Original Article

Pattern of liver diseases in children admitted in Dhaka Shishu Hospital

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Abstract

Background: Liver diseases cause a significant health problem and a considerable drain in the country's resources. Although pediatric hepatology has advanced greatly over the last decade and many children with severe liver disease are now surviving into adulthood, the research efforts are still mostly directed to adult liver diseases. There are some liver diseases which are particularly seen in the pediatric practice. The research efforts should, therefore, be focused on the pediatric liver diseases as well. The present study is one such step to enrich our knowledge base on pediatric liver diseases. **Methods:** A total of 164 paediatric patients aged 1 month to 14 years admitted from January 2007 to December 2009 were consecutively included in the study. Diagnoses were made on clinical grounds and laboratory investigations. Some patients (n = 30) underwent biopsy as well. Diagnoses were classified into four broad categories like infective, metabolic, congenital and idiopathic liver diseases. Outcome of the patients were classified as cured, improved, discharge on request (DOR), leave against medical advice (LAMA) and death. **Result:** The mean age was 4.8 ± 0.3 years and the lowest and highest ages were 5 months and 14 years respectively male to female ratio was roughly of 3:2. Two-thirds (67.1%) of the children belonged to poor social class and 25% to middle class. Broader classification the diseases demonstrated that 66% children had infective hepatitis, 15% idiopathic diseases, 10% metabolic/storage and 9% congenital liver diseases. Specific diagnoses showed that over half (53%) of the cases had acute viral hepatitis, about 8% neonatal hepatic syndrome (NHS) and 6.1% fulminating hepatic failure (FHF). Wilson's disease, storage disease, liver cirrhosis and biliary atresia were less common. Over 70% of the children improved with treatment and 2.4% died. Older children were more prone to have infective, metabolic and idiopathic liver diseases ($p < 0.001$). Sex and socioeconomic status were not found to be associated with liver diseases ($p = 0.757$ and $p = 0.487$ respectively). **Conclusion:** Overall, the prime cause of liver disease in older children of our country is infective (viral hepatitis) Age is a determinant of types of liver disease. But sex and socioeconomic status did not prove so.

Key words: Pediatric liver diseases, pattern, hospital admitted children

Introduction

In every country liver diseases cause significant health problem and incurs a substantial economic loss in terms of direct and indirect costs. The most comprehensive data about the economic impact of liver disease in the United States compiled by Everhart et al., in which for 1985, the total direct costs (e.g., hospitalization, professional fees, and prescription) of liver disease were estimated at $1.5 billion and indirect costs, (economic loss as a result of premature death, illness, and disability associated with liver disease, are substantial) $2.4 billion. A recent report sponsored by the American Gastroenterological Association (AGA), estimated the prevalence and economic burden of common gastrointestinal and liver disorders, which included chronic liver disease and cirrhosis, chronic hepatitis C, liver cancer, and gallbladder disease [1]. These four liver disease categories accounted for approximately one quarter ($9.1 billion) of all direct costs associated with the 17 conditions in the report and also represented approximately 1% of all health care spending in the United States in 1998.

In United States, the overall prevalence of liver disease at birth is approximately 1 in 2,500 live births (LB); the major disorders are biliary atresia (1 in 10,000 LB), metabolic disease (e.g., A1AT, 1 in 2,800 LB), and forms

of intrahepatic cholestasis ("neonatal hepatitis," 1 in 7,000 LB) [2-4]. The predominant forms of liver disease in older children and adolescents are metabolic disorders (e.g., Wilson disease WD), chronic intrahepatic cholestasis, and viral hepatitis [5].

Pediatric hepatology has advanced greatly over the past few years. Many more children with severe liver disease are now surviving into adulthood. There is a number of conditions not seen in adult practice that have been the focus of research efforts. Disorders characterized by intrahepatic cholestasis in particular have now been substantially unraveled. Relatively common conditions such as biliary atresia still remain largely unexplained and the chronic viral hepatitis have no effective form of treatment. However, there remains a hope that the increase in knowledge in the fields of genetics and immunology will translate into advances in therapy [6].

Considered in this context, we still lag much behind as distribution of liver diseases in our country is still unknown. A systematic study regarding the epidemiological distribution is, therefore, necessary. As part of this greater effort, pattern of liver diseases admitted in a tertiary care paediatric hospital (Dhaka Shisu Hospital) was studied.

Methods

It is a retrospective study done in gastroenterology hepatolgy and nutrition unit of Dhaka Shishu Hospial (DSH) the largest paediatric hospital in Bangladesh with various subspecialities. This unit deals with all paediatric patients but special attention is to be paid for gastrointestinal disorders, liver diseases and malnutrition patients in regards to their hospital care and periodic follow up visit. A total of 164 paediatric patients aged 3 months to 14 years admitted from January 2007 to December 2009 were consecutively included in the study. Diagnoses were made on clinical grounds and laboratory investigations. Details liver function tests as ALT, AST, Alkaline phosphatase, STP A/G ratio, PT and all routine investigations were done. Moreover viral markers and neoplastic markers were done in selective patients. In special cases we have also done echocardiography and radiological evaluation. Some patients (n = 30) underwent liver biopsy as well. An ultrasound of liver was routinely performed. Ultrasonography before a liver biopsy identifies mass lesions that are clinically silent and defines the anatomy of the liver and the relative positions of the gallbladder, lungs, and kidneys. Ultrasonographic information is also useful in selecting the spot for insertion of needle. Diagnoses were classified into four broad categories like infective, metabolic, congenital and idiopathic liver diseases. Details genetic information and enzymatic assay could not be done due lack of facilities. After clinical evaluation and laboratory investigations and liver biopsy if no definite cause could be found regarded as Idiopathic. Demographic characteristics of the patients were compared among four disease categories to see whether patients' demographics were associated with a particular category of disease. The outcome of the patients classified as cured, improved, discharge on request (DOR), leave against medical advice (LAMA) and death.

Results

Nearly 20% of children were below 1 year of age, 41.5% between 1–5 years and rest 39.6% above 5 years. The mean age was 4.8 ± 0.3 years and the lowest and highest ages were 3 months and 14 years respectively. About 62% of the children were male giving a male to female ratio of roughly of 3:2 respectively. Two-thirds (67.1%) of the children belonged to poor social class and 25% to middle class. Very few children came from very poor (4.9%) and affluent (3%) families.

Clinical diagnosis demonstrates that over half (53%) was admitted in the hospital with acute hepatitis. About 9% had neonatal hepatitis syndrome (NHS) and 7.9% was suffering from fulminant hepatic failure (FHF). Willson's disese 4.3%, liver cirrhosis 3%, glycogen storage disease, other storage disease, liver abscess and oesophageal varices with portal hypertension each was 2.4% cases. CLD with no definite cause could be evaluated, chronic viral hepatitis and extrahepatic biliary atresia were 1.8% each, 1.2% case was typhoid fever with hepatitis and isolated idiopathic hepatomegaly, Intrahepatic biliary paucity, chronic triaditis, cholestatic hepatitis, secondary biliary cirrhosis, congenital hepatic fibrosis, Allagille syndrome, Crigler-Najjar syndrome. choledochal cyst was 0.6% each. Other liver diseases were seldom found (Table-2). All these diseases were grouped into four broad classes as infective 108(66%), metabolic/storage 15(9%), congenital 16(10%) and idiopathic 25(15%) diseases (Figure.1). Among the infective causes, acute hepatitis due to HAV infection 78.5%, HBV infection 12% and liver abscess and salmonella hepatitis was 3.6% and 1.8% respectively, only 2.7% case was due to chronic hepatitis and one patient was with HCV and HEV both and that was a case of thalassemia major with a history of repeated blood transfusion (Table-5). Outcome of treatment is illustrated in Table III. Over 70% of children was improved and discharged, 16.5% DOR, 4.9% cured, 6.1% LAMA and 2.4% had a history of death.

Comparison of demographic variables among four broad classes of liver diseases demonstrates that 60% of the children with congenital anomalies were below 1 year old, while infective, metabolic/storage and idiopathic diseases were more common among older children ($p < 0.001$). The sex distribution and socioeconomic status were almost comparable among the four groups ($p = 0.757$ and $p = 0.487$ respectively) (Table-4).

Discussion

The demographic characteristics, such as age, gender, race, and ethnicity, are important determinants of epidemiology of liver disease. In our series only age was found to be associated with types of liver diseases with older children being more prone to develop infective, metabolic and idiopathic liver diseases. Sex and socioeconomic status was not revealed to be the determinants of liver diseases. However, the caution is advised to generalize the findings of the study to community children as the sample was collected from the children admitted in the hospital. Among the type of diseases, infective hepatitis comprised the main bulk (66.7%). Of the infective causes, hepatitis A infection constituted the majority (78.5%), HBV infection the 2nd leading infection (12%) and HCV&HEV the least (0.9%). Although, the overall prevalence of liver disease in children is not known, it is estimated that each year 15,000 children are hospitalized in the United States for liver disease [5]. Based on NHANES III data, the overall age-adjusted prevalence of prior HAV infection, defined by the presence of anti-HAV, is 30.6%. The age-adjusted seroprevalence of current and prior HBV infection, defined by the presence of hepatitis B surface antigen (HBsAg) or antibodies to hepatitis B core antigen, is 4.9% [7]. Chronic infection with HCV is present in 1 in 500 children aged 6 to 11 years and 1 in 250 children aged 12 to 19 years in the United States [8]. But in our country HCV infection are seldom found and only found in case of repeated blood transfusion of thalassemic children. The FHF in our setting was mainly due to HAV infection 7 cases out of 13, 2 cases were due to HBV infection and 2 cases definite cause could not be found and 2 cases we did not get enough time to find out the cause. The diagnosis of Crigler-Najjar syndrome was based on the early onset of severe unconjugated hyperbilirubinemia without evidences of haemolysis develops in homozygous infants. Definite diagnosis is established by measuring hepatic glucuronyl transferase activity in a liver specimen obtained by closed biopsy. Although biopsy could be possible but hepatic glucuronyl transferase activity measurement was not possible in our setting. Allagille syndrome was diagnosed by typical characteristic clinical features of facial dysmorphism (broad forehead, deep set- widely spaced eyes, hypoplastic mandible, long straight upturned nose), peripheral pulmonary stenosis by echocardiography and butterfly shaped vertebrae by radiology.

The term "metabolic liver disease" can be applied to inborn or acquired errors of metabolism in which liver disease is a major manifestation. Metabolic liver diseases present largely in adulthood, namely Haemochromatosis (HHC), Wilson disease (WD), and A1AT. The common metabolic/storage liver disease manifested in the children of our country is Wilson's disease (4.3%).

WD is an autosomal recessive inherited disorder of copper metabolism with an estimated prevalence of 1:30,000 to 1:50,000 in the United States. The gene frequency is estimated to be 1:90 to 1:150. Since 1993, when the gene associated with WD was identified as a copper transporter (ATP7B), over 60 mutations have been described in patients with WD; thus, genetic screening is not feasible [9]. Most of the patients with WD present with hepatic symptoms between the ages of 10 and 14. Patients with neurologic symptoms present at an older age, between 19 and 22 years. Untreated, WD is uniformly fatal, primarily due to complications of liver disease. Early detection and institution of D-penicillamine, trientine, or zinc therapy may improve the prognosis [10]. Liver transplantation has been effective for patients with FHF, decompensated cirrhosis, or progressive neurologic disease, although the latter indication remains controversial [11-12].

Over 7.9% of the children presented with FHF in the current series. FHF is a clinical syndrome characterized by the rapid onset of hepatic encephalopathy in conjunction with a marked decline in liver synthetic function in persons without a prior history of liver disease. The natural history of disease is relatively short (days to months) and there are usually no chronic sequelae in survivors, except in those with WD. In our study HAV infection was the main cause of FHF (53.8%), only 15.3% case was due to HBV infection and 30.65 cases definite cause could not be identified due to lack of facilities and patient did not give enough time to find out the cause.

Of the 164 cases, 4(2.4%) died all were due to FHF among them two were due to HBV infection one due to HAV and another cause could not be identified. 10 patients left against medical advice, majority of them were suffering from FHF grade III and IV. Many patients in our series discharged on parents request with little or no improvement due to many reasons we did not know the fate of that unlucky kids. In

the United States the annual number of deaths attributed to chronic liver disease and cirrhosis, listed as the tenth leading cause of death as of 1998, has remained essentially the same (25,000 per year) for the past two decades [3]. There has been a steady increase in the number of liver-related deaths over time mainly attributable to viral hepatitis and hepatic malignancies [13]. Extrahepatic biliary atresia, a neonatal obstructive cholangiopathy that affects the bile ducts, is the most frequent cause of chronic end-stage liver disease and the leading indication (36%) for liver transplantation in children [14,15]. In the United States, extrahepatic biliary atresia is more common in African American babies (0.96 of 10,000 LB) than in white infants (0.44 of 10,000 LB) and in girls than in boys [15,16]. The present study found 3% of neonates with biliary atresia. Seasonal variation in the occurrence of extrahepatic biliary atresia has been suggested in some studies. There is no known curative treatment for biliary atresia. In the United States, the annual cost for biliary atresia has been estimated to be $65 million, mostly related to the cost of transplantation [5,14,15]. In our study we found three patients with extra hepatic biliary atresia all came after three months of age and Kasai operation was not performed and patients left without medical advice after counseling of possible fate of the disease and there was no facility of liver transplantation in our country. Patients with acute liver failure younger than 10 years of age have a survival rate of less than 10% without transplantation compared with 30% to 35% in patients between the ages of 10 and 40 year [17].

Finally the incidence and prevalence of pediatric Non Alcoholic Steato Hepatitis (NASH) are unknown. However, it is likely on the rise due to the epidemic of obesity in children [18]. The NHANES III conducted in the United States from 1988 to 1994 documented that 16% to 20% of children ages 12 to 17 years were overweight (body mass index >85th percentile) and 8% to 17% were obese (body mass index >95th percentile). Elevated alanine transaminase values were present in 10.8% of obese boys and 7.8% of obese girls and in 15% of both boys and girls aged 16 to 18 years in NHANES III [19]. As childhood obesity is increasing in our country as well, it is really a cause of concern that NASH will be a public health problem in the urban area of our country.

Conclusion

Overall, the prime cause of liver disease in older children of our country is viral hepatits due to HAV infection while the predominant forms of liver disease in older children and adolescents in the United States are metabolic disorders (e.g., WD), chronic intrahepatic cholestasis, and viral hepatitis. Majority of the hepatological cases did not complete their treatment course due to many reasons. Population-based studies of liver disease are necessary for accurate information on the burden of disease and the contribution of specific etiologies of liver disease to this burden and a paediatric hepatology department with all facilities and affordable cost is very much essential for better treatment of liver diseases in our country.

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Table 1. Distribution of patients by demographic variables (n = 164)

Demographic variables	Frequency	Percentage
Age (years)		
<1	31	18.9
1-5	68	41.5
>5	65	39.6
Sex		
Male	101	61.6
Female	63	38.4
Socioeconomic status		
Very poor	08	4.9
Poor	110	67.1
Middle class	41	25.0
Affluent	05	3.0

Table 2. Distribution of patients by diagnosis

Diagnosis	Frequency	Percentage
Acute Hepatitis	87	53
Neonatal hepatitis syndrome (NHS) Fulminant Hepatic	15	09
Failure (FHF)	13	7.9
Wilson's disease	07	4.3
Liver cirrhosis	05	3.0
Glycogen storage disease	04	2.4
Other Storage Disease	04	2.4
Liver abscess	04	2.4
Portal hypertension with Esophageal varices	04	2.4
CLD without definite cause	03	1.8
Chronic viral hepatitis	03	1.8
Extrahepatic biliary atresia	03	1.8
Salmonella hepatitis	02	1.2
Isolated hepatomegaly	02	1.2
Intrahepatic Biliary paucity	01	0.6
Chronic Triaditis	01	0.6
Cholestatic hepatitis	01	0.6
Secondary biliary cirrhosis	01	0.6
Congenital hepatic fibrosis	01	0.6
Allagille syndrome	01	0.6
Crigler- Najjar syndrome.	01	0.6
Choledochal cyst	01	0.6

Table 3. Distribution of patients by outcome (n = 164)

Outcome	Frequency	Percentage
Cured	08	70.1
Improved and discharged	115	16.5
DOR	27	16.2
LAMA	10	6.1
Death	04	2.4

Table 4. Comparison of demographic variables among the groups

Demographic variables	Group				p-value
	Infective (n = 108)	Metabolic/storage diseases (n = 15)	Congenital (n = 16)	Idiopathic (n = 25)	
Age (years) <1 1 – 5 >5	 12(11.1) 45(41.7) 51(47.2)	 1(6.6) 6(40) 8(53.3)	 9(56.2) 4(25.0) 3(18.7)	 10(32.3) 5(16.1) 16(51.6)	 < 0.001
Sex Male Female	 68(63.0) 40(37.0)	 8(53.3) 7(46..6)	 10(62.2) 6(37.8)	 15(60.0) 10(40.0)	 0.757
Socioeconomic status Poor Very poor Middle class Affluent	 67(62.0) 6(5.6) 30(27.8) 5(4.6)	 13(86.6) 1(6.6) 1(6.6) 0(0.0)	 10(62.2) 0(0.0) 6(37.8) 0(0.0)	 19(76.0) 1(4.0) 5(20.0) 0(0.0)	 0.487

Table 5. Distribution of Infective causes (n=108)

Diseases	No	%
Acute hepatitis due to HAV	78	72.2
Acute hepatitis due to HBV	11	10.2
Acute hepatitis due to HC&EV	1	0.9
FHF due to HAV	7	6.3
FHF due to HBV	2	1.8
Chronic hepatitis	3	2.7
Liver abscess	4	3.6
Salmonella hepatitis	2	1.8

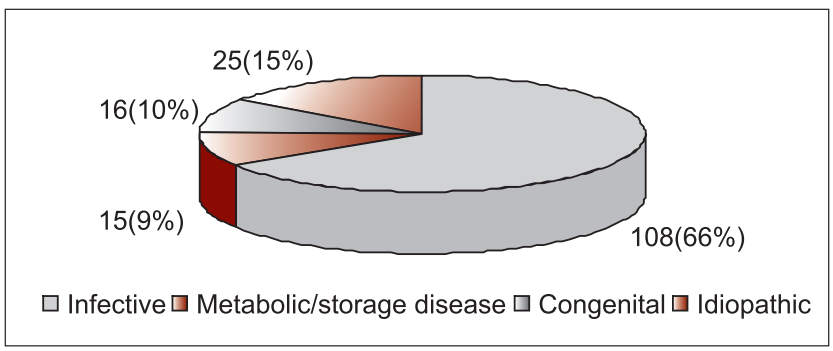

Figure 1. Distribution of children by types of diseases (n = 164)