

Pattern of chronic liver disease in Omani children – A clinicopathological review

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Summary

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

Study Design: Seventy six children {43M : 33F } aged 4 days to 10 years, referred to the Paediatric Gastroenterology clinic of the Sultan Qaboos University Hospital, Muscat, Oman, between 1995-2000 for evaluation of liver disease were studied. Liver biopsies were performed in all and tissues obtained processed and examined for histological lesions.

Result: The main histological diagnoses were neonatal hepatitis (22) biliary atresia (9) biliary hypoplasia (7), cirrhosis (7) and congenital hepatic fibrosis (5). Hepatomegaly with or without jaundice was the indication for liver biopsy in the majority of patients studied.

Conclusion: The study has provided background information on the occurrence of specific liver diseases in Omani children. Neonatal hepatitis syndrome was the most common diagnosis before the age of 2 years.

Keywords: *Chronic liver disease, Childhood.*

Résumé

Objectif: Déterminer la tendance de la maladie du foie chronique chez des enfants Omani.

Plan d'étude: Soixante quatorze enfant (43M:33F) âgés entre 4 jours et 10 ans envoyés au service de la Pédiatrie gastroentérologie de centre hospitalier universitaire du Sultan Qaboos, Muscat, Oman entre 1995 -2000. Pour une évaluation de la maladie du foie ont été étudiés. Les biopsies du foie ont été fait dans tous les tissus obtenus évalués et étudiés pour des lésions histologiques.

Résultats: Les diagnostics histologiques principaux sont hépatite néonatale (22), atresie biliaire (9) l'hypoplasie biliaire (7), et fibrose hépatique congénitale (5). L'hépatomégalie avec ou sans la jaunisse était une indication pour la biopsie du foie chez la majorité des patients étudiés.

Conclusion: A travers cette etude, on arrive à avoir informations de base sur le phénomène spécifique des maladies de foie chez des enfants d'Omani. Syndrome d'hépatite néonatale était un diagnostic le plus courant avant l'âge de 2 ans.

Introduction

The pattern of chronic liver disease in childhood

varies from one geographical area to another. Indian childhood cirrhosis occurs commonly in South Asia¹, veno-occlusive disease in Jamaica², while in Europe, idiopathic hepatitis and biliary atresia are the most common chronic liver diseases in infancy³. In the Far East early childhood hepatitis B infection is very common and accounts for the high incidence of hepatocellular carcinoma in the area⁴. Chronic biliary tract diseases in children occur worldwide with variable frequency. While the incidence of biliary atresia throughout the world is relatively constant with a frequency of approximately 1 per 12,000-15,000 live births⁵, choledochal cyst occurs with the highest frequency in the Japanese with an incidence of 1 per 1000 population compared with the much lower incidence of 1 per 15,000 population in the rest of the world⁶ Chronic liver diseases, usually lead to end stage liver disease which may require liver transplantation⁷ Thus early recognition and management of these diseases can prevent development of complications and lead to reduction in the need for liver transplantation and its attendant high cost and complications. In this study, we reviewed the pattern of chronic liver disease in Omani children as there is dearth of information on this.

Materials and Methods

Two thousand and fifty children were referred to the Gastroenterology unit of Sultan Qaboos University Hospital (SQUH) between 1995-2000 and 92 of these children were suspected to have chronic liver disease. SQUH is one of the two tertiary referral hospitals in Oman, a nation with a population of 2.28 million people, 58% of which are children below the age of 15 years.

A detailed history was taken in the 92 children, with particular reference to the onset, nature of symptoms and existence of any family history of liver disease as well as parental consanguinity. Physical examination was performed on all patients. Preliminary investigations included full blood counts, reticulocyte count, coagulation profile, total and direct serum bilirubin and liver enzymes. Liver biopsy was performed under ultrasound guidance using the disposable Trucut needle under sedation with intravenous midazolam and/or oral chloral hydrate. The specimens were fixed in 10% formalin and in cases of suspected storage disorder, also in alcohol. The tissues were processed and stained using standard methods.⁸

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Results

Liver histology were available in 76 (83%) of these children. The ages of the children ranged from 4 days to 10 years (median 1.2 year). There were 43 males and 33 females (M:F = 1.3:1). The major indications for liver biopsy in these children included jaundice and hepatosplenomegaly (36/76) and hepatomegaly (19/76) [Table 1]. The histological diagnoses are shown in Table 2.

Table 1 Indication for liver biopsy in 76 children with chronic liver disease

Indications	No. of cases
Jaundice and hepatosplenomegaly	36
Hepatomegaly	19
Persistent conjugated hyperbilirubinaemia	16
Pyrexia of undetermined origin	3
Storage disorder	2

Neonatal hepatitis syndrome (neonatal hepatitis/biliary atresia/hypoplasia)

Below the age of 2 years, neonatal hepatitis syndrome was the most common diagnosis, accounting for 56.4% of patients. Clinical features in this group of patients included persistent jaundice, dark urine, hepatosplenomegaly and pale stool, especially in the cases with extrahepatic biliary atresia (EHBA). Pruritus was a prominent feature (62%) in those with biliary hypoplasia who were all of the non-syndromic type.

The age range of those with neonatal hepatitis (NNH) was 5 days to 32 days (median 20 days). Among the cases of NNH, alpha - 1 - antitrypsin globules were detected in the liver in one case with low alpha-1- globulin fraction on serum electrophoresis. In one patient, IgM antibody to cytomegalovirus was positive while in an-

Table 2 Histological diagnosis in 76 children with chronic liver disease

Diagnosis	No. of cases
Neonatal hepatitis	22
Extrahepatic biliary atresia	9
Biliary hypoplasia	7
Cirrhosis	7
*Wilson	1
*Secondary Biliary	2
*Viral	1
*Cryptogenic	3
Congenital hepatic fibrosis	5
Glycogen storage disorder	4
Galactosaemia	4
Cystic Fibrosis	3
Chronic hepatitis (HBV x 2)	3
Fatty Liver	3
Progressive familial Intrahepatic cholestasis	2
Budd Chiari Syndrome	1
Chronic granulomatous disease	1
Non diagnostic	5

other one hepatitis B surface antigen and the e antigen were positive. Their biopsies showed diffuse swelling of the hepatocytes with or without feathery degeneration and usually with giant cell transformation, cholestasis, portal and intra-acinar inflammation (fig. 1).

Nine children with a median age of 28 days (range 10-48 days) were confirmed as EBHA. Their hydroxyiminodiacetic acid radioisotope excretion study was suggestive of extrahepatic biliary obstruction. Five underwent laparotomy and 3 of them had correctable defect and bile drainage at surgery. The characteristic histological features were expansion of the portal tracts, marked cholestasis with bile concretions, ductal proliferation and periportal fibrosis (fig 2). Extensive periportal fibrosis with destruction of lobular architecture and re-

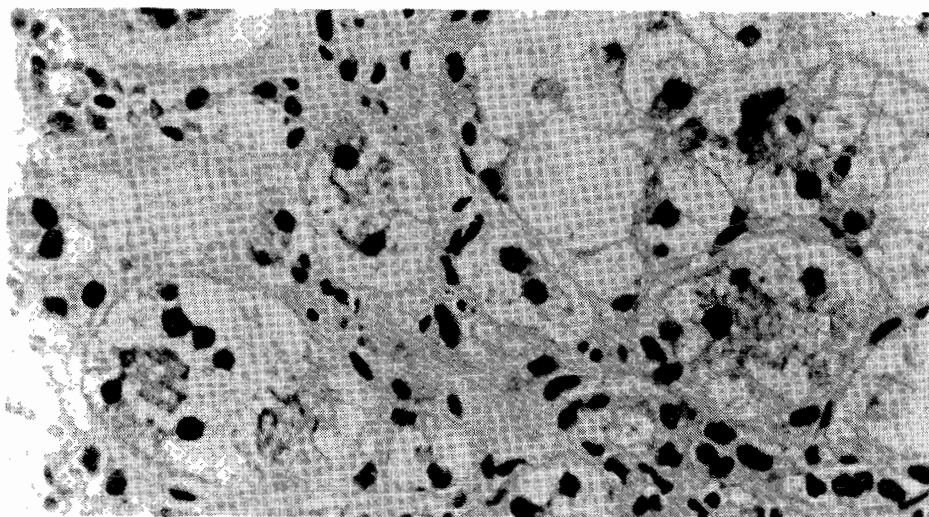


Fig. 1. Neonatal hepatitis in a 2 month old child. Photomicrograph shows ballooning of hepatocytes, and multinucleate giant cells. Inflammatory infiltrate is seen in the lower right corner, haematoxylin-eosin x 400.

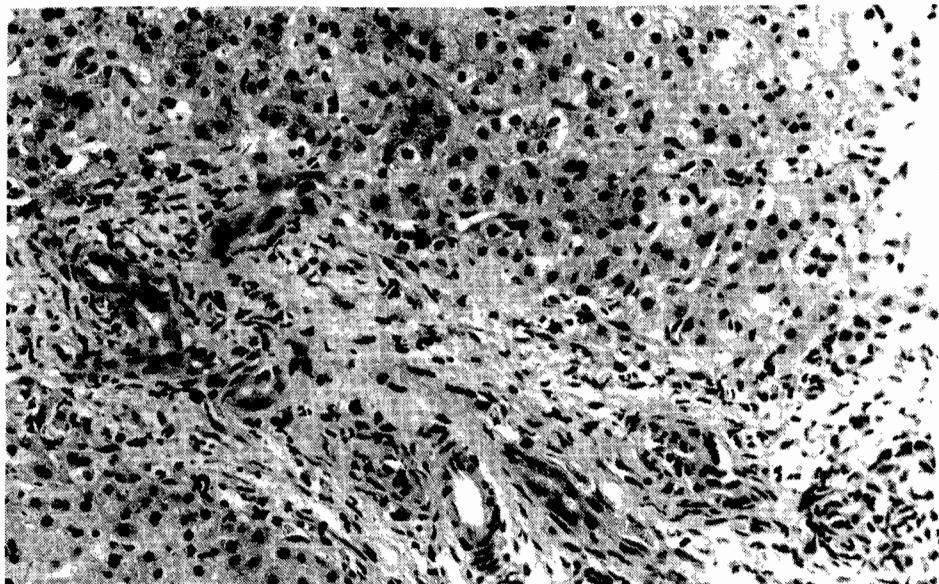


Fig. 2. Section of liver showing periportal fibrosis and bile duct proliferation in a child with extrahepatic biliary atresia; haematoxylin-eosin x 200.

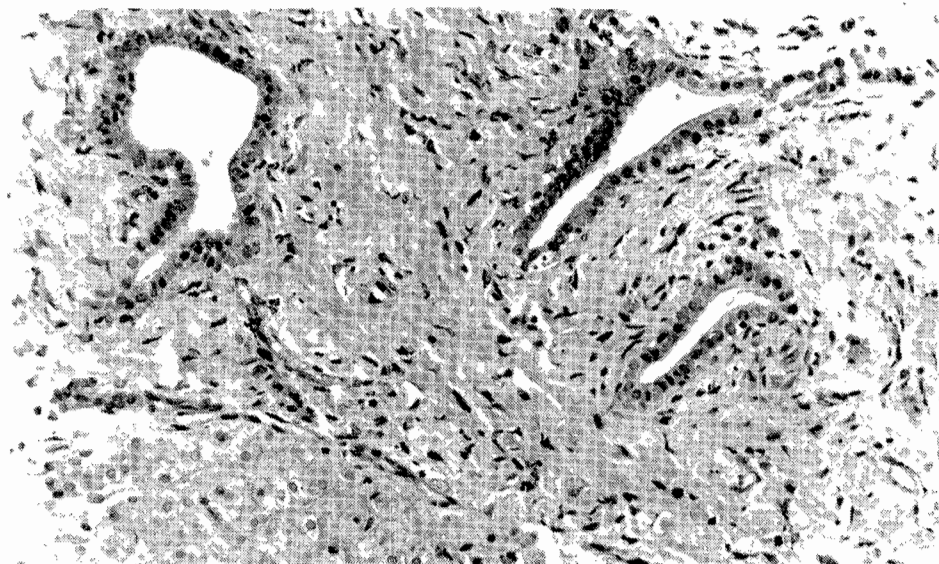


Fig. 3. Portal area in a child with congenital hepatic fibrosis showing abnormal elongated ducts and dense collagen; haematoxylin-eosin x 200

generating nodules indicative of cirrhosis were seen in 3 cases.

Congenital hepatic fibrosis

Congenital hepatic fibrosis was diagnosed in 5 children with a median age of 2.8 years (range 1-4 years) who presented with asymptomatic hepatosplenomegaly. Hepatocellular function was preserved in all, while in 2 of these children, renal cystic changes were seen on abdominal ultrasound. Biopsies showed diffuse periportal and perlobular fibrosis interspersed between numerous bile ductules (fig 3).

Storage disorders

Three girls and one boy aged between 1 and 4 years

who presented with frequent episodes of hypoglycaemic seizures and hepatomegaly and in addition in one, recurrent episodes of lactic acidosis were confirmed to have glycogen storage disorder. They all had doll like facies, stunted growth and protuberant abdomen. Three were considered to have type 1a and one who had neutropenia and recurrent bacteria infection, type 1b. Liver biopsy findings in these children revealed enlarged hepatocytes containing numerous fat droplets and well glycogenated nuclei (fig 4).

Cirrhosis

Seven children had biopsies showing cirrhosis. Of these, 2 had secondary biliary cirrhosis, one each HBs antigenaemia, and Wilson disease. In the child with Wil-

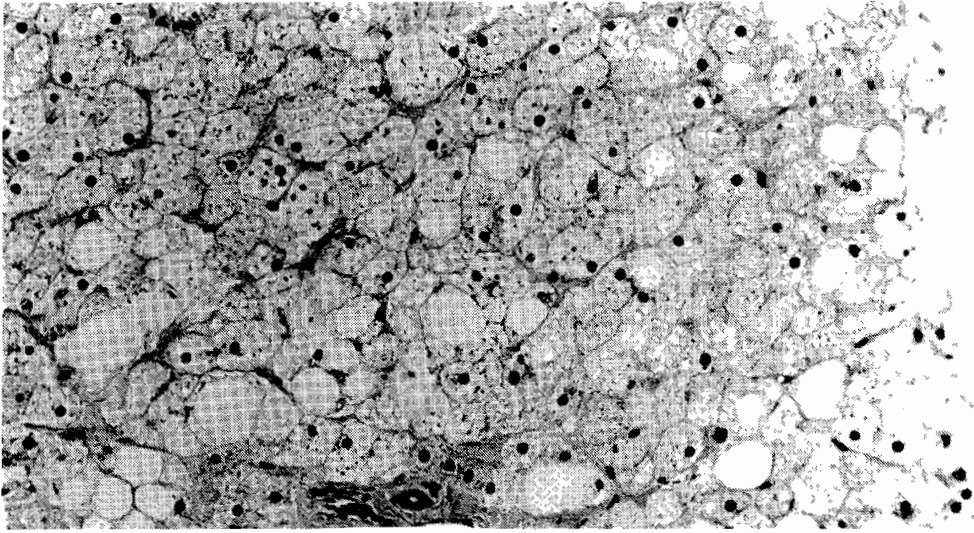


Fig.4. Glycogen storage disease in a 4 year old girl. Biopsy specimen shows enlarged hepatocytes with glycogen rich cytoplasm and central nuclei. Lipid vacuoles are also present; haematoxylin-eosin x 200.

son disease, the serum copper of 80 μ g/dl and ceruloplasmin levels of 15mg/dl were low, while the urine copper of 50 μ g/hr was increased. The histological picture in this patient showed chronic active hepatitis with stained copper seen and he was treated with penicillamine and steroid. In spite of these however his condition continuously deteriorated and he died 9 months later. The remaining 3 patients had cryptogenic cirrhosis. No stainable copper, or HBsAg or alpha-1-antitrypsin globules were seen in these cases.

Other Liver Disorders

Four patients with galactosaemia confirmed by absent red blood cell galactose-1-phosphate uridyl transferase presented with diarrhoea and failure to thrive and two of these patients also had cataract at birth. Histology showed steatosis, cholestasis and in addition in one of them early cirrhotic nodules. They all responded well to dietary manipulation. Cystic fibrosis was diagnosed in 3 patients on clinical grounds and a high sweat chloride (>80mmol/l). Three cases each had fatty liver and chronic active hepatitis. The sera of 2 of the cases with chronic hepatitis were positive for HBsAg and their biopsies showed bridging necrosis. Two siblings aged 5 months and 2 years had progressive familial intrahepatic cholestasis. They presented with failure to thrive, marked pruritus, steatorrhoea and low serum gamma glutamyl transpeptidase levels. The older sibling also had signs of rickets and eventually died of liver failure.

One case had chronic granulomatous inflammation due to tuberculosis and another, Budd Chiari syndrome. The latter presented with a 2 week history of abdominal distension, vomiting and signs of portal hypertension and a biopsy showed severe centrilobular congestion and central venous dilatation.⁹ In 7 cases (9.2%), liver biopsies were non diagnostic. Of these, 3 showed a normal morphology, while the rest only showed mild non-specific

changes.

Discussion

This retrospective study of children with chronic liver disease from a tertiary referral hospital in Oman has revealed that the common liver disorders in infants and children are neonatal hepatitis syndrome, congenital hepatic fibrosis and cirrhosis. This pattern is similar to an earlier study by Raju et al¹⁰ from India. However, Dangwal et al¹¹ from another part of India have reported infantile obstructive cholangiopathy in 20% of their patients followed by cryptogenic cirrhosis and idiopathic chronic active hepatitis in 17.5% each.

In our study neonatal hepatitis syndrome comprising of neonatal hepatitis, biliary atresia and hypoplasia was the most common diagnosis in children below the age of 2 years, accounting for 50% of all the cases. Ramakrishna et al¹² found 17% prevalence for neonatal hepatitis syndrome among the 134 liver biopsies studied. However the latter study showed a much higher proportion of cirrhosis (19%) compared to the relatively low value of 9% noted in our study which may reflect the early diagnosis of chronic liver disease in Oman. In this report, 2 cases of cirrhosis which were considered secondary to biliary obstruction presented late to us as they had earlier been seen in another hospital where possibility of biliary atresia was entertained but their parents refused liver biopsy.

The evaluation of neonatal cholestasis necessitates a series of screening laboratory investigations. In early infancy, hepatocellular disease, biliary hypoplasia and biliary atresia all have similar clinical and laboratory features, which make differentiation difficult. Jaundice, dark urine and pale stool, the signs of conjugated hyperbilirubinaemia are found in all the three groups as was observed in this study. In the infant with cholestasis, the clinician must promptly either diagnose or exclude

biliary atresia as biliary atresia is the most common surgical cause of neonatal cholestasis, the most frequent cause of death from liver disease and indication for liver transplantation in children.^{13,14} Differentiation of biliary atresia from the other major causes of neonatal cholestasis at an early stage is very important if surgery in the former is to be successful¹⁵. Preoperative evaluation of a child with biliary atresia varies between medical centres. Some clinicians perform only radioisotope scan, others perform liver biopsy and some both, however the definitive diagnosis is made surgically. In this study, we found combination of fasting abdominal ultrasound, radioisotope excretion study and liver histology to be very useful in differentiating biliary atresia from the other causes.

The identified causes of neonatal hepatitis in our study were galactosaemia, and one case each of cytomegalovirus and alpha - 1 antitrypsin deficiency. This is in contrast to findings in Europe, where alpha -1 antitrypsin deficiency is an important cause of neonatal hepatitis.¹⁶ Though alpha -1 antitrypsin globules were looked for and alpha - 1 antitrypsin level routinely done in all our cases, alpha- 1 antitrypsin globules were only detected in one case. It is possible that some cases may have been missed, even though their liver did not show alpha- 1 globules, as we could not determine the alpha-1- antitrypsin phenotype. Among the other categories, the children with glycogen storage disorder were readily suspected clinically by their characteristic doll facies, history of hypoglycaemic seizures and marked hepatomegaly and they all responded to dietary management.

The indication for liver biopsy in most cases was organomegaly with or without jaundice and if the child is below 2 years of age, the diagnosis was more likely to be neonatal hepatitis syndrome. But it is critical to identify patients with extra-hepatic biliary atresia early and institute palliative surgical intervention. Late referral affects the ultimate prognosis as it has been demonstrated that favourable prognosis is in inverse proportion to the age at surgery¹⁵.

End stage liver disease and eventually death result from untreated chronic liver disease. The advent of liver transplantation in children has improved the prognosis of most cases of liver disease. However liver transplantation has its attendant problems such as, rarity of donor organs, high cost, and complications such as rejection, graft versus host disease, primary graft non function and infection^{17,18}. These problems are enormous and make liver transplantation a second choice therapy in treatment of chronic liver disease in children. Thus prevention where possible and early diagnosis and prompt institution of appropriate treatment of these diseases will still be the preferred first choice in many countries including Oman.

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