
Original Articles

CURRENT SPECTRUM OF HEPATOBILIARY DISORDERS IN NORTHERN INDIA**S.K. Yachha, B.C. Sharma, A. Khanduri and A. Srivastava**

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Objective: To evaluate the current spectrum of hepatobiliary disorders in children in Northern India. **Setting:** Tertiary level referral hospital. **Methods:** All children with hepatobiliary disorders presenting between January 1992 through July 1995 were evaluated by clinical assessment, liver function tests, viral and autoimmune markers, liver biopsy, copper studies and other relevant investigations. **Results:** Two hundred and thirty five children with hepatobiliary disorders were seen over three and a half years period (67 cases per year). Acute hepatitis (28%), chronic liver disease (36%) and neonatal cholestasis syndrome (NCS) (26%) were the most common patterns of liver diseases. Chronic liver diseases were constituted by ICC (2%), post-hepatitic etiology (13%), Wilson's disease (21%), autoimmune (4%), non-Wilsonian metabolic diseases (16%), hepatic venous outflow obstruction (2%) and non-cirrhotic portal fibrosis (1%). Cirrhosis was documented in 71% and chronic hepatitis in 12% of cases with chronic liver disease. Fulminant hepatic failure was the presentation in 4% of children with liver diseases. **Conclusion:** Chronic liver diseases in Northern India are mainly constituted by post-hepatitic, metabolic and cryptogenic etiology and ICC is rarely encountered. NCS is also one of the major subgroups of liver diseases in children.

Key words: Cirrhosis, Hepatobiliary disorders, Neonatal cholestasis, Viral hepatitis.

CHILDHOOD liver disorders constitute a major proportion of hospital admissions in India. Over the last few years, Indian Childhood Cirrhosis is disappearing with only an occasional case being reported annually from large medical centers (1). The outlook of hepatobiliary disorders has also undergone tremendous change with the advent of better diagnostic tools like ultrasound, radionuclear scan, viral and autoimmune markers, endoscopic retrograde cholangiopancreatography

(ERCP), digital subtraction angiography (DSA) and improved sectioning and staining techniques of liver tissue specimens. Legalization of brain death recently in India has paved the way for liver transplantation in this country. Thus, it is important to have knowledge of the current spectrum of hepatobiliary disorders in Indian children. The present study was therefore done to look at the existing pattern of hepatobiliary disorders in children presenting at a tertiary care center in

Northern India.

Subjects and Methods

Two hundred and thirty five children presenting to our hospital with hepatobiliary disorders over 3.5 years (January 1992-July 1995) were included in this study. Clinical examination, hematology and liver function tests were recorded. Other investigations like ultrasound and upper gastrointestinal (GI) endoscopy, ERCP, viral and autoimmune markers, copper studies and liver biopsies were performed as and when indicated {Table I}.

Results

The observed distribution of hepatobiliary disorders is shown in Table II.

Acute Liver Disease

Of the 66 children with acute hepatitis, the majority (86%) were of viral etiology, 11% had drug induced hepatitis (isoniazid and rifampicin in 86% cases and sodium valproate in 14%) and 3% had hepatitis due to septicemia. Among children with viral hepatitis, 26% were HBsAg positive and others had either hepatitis A or E virus infection, 4% children had anicteric hepatitis and 14% presented with fulminant hepatic failure,

Chronic Liver Diseases (CLD)

The etiology of CLD is shown in Table III. Of the 60 children presenting with cirrhosis (Table III), metabolic group was con-

Table I- Diagnostic Methods Employed.

Disease	Investigation
Chronic hepatitis and cirrhosis	Liver biopsy
HBV	HBsAg positive
HCV	Anti-HCV antibody positive
Autoimmune	SMA/ANA/LKM antibody positive.
Cryptogenic	Negative for above tests and metabolic disorders
Neonatal cholestasis	Ultrasound
	Radionuclide scan
	Liver biopsy
	Per-operative cholangiography
Wilson's disease	Serum ceruloplasmin <20 mg/dl
	Urinary copper > 100 µg/24 h
	Cupriuresis (>25 µmol/24 hr)
	after d-penicillamine challenge
	KF ring
Other metabolic diseases	Liver biopsy &/or
	Bone marrow biopsy
Liver tumors	CT scan
	Histology
Acute hepatitis	Clinical features
	Liver function tests
	Follow up

HBV—Hepatitis B virus; HCV—Hepatitis C virus; HBsAg—Hepatitis B surface antigen; SMA—Smooth muscle antibody; ANA-Antinuclear antibody; LKM-Liver-kidney-microsomal antibody.

TABLE II- Observed Pattern of Hepatobiliary Disorders (n=235)

Category	n	%
Acute hepatitis	66	28
Chronic liver disease	85	36
Neonatal cholestasis syndrome	60	26
Others	24	10

TABLE III- Etiology of Chronic Liver Disease (n=85)

Category	n	%
• ICC	2	2
• Cryptogenic Cirrhosis ^f (n=32) CH (n=2) [§]	34	40
• Post hepatic Cirrhosis ^f (n=10) CH [§] (n=1)	11	13
• Wilson's disease Cirrhosis ^f (n=10) CH [§] (n=7) FHF (n=1)	18	21
• Autoimmune Cirrhosis ^f (n=3)	3	4
• Metabolic diseases* Cirrhosis ^f (n=3) Non cirrhotic (n=11)	14	16
• Hepatic venous outflow obstruction	2	2
• NCPF	1	1

ICC-Indian childhood cirrhosis; CH-Chronic hepatitis; \$CH-(n=10) FHF-Fulminant hepatic failure, *-Excluding Wilson's disease, 2 cases of cirrhosis were due to alpha-1-antitrypsin deficiency. NCPF-Non-cirrhotic portal fibrosis; f-Cirrhosis (n=60).

stituted by 22% [Wilson's disease (WD)-10 cases and alpha 1 antitrypsin deficiency (AATD)-3 cases] and non metabolic group by 78% [post-hepatic-10 cases (HBV 7, HCV 3,) autoimmune-3 cases (ANA

positive 2, LKM antibody positive 1), ICC-2 cases and cryptogenic 32]. Among the non-metabolic cirrhosis (n=47), presenting clinical features were jaundice (19%), ascites (66%), upper gastrointestinal (GI) bleeding (19%), encephalopathy (17%) and spontaneous bacterial peritonitis (6%). Esophageal varices were present in 30% of these children. The duration of presentation was less than 3 months in 61%, 36 months in 17% and more than 6 months in 21% of cases. Chronic hepatitis (Table III) was diagnosed in ten (14%) children (Wilson's disease in 7; HBV in 1 and cryptogenic in 2). Of the 34 children with metabolic etiology (Table IV), WD was diagnosed in 18 children (age 5-12 years, mean 9 yrs: 10 boys). The clinical presentation was cirrhosis in 10 cases, chronic hepatitis in 7 and fulminant hepatic failure (FHF) in one child (Table III). Jaundice was present in 11 cases, ascites in 6, encephalopathy in 2 and upper GI bleeding in 1 child. The duration of presentation was less than 3 months in 6, 3-6 months in 1 and more than 6 months in 11 cases. Seven patients had esophageal varices. Slit lamp examination revealed Kayser Fleisher rings

TABLE IV- Distribution of Metabolic liver Diseases (n=34)

Category	n	%
Wilson's disease	18	53
AAT deficiency	3	8
Glycogen storage disease	3	8
Galactosemia*	2	6
Neimann-Pick disease	2	6
Gilbert's syndrome	2	6
Rotor's syndrome	2	6
Crigler-Najjar syndrome*	2	6

AAT-Alpha-1-antitrypsin deficiency

* Presented as neonatal cholestasis syndrome (NCS), number of these cases is included in NCS group but excluded from chronic liver disease (Table III).

§ One each of types 1 and 2.

in three children, two of whom had extrapyramidal dyskinesia. On investigations, serum ceruloplasmin was low (mean 13.9 ± 5.15 mg/dl) in all and 12 children had high urinary copper levels. Six children with normal urinary copper had significant cupriuresis following d-penicillamine challenge test.

Neonatal Cholestasis Syndrome

This constituted 26% (n=60) of total children; extrahepatic biliary atresia (EHBA) was present in 33, neonatal hepatitis (NH) in 14, intrahepatic bile duct hypoplasia (IHBDH) in 2 and indeterminate etiology in 11 cases. Of the 14 children with NH, 4 had cytomegalovirus infection, 2 galactosemia, 1 urinary tract infection and 7 were of idiopathic etiology.

Miscellaneous

The etiology of hepatobiliary disorders in 24 other children is shown in *Table V*. The histology of liver tumors was hepatoblastoma in 3, hemangioendothelioma in 1, lymphomatous infiltration in 1 and liver metastasis in 3 (primary site-neuroblastoma in 2 and Wilm's tumor in 1).

TABLE V—Miscellaneous Hepatobiliary Disorders (n=24)

Category	n
Liver tumors	8
Choledochal cyst	5
Liver abscess	3
Biliary ascariasis	2
Tuberculosis	2
Hydatid cyst	1
Gall stone disease	1
Acute cholecystitis	1
Benign non-traumatic, non-inflammatory stricture of bile duct	1

Discussion

The most striking observation in our series is rarity of ICC. In the past, ICC was one of the most common hepatic disorders(2). However presently its incidence is decreasing. In Pune, ICC decreased from 50% in 1981-82 to 1.9% in 1992-93 and contributed to only 0.01% of all pediatric admissions in later years as compared to 5% in earlier years(1). The exact etiology of ICC is still unknown. Copper accumulation in liver, probably due to consumption of milk stored and boiled in brass vessels during early infancy is thought to play an important role (3,4). The present decrease in ICC can probably be attributed to current emphasis on exclusive breastfeeding and increased public awareness about adverse effects of milk storage in brass vessels in India(5).

In our study, WD constituted 53% of children with metabolic liver diseases (*Table IV*) and 21% of children with chronic liver disease (*Table III*). In earlier series from India, WD formed a minor proportion (1.6%) of children with chronic liver disease(6). An average annual incidence of 5 cases/year of WD as observed by us is comparable to 4 cases/year currently observed at Pune (1). WD is being recognized with greater frequency due to increased awareness as well as referral and greater applicability of specific diagnostic investigations. Hepatic manifestations of WD, encompass a broad spectrum of acute and chronic liver diseases(7-9). In our series, 10 children had cirrhosis, seven had chronic hepatitis and one had fulminant hepatic failure.

In our study, other causes of cirrhosis were HBV infection (12%), HCV infection (5%), autoimmune liver disease (5%) and cryptogenic (53%). The prevalence of HBV infection varies in different geographical

regions. In children with chronic liver diseases, prevalence of HBV infection has been reported to be high from Italy (93%)(10) and low from North Europe and United States(11-13). The difference in our prevalence of HBV related chronic liver disease could be due to geographical variation and variations in mode of transmission. In India, majority of children acquire HBV infection later in life by horizontal route (85%) and therefore tend to present in adulthood(14).

Three (5%) of our children had autoimmune liver disease (type 1 in 2 and type 2 in 1)(15) which is similar to 4.5% frequency in adults with chronic liver diseases in India(16). However, this frequency is lower as compared to Western and European countries(11-13).

Despite applicability of all known diagnostic investigations more than half of our cirrhotic children had cryptogenic etiology. The average annual incidence of cirrhosis has increased from 3 cases/year (1) to 9 cases/year in the present series. Although newer and as yet unknown viruses (non A, non B, non C) have been postulated as additional etiological agents in cryptogenic cirrhosis (17,18) the exact reason for this change in etiological pattern is unknown.

Neonatal cholestasis syndrome accounted for 26% of subjects in this series. Extrahepatic biliary atresia was diagnosed in 55% and neonatal hepatitis in 23% of these children. A similar profile has been reported by others in India and West(1,19). Two children were diagnosed to have hepatic venous outflow obstruction. Digital subtraction angiography of inferior vena cava (IVC) revealed a block in intrahepatic portion of IVC with patent hepatic veins.

A significant proportion of our children had metabolic etiology (*Table IV*). Non-Wilsonian group constituted 47% of meta-

bolic liver diseases. Although these disorders have been described in the West, scarce data was available from our country in this respect. Recognition of these disorders is essential to render specific management and genetic counselling in the family. Of the miscellaneous group of hepatobiliary disorders, a 6 year old girl was diagnosed to have benign non-traumatic, non-inflammatory stricture of bile duct which is a rare entity (20).

In conclusion, chronic liver diseases in Northern India are mainly constituted by post-hepatic, metabolic and cryptogenic etiology and ICC is rarely encountered. Neonatal cholestasis syndrome is also one of the major subgroups of liver diseases in children.

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