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Chronic Liver Diseases in Children: Clinical Spectrum and Etiology

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ABSTRACT

Objectives: To study the magnitude of chronic liver disorders in children attending the only tertiary care hospital. To study the spectrum of chronic liver disorders in children.

Study design: Prospective observational study

Material and methods: The study included prospective (July 2007 to Dec.2008) analysis of all children < 18 yrs with chronic liver disorders. A total of 94 children with confirmed diagnosis of chronic liver disease were included in the study. The diagnosis of all liver diseases was based on established clinical and diagnostic criteria. Severity of chronic liver disease was defined using Child grading.

Results: Mean age of patients was 10.4 ± 4 yrs with a range of 1-18 yrs. Jaundice(75%), ascites (64%),encephalopathy (29%) were presenting symptoms in chronic liver disease patients indicating decompensation at presentation .Features of portal hypertension were seen in 65%.Etiology was found to be HBV in 18%, Wilsons disease in 16% ,HCV in 6.4%, autoimmune in 5.3% and alpha-1 antitrypsin deficiency in 1.1% and no etiology could be found in 52%(cryptogenic) .In acute liver diseases HAV was cause in 43%, HBV in 27% and HEV in 7% cases.

Conclusion: Chronic liver diseases in our set up are mainly constituted by post hepatic, metabolic and cryptogenic etiology .Lack of advanced biochemical and specific diagnostic tools resulted in high percentage of cryptogenic cirrhosis our study.

Introduction

A variety of liver disorders are encountered in children and they constitute a good proportion of hospital admissions. Liver diseases are one of the significant causes of morbidity and mortality in this age group and includes a broad spectrum of disorders such as infections, developmental abnormalities, genetic and metabolic disorders that finally result 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 disorders. The pattern of liver diseases especially with genetic and metabolic basis show variation in different geographical locations. These reported variations are attributable to different factors, eating habits, socio-economic factors and other reasons. There is emergence of relatively newer liver disorders in children like NAFLD (non-alcoholic fatty liver disease) that were rare in our subcontinent especially in children. There is therefore a continuing need for studies on various aspects of liver diseases in different communities and environments.

Acute and chronic liver diseases constitute the majority of liver disorders in children. The etiologic profile of chronic liver diseases also shows geographical variation. Where as hepatitis virus is leading cause (96.6%,75.4%HBV) of chronic liver disease in South East Asia, middle east and some of other asian countries (Zhang *et al*)¹. It is predominantly due to high prevalence of hepatitis in general population in these countries.

Some of the biliary disorders such as biliary atresia present as chronic liver disease in regions where diagnosis is delayed beyond twelve weeks. Such children often present with cirrhosis and portal hypertension. Likewise in some regions of world where oriental cholangiohepatitis (OCH) is endemic can cause secondary

biliary cirrhosis, portal hypertension in children if left untreated. The profile of metabolic diseases producing chronic liver disease has not been well documented from developing and underdeveloped countries because of lack of diagnostic facilities in these regions. Therefore the metabolic diseases causing chronic liver disease do not figure well in the studies reported from these underdeveloped countries.

It is worth mentioning that a chronic liver disease named Indian childhood cirrhosis which was a predominant disease in children in Indian subcontinent has been vanishing due to adaption of preventive measures. This disease used to kill affected children before 5 years of age and is now rarely reported from India (*Bhave SA et al*)². Some of the parasitic liver disease such as hydatid, schistosomiasis continue to form a part of liver disease in endemic belts.

In recent years, non-alcoholic steatohepatitis (NASH) has been described as a common cause of liver disease in children which is related to obesity, hyperinsulinemia, insulin resistance, and liver cell injury from free fatty acid toxicity or other oxidant stress (*Roberts EA*)³. Overall prevalence of fatty liver in children is 2.6-12.5% (*Tominaga K et al*)⁴.

The department of Gastroenterology Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir regularly admits children with suspected hepatobiliary and pancreatic disorders for management. Our institution is only speciality-oriented medical centre in Kashmir and serves an indigent population of about 4.2 million people. It is the only centre in Kashmir having facilities for therapeutic endoscopic procedures related to gastrointestinal and biliary diseases. Consequently we are referred patients from whole Kashmir.

Materials and Methods

This study was conducted in the department of Gastroenterology Sher-i-Kashmir Institute of Medical sciences Srinagar Kashmir India After institutional ethical approval. This study included prospective (from July 2007 to Dec. 2008) analysis of all children aged <18 years with liver disorders.

For patients registered during prospective period, a detailed history and clinical examination was performed in all children with suspected liver disorders as per proforma. All patients underwent routine laboratory investigations and ultrasound scan of abdomen. Complete blood count, serum biochemistry including complete liver function tests, coagulogram, hepatitis serology were sent. In patients with suspected chronic liver disease in addition to baseline investigations, ANA, ceruloplasmin level, iron profile, 24 hr urinary copper and slit lamp eye examination for Kayser-Fleischer ring were done. Alpha-1-antitrypsin levels were sent in those patients in whom no etiology was found. Upper gastrointestinal endoscopy was done for esophageal varices. Liver biopsy was done in those cases where there was no contraindication and parents gave written consent. Severity of chronic liver disease was defined using Child grading.

Blood samples were drawn by venipuncture, and after clotting serum was immediately separated by centrifugation. Serum bilirubin was determined by method of Malloy & Evelyn. Alanine transferase (ALT) by method of Reitman and Frankel. Total proteins by Biuret method, Albumin by method of Daumas and Biggs, total globulins by Goldenberg and Drewan, HBsAg by Kit method, Anti-HCV by ELISA and prothrombin time by Quick.

Liver biopsy was done using automatic biopsy gun (tru-cut) sometimes under general anaesthesia.

Upper gastrointestinal endoscopy was done using pediatric endoscope (Pentax GIF24V scope) for both diagnostic as well as therapeutic (sclerotherapy, endoscopic variceal ligation). The grading of esophageal varices was done as per previously defined criteria (Zarger SA *et al*)²⁶.

Grade 0: No definite varices visible.

Grade 1: One or more varices less than 4mm diameter and less than 4 cm in length.

Grade 2: Multiple varices 4-10 cm in extent.

Grade 3: Multiple varices more than 10 cm long.

ERCP (endoscopic retrograde cholecysto-pancreatography) was done whenever indicated using Pentax ED3480TK scope.

Informed consent for all invasive procedures was taken from parents/guardian. The diagnosis of all liver diseases was based on established clinical and diagnostic criteria.

Statistical Analysis

Summary statistics for quantitative data will be mean and standard deviation (SD) presented as "mean (SD)". Quantitative data between two treatment groups will be compared with the use of Student t-test for parametric data and Mann-Whitney U test for non-parametric data (hospital stay and medical costs). Pearson chi-square test or Fisher's exact test were used for categorical data. All p values will be two tailed; p values <0.05 will be considered statistically significant. All statistical analysis was performed with statistical software program (SPSS10).

Discussion and Review

This study was conducted in the department of Gastroenterology Sher-i-Kashmir Institute of Medical sciences Srinagar Kashmir India. This study included prospective (from July 2007 to Dec. 2008) analysis of all children aged <18 years with liver disorders.

The present study has number of limitations. Firstly, many patients with chronic liver disease were missed because such patients were treated outside by general practitioners and other hospitals. Therefore the present study underscores the number of with chronic liver disease. Second, due to non-availability of advanced biochemical laboratory and investigation rarer metabolic disorders were missed. Although metabolic profile including Wilsons, alpha-1-antitrypsin levels, autoimmune, glycogen storage disorders etc. were screened, patients with rarer metabolic disorders might have been missed due to non-availability of such investigations in our set up.

In our study Chronic liver disease was diagnosed in 94 children. This is in accordance with Yachha *et al*⁵ This finding is in contrary to Ramakrishna *et al*⁶ (20%), Obafuna *et al*⁷ 25% and Burki *et al*⁸ (0%). The mean age of chronic liver disease patients in our study was 10.4 ± 4.0 years which is higher than 5 years as reported by Al-Lawati *et al*⁹, 4.5 years in study conducted by Mehnaz A¹⁰. And 8.28 years by Hanif *et al*¹¹. The reason for higher mean age in our study was that neonates were not admitted in our department. The male (42, 45%): female (52, 55%) ratio in our study was slightly favourable to females which is in contrary to other studies reporting a male predominance Akinbami *et al*¹² (male 56%) and Hanif *et al*¹¹ (male 58%). Jaundice (75%), ascites (64%) and encephalopathy (29%) were presenting symptoms in chronic liver disease patients in our study as

reported by Dangwal *et al*¹³. This was lower than reported by Hanif *et al*¹¹, (80%), and higher than as reported by Mehnaz A¹⁰. And Malik *et al*¹⁴. This high incidence of ascites, jaundice and encephalopathy in our study indicates fairly advanced liver disease with decompensation at presentation. Hepatomegaly was seen in 22% cases while in remaining liver was shrunken or normal in size signifying that liver may be shrunken, normal or enlarged in size depending upon stage of chronic liver disease. Ultrasonographic splenomegaly and dilated portal vein was seen in 65% cases denoting portal hypertension as reported by Hanif *et al*¹¹ and Dangwal *et al*¹³ reported. In our study 39 (42%) were in Child-Pugh grade-C, 33 (35%) in grade-B and 22 (24%) in grade-A further indicates fairly advanced liver disease with decompensation. These results were in accordance with Hanif *et al*¹¹, but in contrary to Dangwal *et al*¹³. Out of 94 patients 44 patients had varices grade-1 in 5 grade-2 in 25, grade-3 in 11 and grade-4 in 3. Upper gastrointestinal bleed history was present in 16% cases of liver disease indicating that these patients have esophageal varices without history of GIT bleed. Prophylactic beta blockers and endoscopic ligation can prevent bleeding. On evaluation we found that no etiology could be found in 50 patients (52%), HBV (18%), Wilson (16%), HCV (6.4), autoimmune (5.3%), alpha-1-antitrypsin deficiency (1.1%). Similar pattern was noticed by Murtaza *et al*¹⁵, Yachha *et al*¹⁶ and Rajeshwari, Gogia¹⁷ while as Al-Lawati *et al*⁹ and Hanif *et al*¹¹ noticed a different pattern.

In this study HBV was commonest etiologic factor causing CLD in 18% patients as observed by Mehnaz A¹⁰. (18%), while as Malik *et al*¹⁴ (47%) and Murtaza *et al*¹⁵ (32%) reported higher incidence. Dangwal *et al*¹³ reported lower incidence of 12%.

HCV was causative agent in about 6.4% cases of CLD is same as observed by Murtaza *et al*¹⁵ (8.5%), Dangwal *et al*¹⁵ (7.5%) while Hanif *et al*¹¹ reported no case with HCV infection.

In 16% patients cause of CLD was identified as Wilson's disease. Similar results were seen in other studies by Hanif *et al*¹¹ (16%), Murtaza *et al*¹⁵ (17%) and Mehnaz A¹⁰, however Yachha *et al*¹⁶ (21%), Zhang *et al*¹ (20%) reported higher incidence. The high incidence of Wilson's disease in our and other local studies is alarming and has remained under diagnosed so should be searched for in any child in whom etiology remains undetermined otherwise.

In present study autoimmune hepatitis was established as etiology in 5 (5.3%) patients of CLD as shown by Yachha *et al*¹⁶ (4%), Rafeey *et al*⁸ (5.6), Zhang *et al*¹ (7%). Other authors showed a higher incidence like Hanif *et al*¹¹ (16%), Mehnaz A¹⁰ (1.2%), Choudhari *et al*¹⁹ (1.7%) and Murtaza *et al*¹⁵ (2%) reported a lower incidence.

Another autosomal recessive disorder, alpha-1-antitrypsin deficiency was found to be cause in 1(1.1%) patient. Studies conducted by Murtaza *et al*¹⁵ and Khanna *et al*²⁰ reported no case of alpha-1-antitrypsin deficiency as cause of CLD whereas Yachha *et al*¹⁶ (3.5%) and Odeivre *et al*²¹ (4.7%) showed its presence. It is a rare cause of CLD and liver transplant is only modality of treatment, Carlton *et al*²².

Fifty percent of CLD patients in our study remained idiopathic. The incidence in other studies are as follows, Murtaza *et al*¹⁵ (42.5%), Hanif *et al*¹¹ (44%), Yachha *et al*¹⁶ (40%), Malik *et al*¹⁴ (26.7). This high frequency of idiopathic CLD reflects our financial constrains as well as non-availability of advanced and specific diagnostic tools to find out the underlying cause of CLD. The frequency of idiopathic CLD varies in different parts of world e.g.

United Kingdom it is about 5-10%. As specific diagnostic tools appear, percentage of idiopathic CLD falls, like advent of HbsAg and anti-HCV transferred many previously labeled idiopathic CLD. Still there remains significant percentage of patients as idiopathic and etiological diagnosis in these patients awaits development of specific diagnostic tools.

Conclusions

Chronic liver disease was diagnosed in a total of 94 cases the mean age of chronic liver disease patients was 10.4 ± 4.0 years. Jaundice (75%), ascites (64%) and encephalopathy (29%) were presenting symptoms. This high incidence of ascites, jaundice and encephalopathy in our study indicates fairly advanced liver disease with decompensation at presentation. Out of 94 CLD patients 39 (42%) were in Child-Pugh grade-C, 33 (35%) in grade-B and 22 (24%) in grade-A further indicates fairly advanced liver disease. 44 patients had varices grade-1 in 5 grade-2 in 25, grade-3 in 11 and grade-4 in 3. Upper gastrointestinal bleed history was present in 16% cases of liver disease. No etiology could be found in 50 patients (52%), HBV in 18%, Wilson in 16%, HCV in 6.4%, autoimmune in 5.3% & alpha-1-antitrypsin deficiency in 1.1% cases of CLD. The high frequency of idiopathic CLD reflects our financial constrains as well as non-availability of advanced and specific diagnostic tools.

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