (37.5%) cases exhibited inflammation of the liver. In 29 (62.5%) cases, the liver was otherwise normal.

## DISCUSSION

Liver histology showed significant changes in all cases of choledochal cysts that were studied; even livers that appeared normal exhibited evidence of notable alterations. The presence of cirrhosis correlated with jaundice, deranged liver function tests, obstructive features on hepatobiliary scintigraphy, and an increased risk of postoperative complications. The mean age of patients in the present study was 5.4 years, with patients presenting with varied findings ranging from a minimum age of one month to a maximum of 12 years. Most of the patients (47.91%) were between 1 year and 6 years of age.

Based on Ohkuma's classification, liver fibrosis was assessed, showing that the mean age of patients with fibrosis was 3.5 years, while the mean age of patients without fibrosis was 5.8 years. This is consistent with the finding that decreased age is a significant risk factor for liver fibrosis in cases of choledochal cyst, as stated in various standard literatures. This finding was similar to those in the studies by Vijayaraghavan P et al., and Nambirajan L et al., where most cases of liver fibrosis belonged to those under 1 year of age [12,14]. It was observed that cases in the slightly higher age group (1-6 years) were more prevalent; this may be due to a limited number of cases in those below one year.

The mean age of patients in the present study was 5.4 years, with a minimum age of one month and a maximum age of 12 years. Most of the patients (52%) were in the 1-6 year age group. This finding aligns closely with the studies by Vijayaraghavan P et al., and Nambirajan L et al., which indicated that most cases of liver fibrosis were in children under 1 year of age [12,14]. In the present study, the male-to-female ratio was 1:3, which is consistent with findings in standard literature and various studies worldwide. In all reported series, there has been a preponderance of female patients with choledochal cysts (F:M=4:1). Yamaguchi M studied a total of 1,433 cases, with a ratio of men to women was 1:3 [15]. Nambirajan L

et al., found that the sex ratio was 1:2.7 (M:F) [14]. In the present study, abdominal pain was the most common symptom among the patients, followed by jaundice. The maximum number of cases with abdominal pain accompanied by a palpable lump was 12 (85.7%), with these occurring in patients older than 1 year. Only 2 (14.3%) cases were found in children under one year, which is similar to the findings of Lipsett PA et al., [16]. In the present study, a total of five cases presented with features of pancreatitis, all of which occurred in patients older than 1 year (100%). The study indicates that pancreatitis is the most common associated condition found in patients with non alcoholic biliary tract disease [16]. Poddar U et al., reported that the presentations included jaundice in 18 cases, abdominal pain in 15, fever in 12, and abdominal lump in nine cases [17]. The classical triad of jaundice, pain and lump was only present in four cases.

Endoscopic Retrograde Cholangiopancreatography (ERCP) was performed in seven cases, and Percutaneous Overt Catheterisation (POC) was conducted in 14 cases, yielding positive findings in all. Clinically, there were two distinct forms of presentation: (i) the infantile form ( $\leq 1$  year), which included nine infants, all of whom presented with jaundice, six with acholic stools, four with abdominal lumps, and only one with the classical triad; and (ii) the childhood form (>1 year), which presented with abdominal pain in 12 patients and jaundice and cholangitis in nine patients each.

The present study showed that type-1 choledochal cyst was the most common type, comprising 31 (64.6%) cases. The second most common type was type-2, which accounted for 12 (25%) cases. Other types were much less common, comprising only 5 (10.4%) cases. This finding is consistent with the results of a study conducted by Todani T et al., [9].

Various findings were noted in the choledochal cyst wall, gallbladder and liver biopsy specimens during histopathological examination. Many histopathological features were identified in the liver. The most common finding was cholestasis (60.4%), followed by bile duct proliferation. Other features included giant cell reaction, inflammation, fibrosis and cirrhosis. The least common presentation was necrotic features. Only 18 (37.5%) cases presented with inflammation of the liver, while in the remaining 30 (62.5%) cases, the liver appeared otherwise normal. In the majority of cases, there was no giant cell reaction in the liver, 40 (83.8%) cases. Only 8 (16.7%) cases showed the presence of a giant cell reaction. In nearly all cases, no necrotic features were observed in the liver (91.7%).

It was found that the majority of patients with histologically proven liver fibrosis, 5 (62.5%) cases were from the 1-6 year age group. The minimum age of a patient was one month and the maximum age was eight years. Two (25%) cases of fibrosis were found in children under one year, while 1 (12.5%) case was present in the >6-12 years age group. This finding differs somewhat from those in other studies. The study by Vijayaraghavan P et al., showed that fibrosis could occur, as early as, four weeks of age and was seen in all 9 (100%) infants who had liver histology available. Seven of these nine infants had bridging fibrosis (n=4) or cirrhosis (n=3) on liver histology. The outcome was satisfactory in 9 of the 14 (64.3%) infants, despite bridging fibrosis (n=4) or cirrhosis (n=1) in five of these nine babies [12]. In the study by Hua MC et al., [18], liver fibrosis was assessed based on Ohkuma's classification: grade 0, no fibrosis; grade 1, mild fibrosis confined to the 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 reconstruction of hepatic lobules [19-21].

### Limitation(s)

This is a single-institute based study, and due to a lack of awareness, as well as, fear of surgical interventions, many patients were not included in the present study. This may explain the apparently lower number of cases observed. Follow-up was not conducted in the present study, which could have been more fruitful and informative, if it had been implemented.

### CONCLUSION(S)

The present study was conducted only on the paediatric population, and it was found that most infants presented with acholic stools and jaundice as clinical features, in contrast to the classical paediatric group, who primarily presented with abdominal pain and a palpable mass in the abdomen. Urgent intervention is necessary for these patients, especially those presenting with severe symptoms, and histopathological examination is mandatory to identify hepatocellular changes. Histopathological examination revealed that all cysts were lined by a fibrocollagenous wall with inflammatory infiltrate, with a few showing congestion in the wall. The gallbladders mostly exhibited features of chronic cholecystitis. Liver biopsies displayed varied features, and it was noted that fibrosis and cirrhosis were more common in the 1-6 years age group compared to older children. Reticulin is an excellent stain for confirming the presence of increased fiber meshwork in the liver. Details of hepatocellular changes obtained from histopathological examination reports are crucial for assessing prognosis and follow-up in patients.

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