

FREQUENCY OF CAUSES OF CHRONIC LIVER DISEASE IN CHILDREN

Syed Zubair Shah, Rahat Malik*, Syed Fahd Shah**, Sara Idrees***, Sania Hameed****

Combined Military Hospital Lahore/National University of Medical Sciences (NUMS) Pakistan, *Combined Military Hospital Jhelum/National University of Medical Sciences (NUMS) Pakistan, **Federal General Hospital Islamabad Pakistan, ***Armed Forces Institute of Radiology & Imaging (AFIRI)/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, ****Poly Clinic Islamabad Pakistan

ABSTRACT

Objective: To determine the etiology of chronic liver disease in children.

Study Design: Descriptive cross sectional.

Place and Duration of Study: Department of Paediatrics, Combined Military Hospital Lahore, from Jun 2014 to Dec 2014.

Material and Methods: This is a descriptive cross sectional study conducted at department of Paediatrics, Combined Military Hospital Lahore from 1st June 2014 to 31st December 2014. It included 150 consecutive paediatric patients (1-14 years) with chronic liver disease.

Results: Out of 150 children 95 (63.33%) were male and 55 (36.66%) were females. The mean age of the children included in the study was 7.2 ± 4.6 years and the age range was 1 year to 14 years. Viral hepatitis (61, 40.67%) was the commonest cause of the liver disease followed by glycogen storage disease (11, 7.33%) and Wilson's disease in 13 (8.6%).

Conclusion: There are various causes of chronic liver disease in children most common being hepatitis B & C infection. The early identification of etiology of chronic liver disease in children is of cardinal importance for optimal management of these cases.

Keywords: Autoimmune Hepatitis, Neonatal Jaundice, Wilson's disease.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Chronic liver disease is one of the most significant causes of morbidity and mortality in paediatric patients. The severity is variable. The diseased child may have only raised liver enzymes as evidence of liver disease or may have full sign and stigmata of chronic liver disease¹. Chronic liver disease of various etiologies can progress into liver failure and end-stage liver disease. Hepatocellular insufficiency might lead to secondary failure of other organs such as the kidneys, lungs, the gastrointestinal tract and finally the central nervous system².

There are variable etiologies of chronic liver disease in children according to age of the patients. It includes a broad spectrum of disorders such as infections, developmental abnormalities, metabolic and neoplastic disorders

that finally result in hepatic dysfunction and cirrhosis³.

The outcome of the chronic liver disease depends on the cause of the liver disease. It is imperative that etiology of the chronic liver disease in children must be determined. It needs clinicopathological assessment of the child which includes detail history, examinations and various investigations⁴.

There are limited studies conducted in this age group in our set up. We conducted this study to establish the causes of the chronic liver disease in our paediatric patients in our set up. For identifying the cause and to make local guidelines that will help in classifying our paediatric patients with chronic liver disease and their management.

PATIENTS AND METHODS

This descriptive cross sectional study was conducted at the Department of Paediatrics, Combined Military Hospital, Lahore. We used WHO calculator for sample size and included

Correspondence: Dr Syed Zubair Shah, House No 432, Street No 105 I-8/4 Islamabad Pakistan (Email: zubair2174@yahoo.com)

Received: 16 Jun 2016; revised received: 07 Dec 2016; accepted: 08 Dec 2016

consecutive 150 paediatric patients from outdoor clinic and emergency department for 6 months from 1st June 2014 to 31st December 2014. All paediatric patients (1-14 years) who had chronic liver disease of both gender presented were included in the study. Children with metastatic liver disease were excluded from study. All patients and their parents were informed about inclusion in the study and well understood informed consent was obtained. The relevant data were collected on a structured proforma. A detailed history, thorough clinical examination was performed. The laboratory tests included complete blood picture with retic count, hepatitis B surface antigen, antibody to hepatitis C, liver

disease were calculated. Frequency and percentage were calculated for gender, jaundice, vomiting, hematemesis, abdominal distension, itching, weight loss, fever, stool color, steatorrhea, blood transfusion, pallor, edema, spider naevi, bruise, ascites, hepatomegaly, splenomegaly, caput medusae, encephalopathy and etiology of the chronic liver disease.

RESULTS

This study included 150 children. Out of these 150, 95 (63.33%) were males and 55 (36.66%) were females. The mean age of the children included in the study was 7.2 ± 4.6 years and the age range was 1 to 14 years. Out of these 150

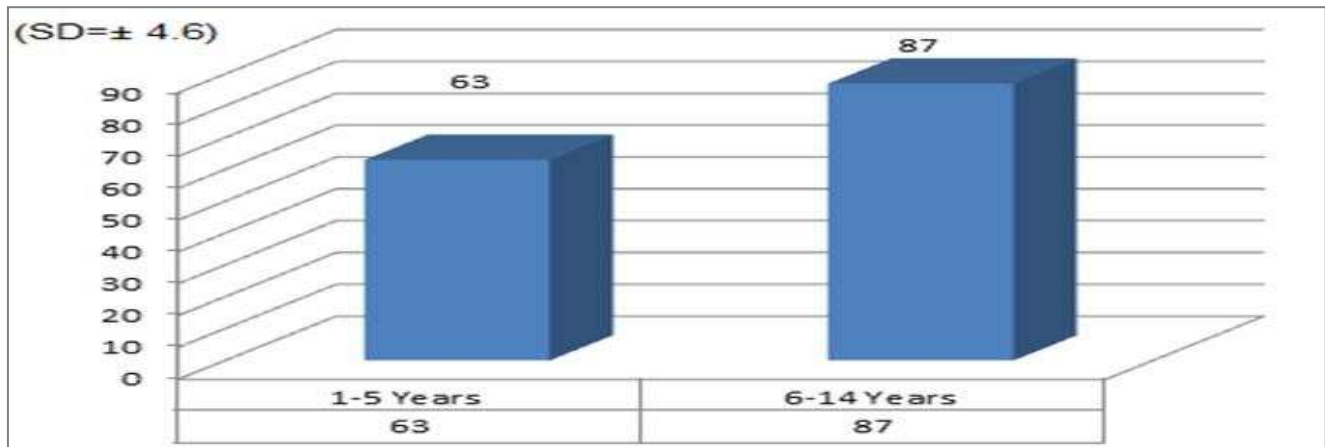


Figure: Age distribution (n=150).

functions test, serum albumin, prothrombin time, antinuclear antigen and ultrasound abdomen. Slit lamp examination of eyes for Keyser-Fleischer ring was performed at ophthalmology department, 24 hours urinary copper estimation with and without pencillamin challenge, alpha 1 antitrypsin were also performed. Liver biopsy was performed where required to establish the etiology of chronic liver disease. All investigations were done at Pathology department of CMH Lahore. Specialized test were sent to Armed Forces Institute of Pathology, Rawalpindi.

SPSS version 17 was used to enter and analyze gathered data. Mean and standard deviation for age and duration of chronic liver

children 63 (42%) were between 1 and 5 years and 87 (58%) were between 6-14 years of age. Age wise distribution of the patients is shown in figure. The detail of patients symptomatology are shown in table-I, findings of clinical examination are shown in table-II, investigations results are shown in table-III, and the frequency of different causes of chronic liver disease in children are shown in table-IV.

DISCUSSION

Liver disease in child is labelled as chronic if the duration of liver disease is more than 3 months and by the presence of characteristic of chronic liver disease which include, hepatosplenomegaly, clubbing and spider naevi⁵. It includes a broad spectrum of disorders such

as infections, developmental abnormalities, metabolic and neoplastic disorders that finally result in hepatic dysfunction and cirrhosis¹.

Some of these causes of chronic liver disease in children are more common in different ages of childhood. Biliary atresia and neonatal hepatitis are the two most common causes of cholestasis in

atresia, Alagille's syndrome, congenital liver fibrosis, choledochal cyst⁸⁻¹⁰.

Infectious diseases may be caused by bacteria, viruses or parasites, for example: hepatitis B, hepatitis C, cytomegalovirus and Epstein-Barr virus¹¹. Inborn errors of metabolism are defects in the synthesis, turnover, breakdown

Table-I: Frequency of different symptomatology (n=150).

Symptoms	Number of Patients	Percentage of patients
Jaundice:	150	100
Vomiting:	70	46.67
Hematemesis:	10	6.67
Abdominal Distension:	35	23.33
Itching:	40	26.67
Weight loss:	100	66.67
Fever:	80	53.3
Stool color:	50	33.33
Steatorrhoea	20	13.33
Transfusion:	40	26.67
Family History:	10	63.33

Table-II: Frequency of examination findings (n=150).

Sign	Number of Patients	Percentage of Patients
Jaundice:	150	100
Pallor:	84	56
Edema:	30	20
Spider Naevi:	10	6.67
Bruise	50	33.33
Ascites:	40	26.67
Hepatomegaly:	70	46.67
Splenomegaly:	35	23.33
Caput Medusae:	5	3.33
Encephalopathy:	10	6.67
Kayser Fleischer Ring:	17	11.33

the neonatal period. Acetaminophen intoxication and Wilson's disease are common in the older children. In areas where hepatitis B & C infections are prevalent these are common etiologies of chronic liver disease in the children^{6,7}.

Abnormal development includes micro- and macroanatomical anomalies in the structure of the hepatobiliary system caused during the fetal or early neonatal period, for example: biliary

and elimination of amino acids, proteins, carbohydrates and lipids, causing acute or chronic intoxication by some intermediary product or leading to a defective or absent function. These patients may have hepatic or extrahepatic symptoms. Examples of metabolic diseases with hepatic presentation are tyrosinemia, Wilson's disease, progressive familial intrahepatic cholestasis (PFIC), Aagenaes syndrome, glycogen storage disease, non-alcoholic steatohepatitis (NASH)¹²⁻¹⁴.

Immune-mediated disorders are diseases caused by an inappropriately targeted reaction of the immune system, for example: autoimmune hepatitis, sclerosing cholangitis, neonatal extrahepatic vessels or focal changes in the blood flow, for example portal vein thrombosis, portal vein stenosis, porto-systemic shunt, as well as sickle cell disease, and congestive heart failure.

Table-III: Result of laboratory investigations (n=150).

	Number of Patients	Percentage of patients
Low Haemoglobin:	107	71.33
High TLC	67	44.67
Raised S. Bilirubin	150	100
High ALT	110	73.33
High AST	115	76.67
Raised ALP	13	8.67
ANA Positive	5	3.33
Deerranged PT	28	18.67
Hepatitis B	20	13.3
Hepatitis C	41	27.33
TORCH	7	4.67
24hrs Urinary Copper estimation:	17	11.3
USG sign of CLD	139	92.67
Endoscopic varices	85	55.55

Table-IV: Etiology of chronic liver disease in children (n=150).

	Number of Patients	Percentage of patients
Aetiology		
Viral Hepatitis	61	40.67
Uncertain aetiology	28	18.66
Wilson's disease	13	8.66
Glycogen storage disease	11	7.33
Drug induced hepatitis	11	7.33
TORCH infection	7	4.67
Progressive Familial Intra Hepatic cholestasis	6	4
Chronic granulomatous disease	5	3.33
Autoimmune hepatitis	5	3.33
Hepatoma	3	2

systemic lupus erythematosus, graft versus host disease¹⁵⁻¹⁸.

Xenobiotic-induced liver injury is liver damage caused by pharmaceutical, chemical, herbal or nutritional agents, for example: Reye's syndrome, acetaminophen/ paracetamol-induced damage, venoocclusive disease (VOD), total parenteral nutrition associated cholestasis¹⁹⁻²².

Vascular disorders are symptoms caused by changes in blood flow in intra- and/or

Neoplasms include benign or malignant tumors (primary or metastases) for example: hepatoblastoma, hepatocellular carcinoma, adenoma²³⁻²⁶.

In our study we found that viral hepatitis was the cause of the liver disease in 40.66% paediatric patients. Hepatitis C infection was the cause of chronic liver disease in 27.33% of paediatric patients while chronic liver disease due to hepatitis B was in 13.3% children. In a

study conducted by Tahir et al showed that viral hepatitis was cause of chronic liver disease in 36.7% of paediatric patients¹. In our study in 18.66% of children the cause of chronic liver disease could not be determined so the idiopathic group made the second highest group in our study. Tahir et al concluded the same result and showed that the second most frequent cause of chronic liver disease¹. Wilson's disease was the third most common cause of liver disease in 8.66% of children. In an Iranian study by Monajemzadeh showed that secondary hemochromatosis in patients with thalassemia composed the most prevalent diagnoses (17.5%) of chronic liver disease in the children²⁷. While the European studies point more towards the autoimmune disease as the etiology of chronic liver disease^{28,29}.

Current studies show that non-alcoholic fatty liver disease is becoming common cause of chronic liver disease and estimated to affect 10%-20% children with chronic liver disease³⁰, but still a current study by the Behairy shows the hepatitis is the commonest cause of the chronic liver disease³¹.

The studies have shown that the causes of the chronic liver disease vary according to geographic locations. In our study viral hepatitis was the leading cause of the chronic liver in paediatric population. In third world countries hepatitis C and B infections are common cause of chronic liver disease not only in the adult population but in paediatric population as well.

CONCLUSION

There are various causes of chronic liver disease in children which need complete workup for etiological diagnosis. The early identification of etiology of chronic liver disease in children is of cardinal importance for optimal management of these cases.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Tahir A, Malik FR, Ahmad I, Akhtar P. Aetiological factors of chronic liver disease in children. *J Ayub Med Coll Abbottabad* 2011; 23: 12-4.
2. De Bruyne R, Van Biervliet S, Vande Velde S, Van Winckel M. Clinical practice: neonatal cholestasis. *Eur J Pediatr* 2011; 170: 279-84.
3. Sharif K, McKiernan P, De Ville de Goyet J. Mesoportal bypass for extrahepatic portal vein obstruction in children: close to a cure for most! *J Pediatr Surg* 2010; 45: 272-6.
4. Grimaldi, C, De Ville de Goyet J, Nobili V. Portal hypertension in children. *Clin Res Hepatol Gastroenterol* 2012: 260-1.
5. Benjamin L, Frederick J. Autoimmune and chronic hepatitis. In: Kliegman R, Behrman R, Jensen H, Stanton B. *Nelson Text Book of Paediatrics*. Philadelphia:Saunders 2007: 1698.
6. Hanif M, Raza J, Qureshi H, Issani Z. Etiology of Chronic Liver Disease in Children. *J Pak Med Assoc* 2004; 54: 119-22.
7. Indolfi G, Bartolini E, Olivito B, Azzari C, Resti M. Autoimmunity and extrahepatic manifestations in treatment-naïve children with chronic hepatitis C virus infection. *Clin Dev Immunol* 2012; 2012: 785627.
8. Garazzino S, Calitri C, Versace A, Alfarano A, Scolfaro C, Bertaina C, et al. Natural history of vertically acquired HCV infection and associated autoimmune phenomena *Eur J Pediatr* 2014; 173: 1025-31.
9. Hartley JL, Davenport M, Kelly DA. Biliary atresia. *Lancet* 2009; 374: 1704-13.
10. Fitzpatrick E, Quaglia A, Vimalasvaran S, Basso MS, Dhawan A. Transient elastography is a useful noninvasive tool for the evaluation of fibrosis in paediatric chronic liver disease. *J Pediatr Gastroenterol Nutr* 2013; 56: 72-6.
11. Mazumder MW, Karim MB, Rukunuzzaman M. Penicillamine challenge test in the diagnosis of Wilson's disease. *Mymen singh Med J* 2014; 23: 489-95.
12. Hicks J, Wartchow E, Mierau G. Glycogen storage diseases: A brief review and update on clinical features, genetic abnormalities, pathologic features, and treatment. *Ultrastruct Pathol* 2011; 35: 183-96.
13. Lebensztejn DM, Bialokoz-Kalinowska I, Klusek-Oksiuta M, Tarasów E, Wojtkowska M, Kaczmarski M. Serum fetuin A concentration is elevated in children with non-alcoholic fatty liver disease. *Adv Med Sci* 2014; 59: 81-4.
14. Motamed F, Monajemzadeh M, Seifirad S, Ashrafi M, Rasti A, Mahjoub F. Liver storage disease in Iran: A ten year study of liver biopsies in Children Medical Center Hospital in Tehran-Iran. *Hepat Mon* 2011; 11: 652-5.
15. Elfaramawy AA, Elhossiny RM, Abbas AA, Aziz HM. HLA-DRB1 as a risk factor in children with autoimmune hepatitis and its relation to hepatitis A infection. *Ital J Pediatr* 2010; 36: 73.
16. Di Giorgio A, Bravi M, Bonanomi E, Alessio G, Sonzogni A, Zen Y, et al. Fulminant hepatic failure of autoimmune aetiology in children. *J Pediatr Gastroenterol Nutr* 2015; 60(2): 159-64.
17. Bakula A, Socha P, Klauedel-Dreszler M, Karolczyk G, Wozniak M, Rutynowska-Pronicka O, et al. Giant cell hepatitis with autoimmune hemolytic anemia in children: Proposal for therapeutic approach. *J Pediatr Gastroenterol Nutr* 2014; 58: 669-73.
18. Pratico AD, Salafia S, Barone P, La Rosa M, Leonardi S. Type II Autoimmune hepatitis and small duct sclerosing cholangitis in a seven years old child: An Overlap Syndrome? *Hepat Mon* 2013; 13: e14452.
19. Invernizzi P, Alessio MG, Smyk DS, Lleo A, Sonzogni A, Fabris L, et al. Autoimmune hepatitis type 2 associated with an

- unexpected and transient presence of primary biliary cirrhosis-specific antimitochondrial antibodies: A case study and review of the literature. *BMC Gastroenterol* 2012; 12: 92.
20. Gargouri L, Mnif L, Safi F, Turki F, Majdoub I, Maalej B, et al. Type 2 autoimmune hepatitis overlapping with primary sclerosing cholangitis in a 10-year-old boy. *Arch Pediatr* 2013; 20: 1325-28.
 21. Cantez MS, Gerenli N, Ertekin V, Güllüoğlu M, Durmaz Ö. Hepatoportal sclerosis in childhood: Descriptive analysis of 12 patients. *J Korean Med Sci* 2013; 28: 1507-11.
 22. El-Shabrawi MH, Kamal NM, Halawa FA, El-Guindi MA, Sobhy GA. Serum superoxide dismutase activity in acute and chronic paediatric liver diseases. *Arab J Gastroenterol* 2014; 15: 72-5.
 23. Englesbe MJ, Kubus J, Muhammad W, Sonnenday CJ, Welling T, Punch JD et al. Portal vein thrombosis and survival in patients with cirrhosis. *Liver Transpl* 2010; 16: 83-90.
 24. Fasel JH. Portal venous territories within the human liver: an anatomical reappraisal. *Anat Rec (Hoboken)* 2008; 291: 636-4.
 25. Gana JC, Turner D, Mieli-Vergani G, Davenport M, Miloh T, Avitzur Y et al. A clinical prediction rule and platelet count predict esophageal varices in children. *Gastroenterology* 2011; 141: 2009-16.
 26. Malinowska I, Machaczka M, Popko K, Siwicka A, Salamonowicz M, Nasilowska-Adamska B. Hemophagocytic syndrome in children and adults. *Arch Immunol Ther Exp (Warsz)* 2014; 62: 385-94.
 27. Monajemzadeh M, Shahsiah R, Vasei M, Tanzifi P, Rezaei N, Najafi M et al. Alpha 1 antitrypsin deficiency in infants with neonatal cholestasis. *Iran J Pediatr* 2013; 23: 501-7.
 28. Brissos J, Carrusca C, Correia M, Cabral J. Autoimmune hepatitis: trust in transaminases. *BMJ Case Rep* 2014; 23: bcr2014203869.
 29. Al-Hussaini AA, Alzahrani MD, Alenizi AS, Suliman NM, Khan MA, Alharbi SA, et al. Autoimmune hepatitis related autoantibodies in children with type 1 diabetes. *Diabetol Metab Syndr* 2014; 6: 38.
 30. Temple JL, Cordero P, Li J, Nguyen V, Oben JA. A Guide to non-alcoholic fatty liver disease in childhood and adolescence. *Int J Mol Sci*. 2016; 17(6): E947.
 31. Behairy Bel S, Sira MM, Zalata KR, Salama el-SE, Abd-Allah MA. Transient elastography compared to liver biopsy and morphometry for predicting fibrosis in pediatric chronic liver disease: Does etiology matter? *World J Gastroenterol*. 2016; 22(16): 4238-49.
-