

## ORIGINAL ARTICLE

## AETIOLOGICAL FACTORS OF CHRONIC LIVER DISEASE IN CHILDREN

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**Background:** Chronicity of liver disease is determined either by duration of liver disease or by evidence of either severe liver disease or physical stigmata of chronic liver disease. Chronic liver disease may be caused commonly by persistent viral infections, metabolic diseases, drugs, autoimmune hepatitis, or unknown factors. The objective of this study was to find out the aetiology of chronic liver disease (CLD) in children. **Methodology:** It was a descriptive, prospective study which used a structured proforma designed to collect data of cases of CLD from both indoor and outdoor Paediatrics units of Fauji Foundation Hospital, Rawalpindi, and Children Hospital, Pakistan Institute of Medical Sciences, Islamabad. All children under 12 years having either clinical or biochemical evidence of liver disease and/or elevated liver enzymes for more than 3 months were included in this study. **Results:** Sixty cases of CLD were enrolled from indoor and outdoor units from January 2010 to July 2011. Thirty-nine (65%) cases were male and 21 (35%) were female. Eleven children were less than 1 year, 18 were 1–5 years old and 31 were 5–12 years of age. Viral hepatitis was the most common cause found in 22 (36.7%) cases. Out of these 22 patients with viral aetiology 19 (31.66%) patients had Hepatitis C and 3 (5%) had Hepatitis B. Glycogen storage disease was seen in 8.3% cases, and biliary atresia and Wilson disease in 6.7% each. Other less commonly found cases were autoimmune hepatitis, TORCH infections, hepatoma and drug induced hepatitis (1.7% each). Cause couldn't be established in 35% cases which remained idiopathic. **Conclusion:** Viral hepatitis is the leading cause of chronic liver disease in children, with the highest incidence of chronic Hepatitis C followed by metabolic disorders (glycogen storage disease and Wilson disease) and biliary atresia. Chronic viral hepatitis was most prevalent between 11 months to 12 years of age. Wilson disease was common in 3–7 years age group, and Biliary atresia in 4–7 months age group. Glycogen storage disease was prevalent between 5 months to 3 years.

**Keywords:** Chronic liver disease, Chronic viral hepatitis, Wilson disease

## INTRODUCTION

Chronicity of liver disease is determined either by duration of liver disease (typically >3–6 months) or by evidence of either severe liver disease or physical stigmata of chronic liver disease (clubbing, spider telangiectasia and hepatosplenomegaly). The severity is variable; the affected child may have only biochemical evidence of liver dysfunction, may have stigmata of chronic liver disease, or may present in hepatic failure. Chronic liver disease may be caused commonly by persistent viral infections, metabolic diseases, drugs, autoimmune hepatitis, or unknown factors.<sup>1</sup>

The causes of liver disease in paediatric patients vary with age. Some are associated with certain age groups, such as biliary atresia and idiopathic neonatal hepatitis, which are observed only at birth or shortly thereafter. Conversely, acetaminophen intoxication and Wilson disease are typical of older children, especially adolescents.<sup>2</sup> In countries where HBV is endemic, perinatal transmission remains the most important cause of chronic infection. Perinatal transmission also occurs in non-endemic countries, including the United States, mostly in children of HBV-

infected mothers who do not receive appropriate HBV immunoprophylaxis at birth.<sup>3,4</sup>

The prevalence of Hepatitis C infection was much higher (50–95%) in individuals who received blood products for conditions such as thalassemia or haemophilia before 1990 (when a first-generation ELISA test became available and routine screening of the blood supply began) to as late as 1992 (when the second-generation ELISA test was introduced).<sup>5–7</sup> Seroprevalence rates of 10–20% have been reported among children with a variety of other potential exposures such as malignancy, haemodialysis, extracorporeal membrane oxygenation, or surgery for congenital heart disease.<sup>8–13</sup>

Glycogen storage disorders may present with chronic liver disease. Patients with the autosomal recessive liver-specific type may develop cirrhosis.<sup>14</sup> The hepatic injury in Wilson disease is believed to be caused by excess copper, which acts as a pro-oxidant and promotes the generation of free radicals.<sup>15</sup>

## PATIENTS AND METHODS

A structured proforma was used to collect data prospectively from all Children having either clinical or biochemical evidence of liver disease in the form of

jaundice, hepato-splenomegaly and/or elevated liver enzymes for more than 3 months either admitted or from OPD of Paediatric Departments of Fauji Foundation Hospital (FFH), Rawalpindi, and Children hospital, Pakistan Institute of Medical Sciences (PIMS), Islamabad from January 2010 to July 2011. The clinical profile of chronic liver disease (CLD) was studied focusing on the etiologic factors. Diagnosis of etiological factors was based on serological markers in viral hepatitis. Serum/urinary levels of substrates were done in metabolic diseases. TORCH screening was done to rule out neonatal hepatitis. Hepatobiliary sonography and Scintigraphy (HIDA scan) was done to rule out biliary atresia. Liver biopsy and ascitic tap was done where tissue diagnosis was indicated as in cases with Tuberculosis, Hepatoma, Glycogen storage disorder. Data were analysed on SPSS-15.

## RESULTS

Among total of 60 patients, 39 (65%) were male and 21 (35%) were female. Age of these patients ranged from one month to 12 years. The mean age was  $6.39 \pm 4.29$  years. Eleven children were <1 year old, 18 were 1–5 years, and 31 were 5–12 years of age.

Viral hepatitis was the most common aetiology found in 22 (36.7%) of the children. Out of 60 patients, 19 patients (31.66%) had hepatitis C (anti-HCV positive and PCR was performed in only 10 which was positive in all). Three (5%) children had hepatitis B

(HBsAg positive). Wilson disease was found in 4 (6.7%) children. They all were diagnosed on laboratory evidence of increased urinary copper excretion ( $>100 \mu\text{g/dL}$ ) and/or low serum ceruloplasmin levels ( $<20 \mu\text{g/dL}$ ). Liver biopsy was not done in these, as the parents did not give consent. Glycogen storage disease was found in 5 (8.3%) children confirmed by liver biopsy. 3 children showed evidence of biliary atresia, confirmed by HIDA scan (one was a 7 month old infant who had periportal fibrosis and a fibrosed shrunken gall bladder, 2<sup>nd</sup> patient was 6-month old, he was a post-operative case of Kasai portoenterostomy for biliary atresia and 3<sup>rd</sup> child had co-existent congenital rubella and CMV infections. Autoimmune hepatitis was diagnosed in a 2 years old child, with positive anti-Liver Kidney Microsomal antibodies.

In 21 (35%) children aetiology could not be ascertained. This was probably due to the factor that liver biopsy could not be performed in most of these patients because, either the parents did not give consent or the coagulation profile was deranged.

Four cases had uncommon aetiology; hepatoma, chronic hepatitis due to anti tuberculous drugs, Hepatic caseating granulomas with tuberculous ascites confirmed by liver biopsy and ascitic tap, TORCH infection confirmed by presence of rubella and CMV IgG antibodies positive, respectively (Table-1).

**Table-1: Aetiological spectrum of chronic liver disease in children**

| Aetiology                     | Number | Percent |
|-------------------------------|--------|---------|
| Viral Hepatitis               | 22     | 36.7    |
| Uncertain aetiology           | 21     | 35      |
| Glycogen storage disease      | 5      | 8.37    |
| Wilson disease                | 4      | 6.7     |
| Biliary atresia               | 3      | 5       |
| Chronic granulomatous disease | 1      | 1.7     |
| Drug induced hepatitis        | 1      | 1.7     |
| TORCH infection               | 1      | 1.7     |
| Hepatoma                      | 1      | 1.7     |
| Autoimmune hepatitis          | 1      | 1.7     |

According to age distribution, 46 children were 1–12 years of age. Twenty patients (43.5%) had chronic viral hepatitis, 16 patients (34%) had unknown aetiology, 4 patients (8.7%) had Wilson disease, 2 patients (4.3%) had glycogen storage disease, and 1 patient each had autoimmune hepatitis, hepatoma, drug induced hepatitis and chronic granulomatous infection (2.2% each). 14 patients were less than 1 year of age. Out of these, 5 patients (35.7%) had unknown aetiology, 3 patients (21.4%) had glycogen storage disease, 3 patients had biliary atresia (21.4%), 2 patients had chronic hepatitis (14.2% each) and one patient (7.1%) had TORCH infection.

Chronic viral hepatitis was most prevalent between 1 year to 12 years of age (mean age: 8.37 years). Wilson disease was common in 3–7 years age group (mean age: 5.5 years). Biliary atresia was common in 4–7 months age group (mean age: 5 months). Glycogen storage disease was prevalent between 5 months to 3 years (mean age: 1.4 years). One patient each of autoimmune hepatitis, TORCH infection, hepatoma, drug induced hepatitis and chronic granulomatous infection presented at 2 years, 9 months, 7 years, 11 years and 4 years respectively (Table-1).

**Table-1: Age distribution of aetiologies**

|                              | Diagnosis                       | Number | Percent |
|------------------------------|---------------------------------|--------|---------|
| Neonate and Infant (<1 year) | Uncertain aetiology             | 5      | 35.7    |
|                              | Biliary atresia                 | 3      | 21.4    |
|                              | Viral hepatitis                 | 2      | 14.2    |
|                              | TORCH infection                 | 1      | 7.1     |
|                              | Glycogen storage disease        | 3      | 21.4    |
|                              | Uncertain aetiology             | 16     | 34.8    |
| Children (1-12 years)        | Viral hepatitis                 | 20     | 43.5    |
|                              | Glycogen storage disease        | 2      | 4.3     |
|                              | Autoimmune hepatitis            | 1      | 2.2     |
|                              | Wilson's disease                | 4      | 8.7     |
|                              | Chronic-granulomatous infection | 1      | 2.2     |
|                              | Hepatoma                        | 1      | 2.2     |
|                              | Drug induced liver disease      | 1      | 2.2     |

## DISCUSSION

Chronic liver disease encompasses a wide spectrum of disorders, including infectious, metabolic, genetic, drug induced, idiopathic, structural, and autoimmune diseases. The initial clinical presentation and laboratory

workup in many of these diseases may be similar, and a definitive diagnosis is often made by specialised laboratory investigations and histologic examination of liver tissue where indicated.

In our study viral hepatitis was the most common aetiology found in 22 (36.7%) of the children, among which 19 patients (31.66%) had Hepatitis C and 3 (5%) had Hepatitis B infection. This was followed by metabolic disorder; glycogen storage disease (8.3%). Prevalence of Wilson disease and biliary atresia was 6.7%. Other uncommon causes included autoimmune hepatitis, TORCH infections, hepatoma, drug induced hepatitis, and chronic granulomatous infection. Cause could not be established in 21 (35%) cases.

Chronic viral hepatitis was the commonest aetiology which is comparable to other studies from Pakistan and India<sup>16,17</sup>, but in our study Hepatitis C was commonest while in other studies it has been Hepatitis B. Another study was published in 2004 from National Institute of Child Health, Karachi, showed that out of 55 cases studied, 24% had chronic Hepatitis B, 16% autoimmune disease, 16% Wilson disease and all were anti-HCV negative. Aetiology remained uncertain in 44% cases.<sup>16</sup> In another study from a tertiary care centre in Eastern India, 175 patients were evaluated for aetiology. A total of 62 (35.4%) patients had HBV related CLD followed by HCV in 17/114 (14.9%) cases. Autoimmune hepatitis, Wilson disease and alcohol were the causative factors in 5 (2.8%), 5 (2.8%) and 3 (1.7%) patients respectively. No aetiology could be found in 18/114 (15.8%) patients.<sup>17</sup> The high incidence of hepatitis C infection in our study could be due to the fact that 16 out of 22 patients of viral hepatitis (72.7%) had history of blood transfusions.

Metabolic liver disease constitutes a significant proportion of childhood chronic liver diseases in our country. In our study metabolic liver disease was the second largest group following viral hepatitis which represented 15% of total patients. This included glycogen storage disease and Wilson disease. Our finding is supported by a survey conducted in India, which showed Metabolic liver diseases in 8 to 43% of the reported chronic liver diseases and Wilson disease was the most frequently diagnosed metabolic liver disease.<sup>18</sup>

The causes of liver disease in paediatric patients vary with age, such as biliary atresia and idiopathic neonatal hepatitis are observed only at birth or shortly thereafter. In an infant biliary atresia, TORCH infections and glycogen storage disorders are commonly

found. Conversely, viral hepatitis and Wilson disease are commonly seen in older children.

## CONCLUSION

Viral hepatitis is the leading cause of chronic liver disease in children, among which prevalence of chronic Hepatitis C was highest. Majority of children with Hepatitis C infection had history of blood transfusions in the past, therefore need for proper blood screening should be emphasised to curtail its prevalence.

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