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Histopathological Spectrum of Infantile Cholestasis: A Five Year Study

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Introduction

Infantile cholestasis (IC) is defined as accumulation of bile substances in blood due to impaired excretion. IC should be considered in any infant who is jaundiced beyond two to three weeks of life. [(1)]

1 in every 2,500 infants approximately is affected by IC and is thus infrequently seen by most providers of medical care. IC can lead to significant complications or even death, if not properly managed. BA and NH are most common causes and account for most cases of IC in the first months of life. [(2, 3)]

Unconjugated hyperbilirubinemia (UCH), is a common finding and can result from physiologic jaundice, breastfeeding, red blood cell hemolysis. Conjugated hyperbilirubinemia (CH), conversely, is never physiologic or normal. Hepatomegaly, diarrhea, poor weight gain, hypopigmented or acholic stools, and dark urine, are clues to the diagnosis of cholestasis. [(4)]

Even though interpretation of liver biopsies is challenging in IC, it still provides important clues to the correct diagnosis with a diagnostic yield as high as 95%. Some investigators have reported a worse outcome with increasing fibrosis, whereas others have determined that lobular inflammation, degree of biliary proliferation, or the ductal plate malformation, are associated with a worse clinical outcome. Other investigators have found no correlation between liver histology and outcome. [(5, 6)]

Hence, this study was planned to assess clinical features, radiological, laboratory and histopathological findings in case of IC. This will not only help to understand the disease course of the underlying condition but would also help to plan the treatment for specific causes of cholestasis and manage the patients accordingly.

Methodology

This was a retrospective, observational study of 65 cases of IC over the period of 5 years. Details with respect to age, sex, clinical presentation, investigations and histopathological findings in liver were obtained from the pathology departmental records of the hospital. Detailed review of these cases following which, slides stained by H&E were reviewed along with special stains wherever necessary. The clinical trial protocol was reviewed by the Institutional ethics committee and was approved. Infants in the age group of 0 to 1 year and those infants who presented with less than 1 year of icterus were included. The medical records were assessed, and the pertinent information was retrieved and details were recorded as per the protocol.

Results

The total numbers of surgical specimens received in the pathology department during the study period were 48,004, amongst which 3135 specimens were paediatric. From this, a total of 65 biopsies having cholestasis were studied. The youngest patient was of 18 days male child while the oldest was a 1-year-old male with neonatal hepatitis. Maximum cases were seen in the infants with 0-3 months of age group. Out of 65 patients, there were 48 males and 17 females. The most common presenting symptom was jaundice seen in 65 cases, followed by clay-coloured stools in 23 cases (35.38%), and abdominal distension seen in 10 (15.38%) cases. Biochemical investigations carried out in the patients were SGOT, SGPT, Serum Bilirubin (total and direct) and serological detection of cytomegalovirus (CMV). The mean SGOT was found to be 259.07 U/L, mean SGPT was 199.61U/L, and mean total bilirubin was 11.31mg/dl, mean direct bilirubin was 6.16mg/dl and 1.7% cases were serologically CMV positive. Amongst the 65 cases studied, 28 (43.07%) cases were due to extrahepatic while the remaining 37 (56.92%) cases were due to intrahepatic causes of cholestasis. Core biopsy as well as wedge biopsy was received for histopathological assessment. The histopathological findings of cholestasis due to both intrahepatic and extrahepatic causes, confirmed the diagnosis as Biliary Atresia (BA) in 28 cases, followed by Neonatal Hepatitis (NH) in 20 cases . Other diagnoses were Giant cell hepatitis (GCH) (5 cases), Paucity of bile ducts (PBD) (3 cases), Glycogen storage disorder (GSD) (3 cases), Progressive Familial Intrahepatic Cholestasis (PFIC) (1 case), Fatty Acid Oxidation Defect (FAOD) (1 case), and others (4 cases). The clinical features, investigations, radiological features, gross pathology, histopathology with special stains in all these different types of cholestasis have been discussed in table 2.

Table 2: Different diagnosis of infantile cholestasis and their clinical features

Diagnosis (Cases)	Clinical Features	Radiological	Gross pathology	Histo pathological findings	Special stains (PAS, PAS-D, Mason, Orcein, Retic)
Biliary atresia (28)	Jaundice, Fever & abdominal distension	Triangular sign (USG)-03 & Hepatitis- 01	Multiple grey, white tissue bits ranging from 0.1-0.5cms.	Feathery degeneration -13 Pseudoacinar formation – 14 ,Giant cell transformation -09 Bile duct proliferation-20 Biliary plugging- 04	PAS- 05, PAS-D –Positive-4, Neg- 01 Mason available in 11 cases, Showed portal fibrosis -03, cirrhosis-03, and Nodule formation 04 cases.
Neonatal hepatitis (20)	Fever, Pruritis, clay coloured stools	USG- Hepatomegaly-02, neonatal hepatitis-02, Hepatosplenomegaly-02, liver parenchymal Disease-02	Multiple Grey, white tissue bits from 0.2 to 1 cms. The smallest biopsy received was tissues aggregating to 0.2x0.2x0.1 cm. and the largest was 1x0.7x0.5cms	Partial effacement of lobular architecture- 10, Hepatocytes showing cholestasis- 20 Feathery degeneration-08 Giant cell transformation -12, Interface hepatitis-01 Pseudo acinar formation-4 ballooning degeneration-01 Mild lymphoplasmacytic inflammation- 08	PAS positive in all available 11cases PAS-D available in 7 cases (sensitive in 5 cases and inconclusive in 2 cases. Mason available in 7 cases, positive 1case, negative in 5 cases & not worked in 1case. Orcein available in 9 cases, negative in 7 and focal positivity in 02 cases
Giant cell hepatitis (05)	Jaundice, abdominal distension, dark yellow urine	USG Hepatomegaly-02 HIDA scan-hepatocellular dysfunction- 01 S/O of BA cannot be ruled out-01	Multiple grey, white tissue bits ranging from 0.4 to 1.2 cms. The smallest biopsy received was 0.4cms and the largest was 1.2 cms.	Partial effacement of lobular architecture- 2 Cholestasis - All 5 cases Extensive giant cell transformation- All 05 Feathery degeneration- 03 (60%) Ballooning degeneration-01 case	PAS available in 5 cases-All positive, PAS-D available in 04 (sensitive in 2, positive- 01 and not worked in 01. Mason available in 3 Cases (02 showed fibrosis and occasional bridging respectively), not worked in 01case. Orcein available in 3 cases (negative in 01, positive in 02 cases.
Paucity of bile ducts(03)	Jaundice, Fever, dark yellow urine, pruritis, clay coloured stools	Ultrasonography was suggestive of hepatocellular dysfunction in 2 (66.67%) cases	Multiple grey, white tissue bits ranging from 0.2 to 1 cms. The smallest biopsy received was	Presence of cholestasis-All 03 cases Bile ductular cholestasis-01 Extramedullary	PAS available in 2 cases-All positive PAS-D available in 2 cases-(sensitive in 01 and reduced sensitivity in 01 case.

			0.2x0.2cm. And the largest was 0.5x0.5 cms.	haematopoiesis-01 Kupffer cells prominent- 01 case.	Mason available in 3 cases, occasional nodule- 01 case and no fibrosis- 02 cases Orcein available in 2 cases- Both negative Retic available in 2 cases- Both negative
Glycogen storage disorder (03)	Jaundice and abdominal distension	Hepatomegaly- 01 Hepatosplenomegaly- 02 cases.	Multiple grey, white tissue bits from 0.1 to 1.5 cms. The smallest biopsy received was 0.1 cms and the largest was 1.5 cms.	Cholestasis present in all 3 cases. Hepatocytes uniformly distended in all cases pale and granular cytoplasm in 01, cytoplasmic clearing in 01case. Glycogenotic nuclei in all 3. portal tract fibrosis present in all 3cases.	PAS- available in 2 cases- Both positive PAS-D available in 2 cases- sensitive in both Mason available in 1 case- showing portal fibrosis, Orcein available in 1 case- negative in that case
PFIC (01)	Jaundice	USG was suggestive of fibrosis of tracts.	-	Vague pattern with incomplete and few complete nodules; surrounded by thin fibrous septa. Hepatocytes showed focal ballooning degeneration. Hepatocyte and canalicular cholestasis seen. Portal tract show biliary ductule proliferation. Lobular inflammation.	Mason and Retic were showing fibrosis.
Fatty acid oxidation defect (01)	Jaundice and hyperammonaemia	-	-	Ductular proliferation, portal triaditis. There was presence of diffuse steatosis. Micro and macrovesicular proliferation was also there and at places ductular proliferation.	-

Discussion

Several disorders need to be considered in the differential diagnosis of IC. These disorders account for approximately 30% of all liver diseases encountered in tertiary pediatric health-care centers. [7] The Male: Female ratio was 2.8: 1 in current study. Similar male

predominance with IC has been reported in a few other Asian studies; ranging from 1.2 to 4.5 by Aanpreung et al [8] Najafi et al [9]

In current study, 28 (43.07%) cases were extrahepatic and 37 (56.92%) were intrahepatic cases, similar with study done by Rafeey et al [10] having extrahepatic and intrahepatic causes in 32 (26.4%) and 89 (73.6%) cases respectively. In our research, we found biliary atresia (43.07 percent), neonatal hepatitis (30.76 percent) as most common cause of IC, similar with studies done by Stormon et al [11] and Karim et al. [12] Jaundice (100%), dark urine (45%), clay-colored stools (43%) and pruritus were most common clinical features in our study. Other studies done by Chaudhry et al [13], Rafeey et al [10] and Tlachian et al [6] also showed similar findings.

The average SGOT and SGPT values were 240 and 218 U/L, respectively, while the mean total and direct bilirubin was 12 mg/dl and 7 mg/dl. Additionally, 1.6% of the patients tested positive for CMV. The mean values in studies done by Chaudhry et al [13], Tlachian et al [6] and Rafeey et al [10] were similar to our results.

In our study, BA was the most common cause in 28 cases similar with studies done by Poddar et al [14] Chaudhry et al [13], Tlachian et al [6] and Rafeey et al [10] Biliary atresia is an ascending inflammatory process of the biliary tree leading to progressive obliterative scarring of the extrahepatic and intrahepatic bile ducts, resulting in biliary cirrhosis [15] The diagnostic gold standard of BA is a percutaneous liver biopsy followed by an intraoperative cholangiogram if inconclusive. Liver biopsy leads to the diagnosis in 79–98% of cases. Histology is characterized by inflammatory cell infiltrates around bile ducts, portal tract fibrosis, accumulation of bile typically presenting as bile plugs, and bile duct proliferation. [2, 5]

NH was the most common diagnosis in the studies conducted by Rafeey et al [10] (36.4%) and Chaudhry et al [13] (27.59%) whereas NH was second most common cause for IC (30.76%) in current study. In contrast to these findings, Tlachian et al [6] observed NH only in 9% of cases of IC.

We got 05 cases of GCH, with an M: F ratio of 4:1.Jaundice was present in all cases. Abdominal distension was present in two cases and Dark yellow urine in one case with elevated Liver enzymes in following range SGOT (80-720 U/L), SGPT (75- 623 U/L), Total bilirubin (7-13.1 mg/dl). Torbenson *et al* [16] analyzed the etiology of GCH in 62 newborns: 49% of cases were idiopathic, whereas the remaining patients were variably affected with hypopituitarism (15%), biliary atresia (8%), Alagille syndrome (6%), PFIC (6%), neonatal hemochromatosis (5%), viral infections (4%), and other diseases (8%).

PBD accounted for 4.62% cases of IC in our study, similar with the findings by Chaudhry et al [13] having 3.45% cases. Whereas Tlachian et al [6] got a higher percentage of PBD cases in the study of 11%. Kamath et al [17] found jaundice and pruritus as most common clinical manifestations of cholestasis in neonatal PIBD, with elevated serum aminotransferases. Similarly in our study, all three patients (100%) suffered from jaundice. Pruritus was seen in one patient. Also in our patients, laboratory studies were indicative of cholestasis in all patients with elevated serum aminotransferases.

PFIC was the least common finding accounting for only one case (1.54%) of the all Cholestatic jaundice causes. Similar findings were seen in studies conducted by Tlachian et al [6] and Rafeey et al [10], PFIC accounted for 1.8% and 0.8% of cases of cholestasis respectively.

Conclusion

Study participants with cholestasis were enrolled to investigate the prevalence of various illnesses verified by liver biopsy. After the second week of birth, aberrant direct hyperbilirubinemia characterizes infantile cholestasis, a heterogeneous condition. One of the most common causes of infantile cholestasis is biliary atresia (BA), which necessitates early surgical intervention to prevent cirrhosis, as well as progressive familial intrahepatic cholestasis and idiopathic neonatal hepatitis (INH). When it comes to diagnosing and treating newborns with conjugated hyperbilirubinemia, a liver biopsy is the most reliable and conclusive method. Using the findings of this study, the doctor will be able to better direct their investigation of a baby with conjugated hyperbilirubinemia

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Legend Figures

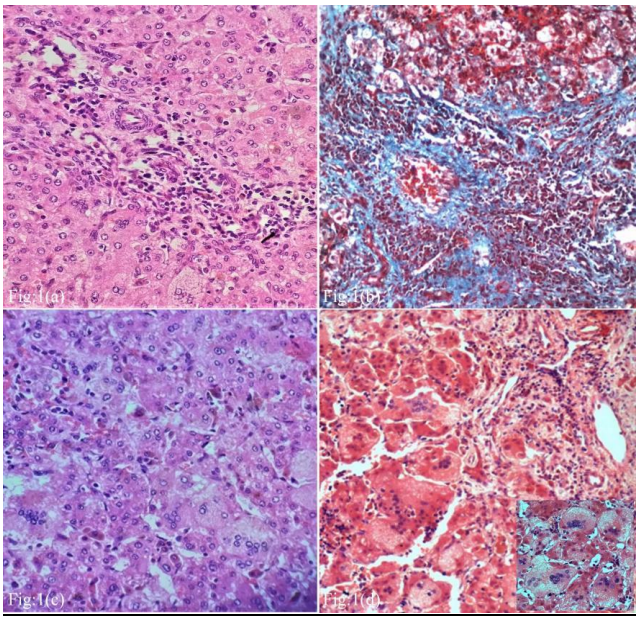

Fig 1(a): Biliary Atresia. Diffuse bile duct proliferation in expanded portal region with canalicular cholestasis. (HE 100x)

Fig 1(b): Biliary Atresia. Extensive fibrosis around portal tract (Masson trichrome 100x)

Fig 1(c): Neonatal Hepatitis. Derangement of architecture, Giant cell transformation, cholestasis, some degenerative changes in hepatocytes (HE 100x)

Fig 1(d): Neonatal Giant cell hepatitis. Giant cell transformation (HE 100X) **Inset:** Many giant cell transformation (HE 400X)

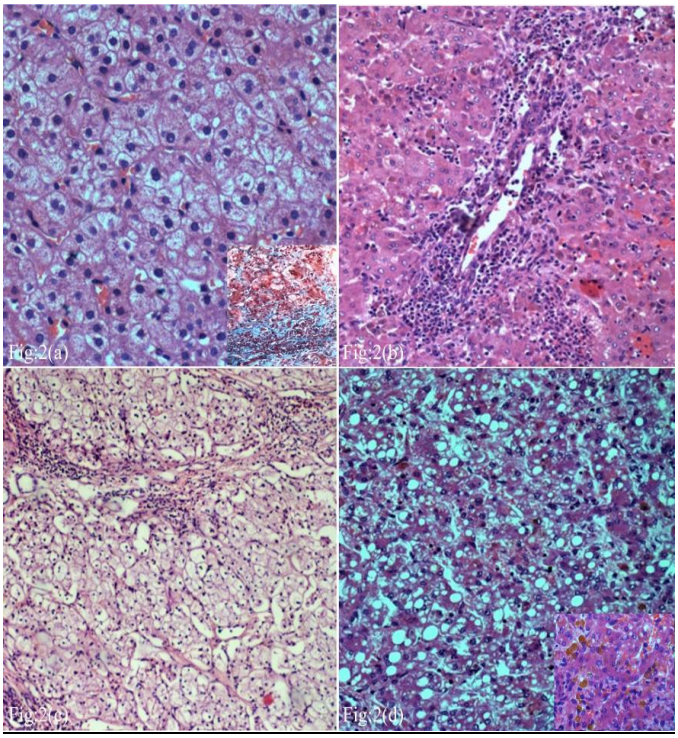

Fig 2(a): PFIC Diffuse cytoplasmic cholestasis of hepatocytes with granular bile. **Inset:** Fibrosis with fine feathery extension into the peripheral zone.(Masson trichrome 100x)

2(b):PBD, portal tract showing no bile ductule, mild inflammation around portaltract, Cholestasis

Fig 2(c): Glycogen Storage Disorder. Hepatocytes distended by glycogen with obliteration of the sinusoids and glycogenated nuclei

Fig 2(d): Fatty acid oxidation defects. Steatosis, Macro and microvesicular change. **Inset:**Pigment laden macrophages, cholestasis