ABSTRACT

Hepato biliary disorders encompass a diverse spectrum of disorders with varying manifestations and degree of morbidity and lethality.

Objectives: To determine the frequency of hepato-biliary disorders among the patients admitted over the past three years.

Study Design: Retrospective descriptive study

Place and Duration: Department of Pediatric Gastroenterology Hepatology & Nutrition; The Children’s Hospital & The Institute of Child Health, Lahore. January 2013 to December 2015

Subjects and Methods: Patients with hepato-biliary disorders admitted over 03 years; January 2013 to December 2015 were included. Data were retrospectively analyzed from hospital record. Incomplete records or duplications were excluded. Qualitative variables such as frequency of various disorders and their gender distribution were described in terms of frequencies and percentages. Age at presentation was described as mean and standard deviation.

Results: Total 644 patients, 01 month to 18 years of age, were entered (mean 5.73 ± 4.31); males 406 and females 238. Most common hepato biliary disorder found was Idiopathic Chronic Liver Disease (87) followed by Biliary Atresia (80), Neonatal Hepatitis (69), Wilson Disease (66), Chronic Hepatitis C (40), Acute Hepatitis A Virus Infection (39), Autoimmune Hepatitis (36), Budd chairi Syndrome (36), GSD (36), Galactosemia (35), Congenital Hepatic Fibrosis (27), Chronic Hepatitis B (24), Portal Vein Thrombosis (22), Choledochal Cyst (22), PFIC (12), Tyrosenemia (8) and Hemophagocytic lymphohistiocytosis (3).

Conclusion: Hepato-biliary disorders are common in children with Idiopathic Chronic Liver Disease, Biliary Atresia, Neonatal Hepatitis, Wilson Disease and Viral hepatitis the most common entities.

Keywords: CLD, Wilson Disease, Acute Viral Hepatitis, HBV, HCV, Biliary Atresia, Neonatal Hepatitis

INTRODUCTION

Liver is a prime homeostatic organ of the body performing numerous important metabolic, synthetic, detoxifying and excretory functions. Hepato-biliary disorders encompass a diverse spectrum of disorders with varying manifestations and degree of morbidity and lethality. The spectrum of liver and biliary tract diseases ranges from Biliary Atresia, Neonatal hepatitis and...
metabolic liver disease which present in neonatal age group; Glycogen Storage Disorders which present in infancy; Autoimmune hepatitis, Wilson Disease, Hepatotropic viral infections (Hepatitis A, B, C and E) and vascular disorders like Budd Chiari Syndrome and Portal Vein Thrombosis etc. which are seen in toddlers, preadolescents and adolescents. Certain conditions e.g. Progressive Familial Intrahepatic Cholestasis and Choledochal cyst can present at any age1-3.

These are very common disorders and combined; constitute an important reason for referral to any Pediatric Gastroenterology, Hepatology unit. Chronic Liver Disease alone constitutes 36% of referral burden of a Gastroenterology unit in the neighboring country4. Common end point in natural history of most of the hepatobiliary disorders, with few exceptions, is cirrhosis and end-stage liver disease. This makes it very important to have a high index of suspicion and establish diagnosis at the earliest5.

Much has been published about pattern of chronic liver diseases in adults and about individual conditions. Scarce data is available and with very limited number of patients from local studies. Therefore, this study was planned to determine the overall spectrum of hepatobiliary disorders among the patients admitted over the past three years.

Objectives: To determine the frequency of hepatobiliary disorders among the patients admitted over the past three years.

Study Design: Retrospective descriptive study

Place and Duration: Pediatric Gastroenterology Hepatology & Nutrition; The Children’s Hospital & The Institute of Child Health, Lahore. January 2013 to December 2015

Subjects and Methods: Data of patients admitted to the Gastroenterology & Hepatology unit over a period of 03 years from January 2013 to December 2015 was retrospectively analyzed from hospital record. All patients having hepatobiliary disorders were included in the study. Records with incomplete data were excluded from the study. In case of any patient admitted more than once; duplication was removed.

Data collected were analyzed using SPSS version 20. Qualitative variables such as various hepatobiliary disorders and their gender distribution were described in terms of frequencies and percentages. Age at presentation was described as mean and standard deviation.

RESULTS
Total 644 patients, 01 month to 18 years of age, were entered (mean 5.73 ± 4.31); males 406 and females 238. Most common hepatobiliary disorder found was idiopathic chronic liver disease (87) followed by biliary atresia (80), neonatal hepatitis (69), Wilson disease (66), chronic hepatitis C (40), acute hepatitis A virus infection (39), autoimmune hepatitis (36), Budd Chairi syndrome (36), GSD (36), galactosemia (35), congenital hepatic fibrosis (27), chronic hepatitis B (24), portal vein thrombosis (22), choledochal cyst (22), PFIC (12), tyrosenemia (8) and hemophagocytic lymphohistiocytosis (3).

DISCUSSION
In pediatric age group liver and biliary tract diseases are one of the most significant causes of morbidity & mortality. They include a broad spectrum of disorders such as infections, structural abnormalities, genetic & metabolic disorders eventually culminating in hepatic dysfunction and cirrhosis. The spectrum of liver disorders in children is different from those of adults and includes a variety of acute and chronic disorders6.

Most common disease in present study was Idiopathic chronic liver disease (CLD), seen in 87 (13.55%) patients. Mean age at presentation was 7.3 ± 4.5 years and a male to female ratio of 4.11: 1. Idiopathic CLD was responsible for 35% of all patients with chronic liver disease in North India in a study by Dangwal7. However, only CLD patients were included in the study. Contrary, present study has wider inclusion criteria, including all hepatobiliary disorders. Idiopathic CLD was the most common entity among patients with CLD in study done by Tahin8, accounting for 35% of patients.

Idiopathic neonatal hepatitis also had a sizable contribution in the etiology. It was the third most common disease in the study population seen in 69 (10.75%) patients. Mean age at diagnosis was 0.45 ± 0.25 years (5.4 months). Male to female ratio was 2.8: 1. Neonatal hepatitis is recognized as one of the two commonest causes of neonatal cholestasis along with biliary atresia9. In another study by Dehghani10, neonatal hepatitis was the second commonest cause of neonatal cholestasis with mean age of about 02 months at presentation and male to female ratio of 2:1. Age at presentation in present study was delayed which could be accounted for, by late referral. Male preponderance is very much in concordance among the two studies.

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TABLE 1: Frequency and Demographic Data

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<th>Diagnosis</th>
<th>Freq.</th>
<th>%</th>
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<th>%</th>
<th>Female</th>
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<td>100</td>
<td>401</td>
<td>62.46</td>
<td>235</td>
<td>37.54</td>
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Biliary disorders such as biliary atresia present as chronic liver disease if diagnosis is delayed beyond twelve weeks, and untreated all the features of decompensated liver disease can develop e.g. cirrhosis and portal hypertension. In our study biliary atresia was second commonest cause of CLD after cryptogenic liver disease and included 80 (12.46%) subjects with mean age 0.24 ± 0.25 years (2.8 months). Male children predominated by proportion of 1.76:1. The results are in slight discordance with Ağın11 in whose study the mean age at diagnosis of biliary atresia was 2 months with almost equal male to female ratio. Diagnostic approach for biliary atresia, used in present study is close match with Ağın11. History of early onset jaundice with pale stools, direct hyperbilirubinemia, high γGT and small or absent gall bladder on ultrasound is highly suggestive of biliary atresia. Liver biopsy was reserved for doubtful cases, or in patients presenting late to assess the degree of cirrhosis.

In present study, 22 (3.43%) patients had choledochal cyst. Mean age was 4.43 ± 2.18 and male to female ratio was 1:1.44. Mean age at diagnosis, in patients with choledochal cyst was 6.2 ± 3.8 years in study done by Gezer12. However, male to female ratio was 1:1.57 in the study done by Gezer which is in close concordance with the results of the present study12.

Progressive familial intrahepatic cholestasis was diagnosed in 12 (1.87%) patients with mean age 0.37 ± 0.28 years (4.4 months) and male to female ratio of 2:1. Diagnosis was made on the basis of positive consanguinity, family history, pruritis, low or high γGT and liver biopsy findings. Genetic mutation analysis is not available in the country. Age at diagnosis was variable between 03 months to 23 years in the study done by Giovannoni13.

Significant proportion of childhood chronic liver diseases in our population is constituted by Metabolic liver diseases. Metabolic disorders in our study included: Wilson disease 66 (10.28%), glycogen storage disease in 36 (5.61%), galactosemia 35 (5.45%) and tyrosenemia 8 (1.25%) patients. These results are consistent with a survey done in India, which revealed metabolic liver diseases in 8 to 43% of reported chronic liver diseases with Wilson disease being commonest metabolic liver disorder14.

Wilson disease is an inherited disorder or copper excretion with resultant accumulation of copper in different organs in the body predominantly liver, basal ganglia and the lens of eye. Clinical presentation is predominantly hepatic in first decade of life but patients who present in later second decade usually present with neurological symptoms15. Wilsons disease was seen in 66 (10.28%) of our patients. Mean age was 9.07 ±
4.06 years and male to female ratio was 1.54:1. In a study done in Bangladesh, mean age at diagnosis of Wilson Disease was 8.5 years which is in close concordance with present study. Male to female ratio was 2:1 which is slightly higher than present study\(^{16}\).

Glycogen storage disorders were diagnosed in 36 (5.61\%) patients, mean age 3.16±3.03 years and male to female ratio 1.57:1. Diagnosis was established on the basis of typical clinical features of hepatomegaly, +/- metabolic acidosis, hyperlipidemia, hyperuricemia and liver biopsy findings of steatosis and PAS positive material within the hepatocytes. Enzymatic assays and mutation analysis is not available in the country. In the study done by Tahir\(^8\), glycogen storage disorders were responsible for 8.3\% of all patients with chronic liver disease. Male to female ratio in study by Melis\(^{17}\) was 0.45:1 which is in discordance with present study.

Galactosemia is among the common metabolic liver diseases. In present study, mean age at diagnosis was 0.30±0.12 years (3.6 months) with an almost equal male to female ratio. Diagnosis was based on typical clinical setting with early onset jaundice and liver dysfunction including hypoalbuminemia and coagulopathy with positive glycosuria on dipstick; along with clinical response to galactose free milk formula. Age at diagnosis is somewhat later in present study than that of Sarma MS\(^{18}\).

Tyrosenemia is much less common than galactosemia. Typical setting is that of an early onset relentless liver failure, usually associated with renal tubular dysfunction along with markedly elevated serum \(\alpha\)-feto protein and urinary succinyl acetone. Early detection is important as early treatment can prevent many complications\(^{19}\).

Viral hepatitis cumulatively constitutes a major cause of liver disease in children. In present study, Hepatitis A, B and C infection was present in 103 (16.04\%) patients. In study by Shah, Hepatitis B and C were responsible for 7\% if all hepato-biliary (16.04\%) patients. In study by Yachha\(^4\). Number of patients with Hepatitis C was among the top contributors to childhood hepato-biliary disorders. In a hospital based screening study done in Bahawalpur, Pakistan; frequency of hepatitis C was 7.3\% which makes it an appallingy emerging problem in children\(^{21}\). In present study there were 39 (6.07\%) patients with hepatitis C infection. Mean age at presentation was 9.44±3.30 years with a male to female ratio of 1.78:1. Chronic HCV infection was responsible for 31.66\% of cases of CLD in a study by Tahir\(^8\), this proportion is higher than present study because only chronic liver disease was included. Mean age was 8.37 years which is in close concordance with present study.

Hepatitis B was seen in 24 (3.74\%) patients in present study with mean age 10.14±3.77 years and male to female ratio of 1.67:1. Frequency of hepatitis B in study by Dar\(^6\) was 18\% of all CLD, while in another local study by Tahir\(^8\), it was 8.3\%. Age range in study by Komatsu\(^{22}\) was 1-17.8 years while male to female ratio was almost equal. This is in slight contrast to present study where there was a male predominance. This could be attributed to more male patients preferentially brought for workup and treatment because of social reasons.

Patients with hepatitis A infection were 39 (6.07\%). Actual incidence of hepatitis A infection is very high because most of the patients have asymptomatic infection or mild self-limiting illness. Admission is only required in patients who develop hepatic failure and/or hepatic encephalopathy. Acute viral hepatitis was responsible for 26\% of all admission with hepatobiliray disorders in an Indian study by Yachha\(^4\).

Budd Chiari Syndrome and Portal Vein Thrombosis are vascular disorders but can have presentation similar to CLD. Hepatic venous outflow obstruction in Budd Chiari Syndrome and resultant congestive hepatopathy has profound effects on liver function, and these patients also develop portal hypertension. Patients with portal vein thrombosis present with splenomegaly and esophageal variceal bleed with usually intact liver functions. However, as portal vein brings two thirds of liver blood supply, long standing disease can develop liver decompensation. Budd Chiari Syndrome was seen in 36(5.61\%) patients with a mean age 6.45±3.40 years. Male to female ratio was 1.25:1. Existing literature about Budd Chiari Syndrome is limited to case reports\(^{23}\). Number of patients with Budd Chiari Syndrome in present study is quite large because of the setting of Children's Hospital & the Institute of Child Health, Lahore which is the only dedicated setup in the country and receives referral from all over the country.

One of the complication of cirrhosis, secondary to any etiology is portal vein thrombosis\(^{24}\). However in present study, 22 (3.43\%) patients with isolated portal vein thrombosis were included with a mean age of 8.34±3.55 years and a male to female ratio of 1.44:1. In most of the patients had no hereditary thrombophilia could be identifiable.
Autoimmune hepatitis was seen in 36(5.61%) patients in present study, in studies done locally autoimmune hepatitis was established as etiology for CLD in 9 patients (16%) whereas in other local study it was seen in one patient only (1.7%). This difference could be due to under reporting of autoimmune hepatitis owing to two reasons: first is due to variable nature of its presentation it is sometimes treated as acute hepatitis and due to relapsing remitting nature they experience periods of normality in between presentations. Secondly, the diagnostic facilities are unfortunately limited and available at few places only.

Congenital hepatic fibrosis is a rare reported entity. In present study 27 (4.21%) were diagnosed with Congenital hepatic fibrosis. Mean age at diagnosis was 6.55 ± 2.65 years. Male to female ratio was 2.85: 1. Presentation of Congenital hepatic fibrosis is with firm hepatomegaly, splenomegaly, portal hypertension and variceal bleeding. Liver enzymes and synthetic functions are normal and there is usually no ascites. The disease has association with renal anomalies, especially polycystic kidneys. Shunt surgery is usually required for portal hypertension. Rarely patient may require liver transplantation25.

Hemophagocytic lymphohistiocytosis was seen in 3 (0.47%) is a rare and lethal disorder affecting infants all were males. incidence of HLH is estimated to be 1.2 children per million per year with a male-to-female ratio close to 1:1 these were suspected & diagnosed on the basis of low fibrinogen level, hypertriglyceridemia, presence of histiocytes on bone marrow biopsy, fever, cytopenias or splenomegaly. We couldn’t get a positive family history in any of our patient. This disorder is characterized by fever and hepatosplenomegaly associated with pancytopenia, hypertriglyceridemia and hypofibrinogenemia27.

CONCLUSION

This study shows the frequency of diverse hepatobiliary disorders which can present in children. The commonest being idiopathic chronic liver disease, biliary atresia, neonatal hepatitis, Wilson Disease and viral hepatitis the most common entities. While investigating for the etiology it’s important to keep in mind all the possible causes of hepato-biliary diseases. Our centre is largest and is catering to the need of nearly all Pakistan, almost all the required metabolic workup for various liver metabolic diseases are being done through various channels. Prompt suspicion and early referral to specialized centre can make a huge difference in outcome.

Author’s affiliation

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