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Pattern of liver diseases among children attending the National Hospital Abuja, Nigeria

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Abstract: *Background:* Diseases of the liver contribute to childhood morbidities and mortality. Early recognition and proper management of liver diseases can limit the progression to irreparable damage which requires liver transplant. However, there is scarcity of data in the pattern of liver disease in Nigerian children.

Objective: To describe the pattern of paediatric liver diseases among children seen at the National Hospital, Abuja.

Methods: A retrospective, descriptive study conducted at the Paediatric Gastroenterology, Hepatology and Nutrition (PGHAN) clinic and the Emergency Paediatric Unit (EPU) of National Hospital Abuja, over a 5-year period (2009 – 2014). The diagnosis of liver diseases was made from clinical and laboratory features. The data extracted from the retrieved hospital records were analyzed.

Results: Forty-two out of 52 documented cases were analyzed. The children were aged 2 months to 15 years with the mean of 7.24 ± 4.77 years. Twenty-six (62.0%) were aged >5 years ($p > 0.05$). They comprised 31 (73.8%) males and 11 (26.2%) females; 28 (66.7%) belonged to the lower

socioeconomic classes while 23 (54.8%) had various forms malnutrition. Common symptoms included jaundice (30; 71.4%), abdominal pain (17; 40.5%), fever (15; 35.7%), abdominal swelling (12; 28.6%) and bleeding (8; 19.0%). The signs included jaundice (30; 71.4%), hepatomegaly (16; 38.1%) and splenomegaly (8; 19.0%). Twenty-four (57.1%) had chronic viral infections while the others included neonatal hepatitis syndrome and biliary atresia (6; 14.3%), acute hepatitis (6; 14.3%) and chronic hepatitis of unidentified aetiology (4; 9.5%). Overall, the mean values of the liver enzymes and serum bilirubin were elevated while the mean values of total serum proteins and albumin levels were reduced. Five (11.9%) children improved and were discharged, 15 (35.7%) were lost to follow up with three deaths.

Conclusion: Risk factors associated with liver diseases in this study included age over 5 years and lower socio-economic classes. Jaundice was the commonest clinical presentation while the most common aetiology was chronic Hepatitis B virus infection.

Key words: Children, Liver Diseases, Pattern

Introduction

Diseases of the liver may be infective, metabolic, toxic, autoimmune, vascular or infiltrative in nature. With the long list of the various aetiologies of paediatric liver diseases, about ten diseases constitute approximately 95% of all cases of cholestasis, and of these, biliary atresia and neonatal hepatitis are responsible for more than 60%.¹ Diseases of the liver contribute significantly to childhood morbidity and mortality.^{2,3} The clinical presentation of liver diseases vary greatly between indi-

viduals, with some age specific features and patterns which differ from one region of the world to another.¹ The clinical features of liver dysfunction may include symptoms related to digestion problems such as abnormal fat absorption and metabolism, coagulopathies, blood sugar abnormalities and immune disorders. Others include features of cholestasis, portal hypertension and oesophageal varices.

Biliary atresia is a liver disease of the newborn which is characterized by abnormalities of the intra- and extra-

hepatic bile ducts, with incidence rates reported to vary between 1 in 8,000 and 1 in 21,000 live births.⁴ Biliary atresia is a major indication for liver transplantation among children.⁴ The autosomal recessive disorder, Alpha-1-antitrypsin deficiency, affects 1 in 1,800 live births and is the most common genetic cause of liver disease in children.¹ Viral hepatitis occurs in patients of all ages, with about 500,000,000 people chronically infected with Hepatitis B virus (HBV) or Hepatitis C virus (HCV) worldwide.⁵ Hepatitis B virus (HBV) infection causes both acute and chronic hepatitis which may progress to liver cirrhosis and hepatocellular carcinoma. The diagnosis of HBV rests on the demonstration of Hepatitis B surface antigen (HBsAg) or anti-HBV core (anti-HB_c) IgM antibody. Chronic HBV infection is associated with the persistence of HBsAg and HBV DNA. The Hepatitis C virus (HCV) causes acute hepatitis, which also progresses to chronic disease in more than 70% of affected individuals. Although end-stage liver disease can occur in up to 10% of cases, fulminant hepatitis has been described, though it is rare. The diagnosis of HCV is suggested by the presence of anti-HCV antibodies and confirmed by polymerase chain reaction for HCV RNA. Hepatitis D virus (HDV) infection occurs only in patients who have HBV infection. HDV is primarily associated with intravenous drug abuse and it usually aggravates on-going liver disease in children with HBV infection. In addition, Hepatitis E virus (HEV) occurs in epidemics in parts of the world that have poor sanitary conditions. Disorders of fat metabolism usually present in late infancy and early childhood while neoplastic diseases of the liver among children and adolescents differ from the types observed among adults.

Chronic hepatitis is traditionally defined as an inflammatory condition of the liver characterized by the persistence of biochemical and histologic abnormalities for more than six months. However, irreversible changes may occur in children within those six months. These chronic hepatitis conditions may be viral infections, autoimmune processes, and exposure to hepatotoxic drugs as well as cardiac, metabolic, or systemic disorders. Most cases of acute hepatitis in children resolve within three months. Progressive liver dysfunction affects childhood nutrition and may be complicated by growth retardation. Unfortunately, the timely recognition of severe liver disease in children remains a major challenge. One factor contributing to this challenge is the manifestation of injuries to the paediatric liver in a finite number of ways, hence different hepatic disorders often have virtually identical initial presentations. Early intervention may reduce the progression of liver diseases from initial inflammation to scarring with irreparable damage in the form of cirrhosis and/or cancerous transformation.^{1,4,6} Therefore, the aim of this review was to determine the pattern of liver diseases among children at the National Hospital, Abuja.

Methods

This was a retrospective, descriptive study of children managed over a five-year period (January 2009 to January 2014) at the Paediatric Gastroenterology, Hepatology and Nutrition (PGHAN) clinic and the Emergency Paediatric Unit (EPU) of the National Hospital Abuja. The PGHAN clinic runs every Wednesday as a specialist out-patient referral clinic while the EPU provides 24 hours emergency services for all sick children. From the EPU, children with liver diseases are referred to the specialist clinic for follow-up care.

The hospital records of the children with liver diseases were retrieved from the Medical Information Department following due permission. The diagnosis of liver diseases was based on the constellation of clinical and laboratory features. The data obtained included symptoms and signs suggestive of liver diseases such as fever, jaundice, abdominal pain, swellings, itching, pale stools, bleeding, weakness, vomiting, anorexia, pallor, hepatomegaly, splenomegaly and ascites. The results of liver function tests such as serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline phosphatase (AP), prothrombin time (PT) and partial thromboplastin time (PTT), international normalization ratio (INR), serum protein and albumin were also recorded. The results of viral serology markers such as HBsAg, HbeAg, and HBV-DNA for hepatitis B infection; HCV, anti-HCV and HCV-RNA for hepatitis C infection as well as HIV screening were also captured. Other investigation reports reviewed were liver biopsies, abdominal ultrasonography and abdominal computed tomography (CT) or magnetic resonance imaging (MRI) reports. Four patients had liver biopsies done, while genetic information and enzymatic assay could not be done due lack of facilities.

The children were classified into three broad categories; namely, infective, non-infective (metabolic, congenital, cholestatic, neoplastic) and idiopathic liver diseases. Specific diagnoses were categorized as chronic liver disease (CLD) when symptoms persisted beyond six months of follow-up care, with or without identifiable viral serological markers. The group classified as idiopathic had no identifiable cause while acute hepatitis had symptoms with resolution within less than six months and were negative for serological markers. A few patients were screened for cytomegalo-virus (CMV) and toxoplasmosis. Facilities for other serological markers were not available. Demographic characteristics and outcome of the care for the children were obtained and classified. Data were analyzed using SPSS 20 version. Pearson Chi-squared test was used for the comparison of categorical data and p values <0.05 were considered statistically significant.

Results

A total of 52 cases were documented in the records from the clinic and the EPU, out of which 42 cases were ana-

lyzed. The age of the children ranged from 2 months to 15 years with the mean (\pm SD) of 7.24 (\pm 4.77) years. There were 31 (73.8%) males and 11(26.2%) females with a male-to-female ratio of 2.8:1. Sixteen (38.0%) subjects were aged 5 years and below; half of these were aged less than one year. The remaining 26 (62.0%) subjects were older than five years. The differences in the proportion of children in the comparison age groups were not significant ($p = 0.897$) (Table 1). The distribution according to the socioeconomic classes were as follows; 28 (66.7%) in the lower socioeconomic class, 6 (14.3%) and 8(19.0%) in the upper and middle socioeconomic classes respectively. Nineteen (45.2%) of the subjects were fully vaccinated for HBV during infancy; 19 (45.5%) had normal nutritional status while 23 (54.8%) had various forms malnutrition with no statistically significant difference in the proportions ($p = 0.058$) (Table 2).

Table 1: Age and sex distribution of children with liver diseases

Age groups (years)	Males	Females	Total (%)	
0-5	12	4	16(38.0)	$2 = 0.217$
>5-10	10	3	13(31.0)	
>10- 15	9	4	13(31.0)	$p = 0.897$
Total	31	11	42(100.0)	

Table 2: Distribution of children with liver diseases according to age and nutritional status

Age groups (years)	Normal	Under-nutrition	Over-weight	Total	
0-5	4	9	2	16	$^2 = 9.125$
>5-10	7	2	5	13	$p =$
>10- 15	8	3	2	13	0.058
Total	19 (45.2)	14(33.3)	9(21.4)	42 (100.0)	

Figures in parentheses represent percentages of the total in the row

The most common symptoms included jaundice (30; 71.4%), abdominal pain (17; 40.5%), fever (15; 35.7%), abdominal swelling (12; 28.6%) and bleeding (8; 19.0%). Physical findings included hepatomegaly (16; 38.1%), pallor (14; 33.3%) and splenomegaly (8; 19.0%) as shown in Table 3.

Table 3: Frequencies of symptoms and signs of liver diseases among children

Features	Frequencies	Percentages
<i>Symptoms</i>		
Jaundice	30	71.4
Abdominal pain	17	40.5
Fever	15	35.7
Abdominal swelling	12	28.6
Vomiting	8	19.0
Weakness	8	19.0
Bleeding	8	19.0
Pale stool	7	16.7
Anorexia	7	16.7
Itching	4	9.5
Unconsciousness/restless	2	4.8
<i>Signs</i>		
Hepatomegaly	16	38.1
Pallor	14	33.3
Splenomegaly	8	19.0
Ascites	5	11.9
Coma	2	4.8

Table 4: Diagnoses among children with liver diseases

Diagnoses	Number (%)
CLD (viral hepatitis)	24 (57.1)
Acute hepatitis	6 (14.3)
CLD (unknown cause)	4 (9.5)
Neonatal hepatitis syndrome (NHS)	3 (7.1)
Biliary atresia	3 (7.1)
Fulminant hepatitis	2 (4.8)
Cholestatic hepatitis(ciliopathy/ choledochal cyst)	2 (4.8)
Portal hypertension with oesophageal varices	2 (4.8)
Malignancy (hepatoblastoma)	1 (2.4)
Galactosaemia	1 (2.4)

Some children had more than one diagnostic classification; CLD – chronic liver disease

CLD of viral aetiology formed 57.1% of all the children studied. Non- infective cases, namely, biliary atresia, cholestatic hepatitis, hepatoblastoma and galactosaemia accounted for 21.4% s while idiopathic cases included acute hepatitis 14.3%, CLD 9.5% and NHS 7.1% as shown in Table 4. Of the 24 (57.1%) subjects positive with viral serological antigen markers, 18 (75.0%) were positive for Hepatitis B surface antigen (HbsAg); 10 with HbeAg and 6 with elevated HBV DNA viral load. Five (11.9%) children were positive for hepatitis C antigen and anti- HCV antibodies, some with co-infections (Table 5).

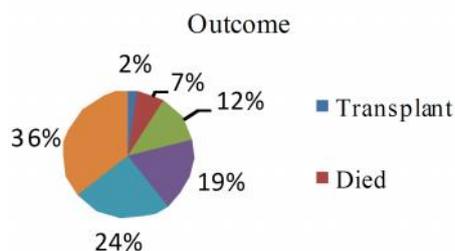
Table 5: Distribution of Infective children with liver diseases

Infective category	Number (%)
HBV(10 HbeAg pos; 8HbsAg carriers)	18 (42.9)
HBV-HCV co-infection	1 (2.4)
HCV (HCV antibodies)	2 (4.8)
HCV-HIV co-infection	1 (2.4)
HCV-CMV co-infection	1 (2.4)
CMV-Toxoplasmosis co-infection	1 (2.4)

The mean (\pm SD) values of liver enzymes and serum bilirubin were elevated, with low total serum proteins and albumin levels (Table 6). Twelve (28.6%) subjects received treatment with antiviral agents and interferon; 5 (41.7%) of these 12 children improved with sero-conversion and were discharged. One subject with biliary atresia had liver transplant overseas, while 15 (35.7%) were lost to follow up (Figure1). There were three deaths, two of which had unknown aetiology and presented with encephalopathy

Table 6: Liver Functions profile of children with liver diseases

Parameters	Mean values	Std. Deviation
Serum Aspartate aminotransferase (AST)IU/L	135.23	171.81
Serum Alanine aminotransferase (ALT)IU/L	176.80	376.40
Serum Alkaline phosphatase (AP)IU/L	261.23	196.22
Serum Gamma glutamyl transpeptidase (GGT) IU/L	155.73	259.66
Conjugated serum bilirubin (umol/L)	22.15	65.37
Total serum bilirubin (umol/L)	79.05	126.21
Total serum proteins (g/L)	33.86	35.28
Serum albumin (g/L)	16.70	17.85

Fig 1: Outcome of children with liver diseases

Discussion

This hospital-based descriptive review focused on the spectrum and magnitude of liver disorders among children aged less than 16 years who were managed over a five-year period in a tertiary health centre. The demographic characteristics suggested that males and children from lower socioeconomic classes were more frequently affected by liver diseases.^{3,7-9} The age of the children in this study ranged between 2 months and 15 years with the mean of 7.24 ± 4.77 years. This was similar to the findings reported by Dar *et al.*,¹⁰ who reported the mean age of 9.34 ± 4.8 years (range of 1-18 years). The age data in the present study were higher than the mean age of 4.8 ± 0.3 years (range 5 months and 14 years) reported by Alam *et al.*⁹ Children aged over five years accounted for 62 percent of the study population in the present report. This observation may suggest exposure to preventable liver infections early in life in this population.⁵ Various forms of malnutrition (underweight, marasmus and overweight) were observed among 54.8 percent of the children studied while 21.4 percent was overweight. Under-nutrition may be a direct consequence of liver diseases while overweight and obesity are predisposing conditions. In a retrospective study of 79 children with chronic liver diseases whose mean age was five years, reported by Al-Lawati *et al.*¹¹, growth retardation was recorded among 75 percent of the children.

The recent rise in the prevalence rates of obesity and overweight in the United States has resulted in the emergence of non-alcoholic fatty liver disease (NAFLD) as the leading cause of chronic liver disease among children and adolescents in the United States.¹² In addition, emerging data suggest that children with non-alcoholic steatohepatitis (NASH) progress to cirrhosis which may ultimately increase liver-related mortality.¹² However, due to non-availability of advanced biochemical laboratory and limited facilities for biopsies, the inability to search for some of these metabolic disorders in the present report may be a limitation in this study. Liver histology remains the gold standard for assessing hepatic steatosis. Nevertheless, only four (9.5 percent) children in our series had liver biopsy. This rate was lower than the 30/164 (18.3 percent) reported in the Dhaka Shishu Hospital study.⁹

Jaundice was the most common clinical feature in over 70 percent of the children in this study. Others included abdominal pain and swelling, fever, vomiting, weakness

and bleeding. In a report by Dar *et al.*¹⁰ on 186 children less than 18 years, jaundice was reported among all the children presenting with acute hepatitis, and 75 percent of those presenting with chronic liver diseases. Some children in this report, presented with features of portal hypertension and esophageal varices such as hepatosplenomegaly, ascites, gastro-intestinal bleeding and encephalopathy. These features were suggestive of fairly advanced liver diseases with decompensation present at presentation. Such children were classified under grades B and C of the Child-Pugh scores. The children had deranged values of laboratory parameters; specifically elevated liver enzymes levels and bilirubin levels and low albumin levels. These findings suggested both acute and chronic liver pathology. According to the Child-Pugh scoring system,¹⁰ total serum bilirubin greater than $50\mu\text{mol/l}$, serum albumin less than 2.8g/dl , prolonged prothrombin time and INR level greater than 2.3, moderately severe ascites and hepatic encephalopathy predicted mortality. Some of the children in this report had chronic liver disease that met the above-stated criteria, though endoscopy was not available for the children with bleeding varices.

The most common aetiologic group in the present study was infective (viral) hepatitis, especially Hepatitis B infections. This report was similar to the findings in a retrospective analysis of 300 children with various liver diseases, at two major teaching hospitals of Karachi where acute viral hepatitis and its sequelae were the most frequent (31 percent) of all hepatic ailments.⁸ The World Health Organization (WHO) reported that about two billion people are infected with the Hepatitis B virus (HBV). In highly endemic areas, HBV infections in children are most commonly spread from mother to child at birth or from person to person in early childhood and adolescence.⁵ Children aged above five years accounted for 66.7 percent of all the known infective cases in this study. Reports have shown that the persistence of viral infections in the liver predisposes to cirrhosis and hepatocellular carcinoma. The diagnosis of HBV was based on sero-positivity for HbsAg and HbeAg as well as the HBV DNA viral load in a few cases who could afford the test where it is available. Children with detectable HBsAg for a period up to six months with or without concurrent HBeAg were considered to have chronic HBV infection. The presence of HBeAg only indicates that the child is highly infectious. Other markers of infection such as the assay of immunoglobulins to hepatitis core antigen (IgMHbCag) and the newer HBsAg quantification assay are not yet routinely evaluated due to non-availability and high cost. Hepatitis C infection cases were also recorded in this study, though less common than expected.¹³ Most often, HCV infection is acquired at birth in the younger child but adolescents can also acquire the infection through activities which facilitate blood contacts such as intra venous drug use, sharing needles and high-risk sexual behaviors.¹⁴ The odds of a child acquiring HCV from an infected mother is 1:20.¹⁴ Reports show that spontaneous clearance of HCV infection can occur in about 40 percent of newborns who acquired the disease vertically, by the age of

two years, and sometimes up to 7 years.¹⁴ Co-infections were recorded in the present study, with HBV/HCV co-infection and HBV/HIV co-infection. HBV/HCV co-infected persons have been shown to have more severe liver injuries and higher chances of progression to cirrhosis or cancerous transformation.¹⁵ CMV co-infections with HCV and toxoplasmosis were also identified in this report. This observation underlines the importance of testing for other non-hepatitis virus in any suspected case of liver disease.

Neonatal hepatitis syndrome and biliary atresia accounted for 14.2 percent of liver diseases among infants in this study. Biliary atresia presenting as cholestatic liver disease, may be caused by intra-or/and extra-hepatic bile ducts obstruction. It is the major indication for liver transplantation in children.⁴ Early presentation is most desirable and portoenterostomy surgery (Kasai procedure) is best carried out within 100 days of life. The success of this procedure in the establishment of bile drainage, is variable and up to 40 percent of children may develop significant fibrosis and progress to require liver transplantation within the first few years of life.⁴ One of the children in the present study had liver transplant within the first two years of life. Other rare causes of liver disease, such as ciliopathy, hepatoblastoma and galactosaemia were seen in this report. A case of liver ciliopathy presented acutely with massive GI bleeding, hepatomegaly and ascites with deranged liver functions. The diagnosis was made with liver biopsy. Ciliopathies are an emerging class of genetic multisys-

tem human disorders caused by a multitude of largely unrelated genes that affect ciliary structure/function. The mode of inheritance is recessive, either autosomal or X-linked, with strong evidence of genetic modifiers which determine expressivity.¹⁶

Some children had liver diseases of unknown aetiology, most of whom had complete resolution and were discharged home. Dar *et al*¹⁰ reported 52 percent with no aetiology (cryptogenic) in a hospital-based descriptive study. Some of the reasons limiting diagnosis of specific liver patterns included the non-availability of routine biopsies, specific diagnostic tools for HbsAg quantification levels, routine HBV- DNA (viral load) and magnetic resonance elastography (MRE) which accurately detects fibrosis. About a third of the children in the present study were lost to follow up for various reasons such as poor finances and non-availability of immediate cure.

Limitation

Incompleteness and loss of data were noted in the present study. Other limitations included lack of adequate investigative capacity mostly due to non-availability of advanced biochemical laboratory and financial constraints.

Conflict of interest: None

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