

PATTERN OF CHRONIC LIVER DISEASE IN CHILDREN IN A TERTIARY CARE HOSPITAL

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Abstract: *The study aimed to identify the different signs, symptoms, and causes of chronic liver disease in children. The study involved patients between the ages of 1 and 12 years who were suspected of having chronic liver disease, excluding those with acute liver disease, congenital anomalies, and liver transplant recipients. The study was conducted in the Department of Pediatrics at Pak Emirates Military Hospital in Rawalpindi from September 2023 to December 2023. The results of the study showed that the most common causes of chronic liver disease in the patients were progressive familial intrahepatic cholestasis, followed by glycogen storage diseases, Hepatitis C, Wilson's disease, and Hepatitis B. Jaundice, abdominal distension, peripheral swelling, ascites, hepatomegaly, and splenomegaly were the most common symptoms of chronic liver disease. Some patients also suffered from variceal bleeding and hepatic encephalopathy. In conclusion, the study found that chronic liver disease in children from Pakistan has a diverse range of causes and symptoms.*

Keywords: Causative Aetiologies, Children, Chronic Liver Disease, Signs and Symptoms

Introduction

Chronic liver disease (CLD) is characterized by the simultaneous process of progressive destruction and decreasing regeneration of the liver parenchyma of at least six months duration, which leads to the replacement of liver tissue by fibrosis/scarring, culminating in cirrhosis (Poudel et al., 2023; Sardar Sr et al., 2022). These changes are usually irreversible, and CLD is a significant cause of morbidity and mortality among adults, while the burden of disease in children is less clear (Moon et al., 2020).

The aetiologies of CLD in the pediatric population are quite different from those in adults, both in terms of diversity as well as frequency, and include genetic mutations/metabolic disorders (hemochromatosis, Wilson's disease, glycogen storage disease), viral infections (hepatitis B, C, CMV) and autoimmune diseases (autoimmune hepatitis, primary sclerosing cholangitis) (Fang et al., 2021; Matarazzo et al., 2022; Tahir et al., 2011). Due to the myriad reasons for CLD in children, how they present is also equally diverse, especially if such patients present for appropriate healthcare late (Poudel et al., 2023). Identifying the signs and symptoms and underlying aetiologies of CLD in pediatric patients is crucial for accurate diagnosis, timely management, and improved clinical outcomes. The etiology of the disease influences the prognosis and treatment of CLD. Thus, it is critical to assess the patient's initial presentation (Pinto et al., 2015). Moreover, studies in adults have shown a significant difference between males and females regarding demographics, clinical findings, and aetiologies of CLD, and it is worth investigating if such differences occur in children or not (Rubin et al., 2020; Sagnelli et al., 2018).

We conducted this study to determine the causes of CLD in the pediatric population, the clinical profile with which such patients present, and the differences in etiology, clinical signs, and symptoms across genders in this age group. Our study has the potential to contribute to our understanding of the features of CLD in a population that has hitherto been largely unstudied. If we find gender-specific differences in the present study, its findings may have important implications for such patients' diagnosis and management strategies. Additionally, our observations may be helpful to public health policies to reduce the burden of CLD in pediatric patients.

Methodology

This descriptive cross-sectional study was conducted between Sep 2023 and Dec 2023 in the Department of Paediatrics, Pak Emirates Military Hospital, Rawalpindi, on 50 pediatric patients diagnosed with chronic liver disease, selected via non-probability consecutive sampling. Informed consent was obtained from parents/guardians before the patient was enrolled in the study. The WHO sample size calculator was used to calculate the sample size, keeping a confidence level (1- α) of 95%, an absolute precision (d) of 0.05, and an anticipated population proportion (P) of 0.2, which were the proportion of pediatric patients with CLD suffering from Wilson's disease, from Dhole et al. (Dhole et al., 2015). The sample size came out to be 20, which we increased to 50 patients.

All children between the ages of 1 and 12 years who have reported suspected chronic liver disease, irrespective of the underlying pathology, were included. At the same time, all

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patients with acute liver disease, liver transplant recipients, and those with significant congenital anomalies were excluded.

All participants underwent a history and clinical examination upon enrollment in the study. Baseline investigations were done, such as complete blood counts and liver/renal function tests. This was followed by specific tests such as viral serologies, protein electrophoresis, α -fetoprotein levels, anti-nuclear antibody (ANA), anti-double stranded DNA antibody (dsDNA), anti-smooth muscle antibody (ASMA), anti-liver kidney microsomal antibody (LKM) VDRL, serum ferritin/ceruloplasmin levels, 24-hour urinary copper levels, slit lamp examination and magnetic resonance imaging (MRI) of the brain. A liver biopsy was performed if the patient had normal coagulation parameters and was warranted for diagnosis. The biopsy was an ultrasound-guided core biopsy needle reported on by a consultant histopathologist with a minimum of five years post-fellowship experience.

Data was analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows version 26, IBM Corp; Armonk, USA). Mean and SD was calculated for quantitative variables, namely age at presentation and duration of illness—qualitative variables like gender, signs and symptoms, and primary diagnosis.

Patients were grouped according to gender. Qualitative variables were compared across groups using the Chi-square/Fischer exact test. In contrast, quantitative variables were compared using the independent samples t-test/non-parametric tests, where appropriate, and a p-value of ≤ 0.05 was considered significant.

Results

Our study was based on a total sample of 50 patients with a mean age at presentation of 6.72 ± 2.64 years. Males accounted for 27 (54.0%) cases. The mean duration from onset of symptoms to enrollment in the study was 8.02 ± 2.90 months. Regarding the etiology of CLD, progressive familial intrahepatic cholestasis was seen most commonly, accounting for 21 (42.0%) cases, followed by glycogen storage diseases, which occurred in 10 (20.0%) cases. Hepatitis C was found in 7 (14.0%) cases, while 5 (10.0%) patients suffered from Wilson’s disease. Hepatitis B and autoimmune hepatitis affected 4 (8.0%) and 3 (6.0%) cases, respectively. Many patients remained undiagnosed and were labeled idiopathic: 10 (20.0%). The patient characteristics are displayed in Table I, where the variables are distributed according to the gender of the patients.

Table-I. Patient characteristics according to gender (n=50)

Variable	Male (n=27)	Female (n=23)	p-value
Gender	27 (54.0%)	23 (46.0%)	-
Age (years)	5.07 ± 1.90	8.65 ± 2.01	<0.001
Duration of Complaints (months)	8.00 ± 3.00	8.04 ± 2.84	0.958
Aetiology of Chronic Liver Disease			
Progressive Familial Intrahepatic Cholestasis	13 (48.1%)	8 (34.8%)	0.763
Glycogen Storage Diseases	6 (22.3%)	4 (17.4%)	
Hepatitis C	3 (11.1%)	4 (17.4%)	
Wilson’s Disease	3 (11.1%)	2 (8.7%)	
Hepatitis B	1 (3.7%)	3 (13.0%)	
Autoimmune Hepatitis	1 (3.7%)	2 (8.7%)	

Table II shows the data for the various signs and symptoms displayed by the patients at the time of diagnosis, divided according to gender. A total of 32 (64.0%) patients had jaundice at the time of presentation, 28 (56.0%) complained of abdominal distension, and 20 (40.0%) reported that they had significant peripheral swelling/edema. Ascites were detected clinically in 23 (46.0%) patients; 30 (60.0%)

patients had hepatomegaly, while splenomegaly was seen in 35 (70.0%) patients. A total of 9 (18.0%) patients presented with a variceal bleed, while 6 (12.0%) suffered from hepatic encephalopathy. Regarding blood counts, 39 (78.0%) patients suffered from anemia at presentation, while thrombocytopenia was seen in 37 (74.0%) patients.

Table-II. Signs and symptoms according to gender (n=50)

Variable	Male (n=27)	Female (n=23)	p-value
Jaundice	20 (74.1%)	12 (52.2%)	0.108
Abdominal Distension	16 (59.3%)	12 (52.2%)	0.615
Peripheral Oedema	11 (40.7%)	9 (39.1%)	0.908
Ascites	13 (48.1%)	10 (43.5%)	0.741
Hepatomegaly	13 (48.1%)	17 (73.9%)	0.064
Splenomegaly	18 (66.7%)	17 (73.9%)	0.577
Variceal Bleed	4 (14.8%)	5 (21.7%)	0.715
Hepatic Encephalopathy	3 (11.1%)	3 (13.0%)	1.00
Anaemia	21 (77.8%)	18 (78.3%)	0.967
Thrombocytopenia	20 (74.1%)	17 (73.9%)	0.990

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Discussion

CLD is a comparatively rare occurrence in children when compared to adults. While viral hepatitis is the most common aetiological factor in the latter population, our study demonstrates that CLD in the pediatric population can occur from a more varied spectrum of aetiologies and can present in a myriad number of ways.

Our study sample had a mean age at diagnosis of 6.72 ± 2.64 years. Sardar et al. reported that the mean age of presentation in their study was 4.42 ± 3.92 years, while Dhole et al. noted that most of the patients in their study were between 6 and 12 years of age (Sardar Sr et al., 2022). Some degree of variability in age is seen across our different studies, likely attributable to the differences in frequencies of different aetiological factors responsible for disease causation in these diverse populations (Pinto et al., 2015). Moreover, in CLD, the onset of symptoms lags far behind the onset of the disease process, particularly in children, which may also account for the late presentation of some children with congenital diseases causing CLD (Della Corte et al., 2016). Additionally, our study showed that males tended to present at an earlier age than females ($p < 0.001$), likely attributable to the antioxidant effect of oestradiol, which suppresses hepatic fibrosis, resulting in a delayed onset of symptoms in females (Shimizu and Ito, 2007).

Males were a slight majority in our study, accounting for 54.0% of our sample. Sardar et al. also reported a preponderance of male children in their study of CLD, 55.9%, while Dhole et al. also noted a male majority of 60.0% (Dhole et al., 2015). While the reasons for the propensity of males to develop CLD have been documented in adults (attributed to higher rates of alcohol consumption and viral infections), the reason for this increase in frequency in children is unclear and requires further study before conclusions can be drawn (Rubin et al., 2020).

In the current study, the most frequently encountered cause of CLD was progressive familial intrahepatic cholestasis, afflicting 42.0% of patients, followed by glycogen storage diseases (20.0%), Hepatitis C (14.0%) and Wilson's disease (10.0%). Less commonly, Hepatitis B (8.0%) and autoimmune hepatitis (6.0%) were the causative agents. In total, viral hepatitis accounted for 22.0% of cases, representing a significant disease burden. Sardar et al. also reported that chronic hepatitis B (22.8%) was the most common cause of CLD seen in their study, while idiopathic (16.9%) cases numbered the second highest. Less common causes included glycogen storage disorders (15.4%), Wilson's disease (10.3%), biliary atresia (7.4%), autoimmune hepatitis (5.1%), progressive familial intrahepatic cholestasis (5.1%), tyrosinemia (4.4%), galactosemia (2.9%) and Budd-Chiari syndrome (2.9%), frequencies and causes that were dissimilar to ours. Tahir et al. also reported an analogous distribution: viral hepatitis was the most common cause (36.7%), glycogen storage disease occurred in 8.3% of cases, while some patients also had biliary atresia (6.7%), and Wilson disease (6.7%) (Tahir et al., 2011). It is important to point out here that viral hepatitis is a rising cause of CLD in Pakistan, and such infections commonly occur in children who require frequent blood transfusions, such as those suffering from β -thalassaemia major (Ahmed et al., 2021; Zahoor et al., 2021). Other factors associated with a high risk of virus transmission may include social factors, such as unhygienic

practices of local barbers and the use of contaminated objects such as razors and scissors. However, this aspect of our study requires further research (Butt, 2015).

Among the symptoms at presentation, jaundice (64.0%) was the most common in our study, followed by a feeling of abdominal distension (56.0%) and peripheral edema/swelling (40.0%) in the current study. Dhole et al. also reported that jaundice (73.0%) was the most commonly encountered complaint of presentation, followed by abdominal distension (51.0%) and edema (30.0%) (Dhole et al., 2015). Hanif et al. reported that edema (44.0%) was their study's most commonly encountered complaint, followed by jaundice (37.0%) (Hanif et al., 2004). It can be concluded from these comparisons that jaundice, peripheral edema, and abdominal distension are frequently encountered findings in children suffering from CLD, and the clinician should remain aware of the potential for the presence of this disorder with such presentations.

Regarding clinical signs, the most common finding in the current study was splenomegaly (70.0%), followed by hepatomegaly (60.0%) and ascites (46.0%). Dhole et al. reported that splenomegaly and hepatomegaly were found in approximately two-thirds of their patients, while ascites occurred in about two-fifths (Dhole et al., 2015). Conversely, while Sardar et al. reported hepatomegaly in 45.6% of their study sample, only 7.4% had splenomegaly (Sardar Sr et al., 2022). In their study sample, Hanif et al. reported that splenomegaly (76.4%) and hepatomegaly (63.6%) were also common (Hanif et al., 2004). We believe the differences in splenomegaly between the quoted studies may be attributable to the underlying diagnosis and the stage of disease in which the patient has presented, and the absence of these findings does not necessarily preclude the presence of CLD.

Decompensated disease in the form of a variceal bleed (18.0%) or hepatic encephalopathy (12.0%) were less frequently seen in our study. In their research, Dhole et al. reported a similar figure of 28.0% of patients suffering from variceal bleeds (Dhole et al., 2015). Dehghani et al. reported that 44.6% of their sample of children with CLD presented with at least one episode of variceal bleeding, while 24.1% of patients presented with hepatic encephalopathy (Dehghani et al., 2007).

Many patients suffered from anemia (78.0%) and thrombocytopenia (74.0%) at the time of presentation in our study. Anaemia occurred in 56.0% of the Dhole et al. (Dhole et al., 2015) samples, while Hanif et al. reported that anemia was present in 94.5% of their study sample. Again, the underlying diagnosis may be associated with anemia. However, CLD itself is associated with anemia, the pathogenesis for which is multifactorial and may include nutrient deficiency, hemolysis, and hypersplenism (Gkamprela et al., 2017).

This study focused on a specific population of children who were the wards of armed forces personnel with CLD, which may not be representative of the broader population of children with liver disease in the country. It relied on a convenience sample of patients who reported to the hospital during a particular period, which may have introduced a selection bias. Moreover, patients may have received some form of initial treatment before enrollment, which may have altered their clinical picture. Our study did not explore the role of social and environmental factors in developing CLD in children, which may be significant contributors to the

disease burden and clinical picture. Lastly, the study did not look at the effect of other medical conditions that may have coexisted with CLD in our pediatric study sample, such as β -thalassemia major, which may have impacted our study results.

Conclusion

Chronic liver disease (CLD) is a common occurrence in Pakistan, particularly among children. It requires special attention and management from the treating clinician as it can be caused by various pathogenetic mechanisms. The most common cause of CLD is progressive familial intrahepatic cholestasis. However, other preventable aetiologies like viral hepatitis can also cause the disease. To control the disease frequency, targeted interventions such as adequate screening and preparation of blood transfusion products are required. However, diagnosing the disorder can be difficult as it may present in several ways due to the myriad causative aetiologies. Therefore, future research should focus on developing a diagnostic pathway for CLD in children to ensure timely and accurate diagnosis.

Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department Concerned.

Consent for publication

Approved

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Conflict of interest

The authors declared absence of conflict of interest.

Author Contribution

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Coordination of collaborative efforts.

Conception of Study, Development of Research

Methodology Design, Study Design,, Review of

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Methodology Design, Study Design,, Review of

manuscript, final approval of manuscript

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