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CASE REPORT

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Indian childhood cirrhosis – like liver disease in an Arab child. A brief report

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Abstract An Arab female child presented with rapidly progressive liver disease, with apparent onset in late infancy and death at 15 months. Microscopy showed panacinar hepatitis, portal and pericellular fibrosis, and diffuse Mallory bodies in the absence of steatosis or significant cholestasis. Hepatic copper concentration was moderately elevated. Known causes of early childhood cirrhosis were excluded. This case meets most of the established criteria of Indian childhood cirrhosis, yet is unusual in its occurrence in a child of Arab ancestry and in having a moderate degree of hepatocellular copper overload.

Key words Indian childhood cirrhosis · Liver Copper storage

Introduction

In 1977, an international group of experts recommended a modified classification of liver cirrhosis based mainly on aetiological considerations (Anthony et al. 1977). Among the various entities in the cryptogenic category, Indian childhood cirrhosis (ICC) stands out as unique in occuring in a special clinical setting and in having an almost diagnostic biopsy appearance (Nayak 1987).

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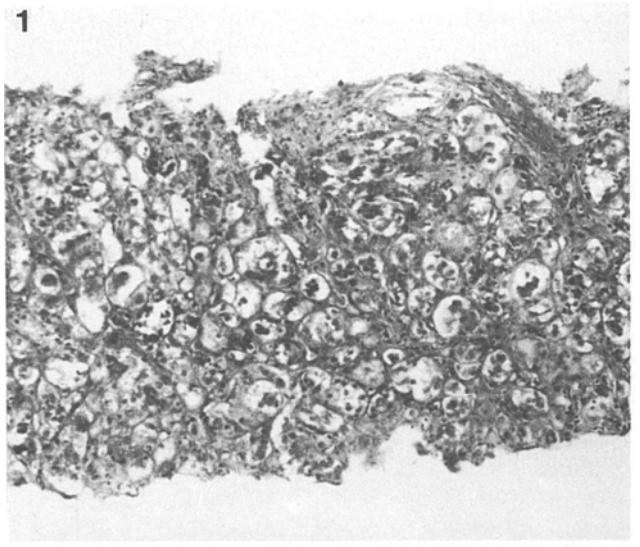
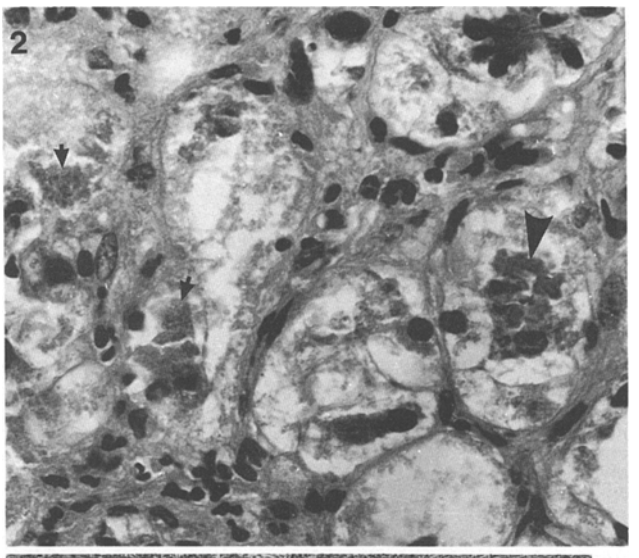
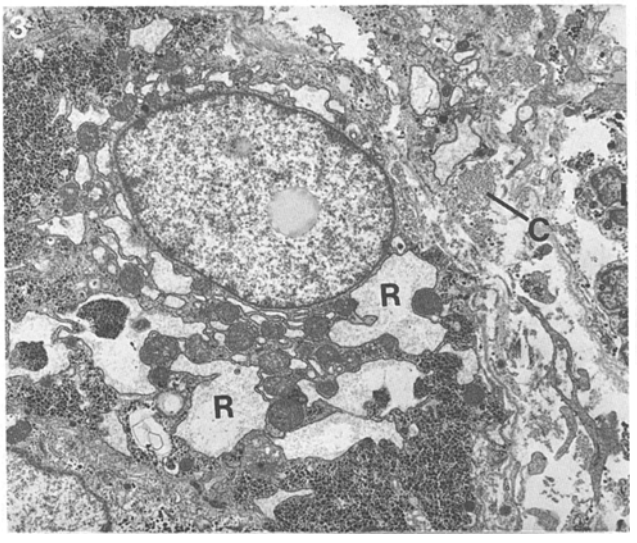
Reports of ICC-like liver disease in non-Indians are few. They include an Australian family (Walker-Smith and Blomfield 1973), five North American children (Adamson et al. 1992; Lefkowitch et al. 1982), three German children (Muller-Hocker et al. 1987, 1988), and an Italian child (Maggiore et al. 1987). We report a case of fatal liver disease that resembled ICC clinicopathologically yet occurred in an Arab child with no known Indian ancestry.

Case report

T.H.N. was a sister of two healthy sibs, the product of normal full-term delivery to first degree Arab Kuwaiti cousins, and an exclusively breast-fed infant. She was admitted for the first time at the age of 40 days, having begun to show poor feeding, vomiting, and lethargy. Physical examination showed pallor, weakness, a palpable liver 2.5 cm below the costal margin, and a barely palpable spleen. CT scan revealed a right-sided cerebral and subdural haemorrhage. A therapeutic subdural tap was performed and the neurological status reverted to normal. One unit of whole blood was transfused to alleviate anaemia. At the age of 50 days and while in the hospital, jaundice was first noted with total and direct serum bilirubin being 170 and 140 mmol/L respectively. Prothrombin and partial prothrombin times (PT and PTT) were normal. The patient was discharged against medical advice before further liver assessment was possible and was lost to follow up. Up to the age of 11 1/2 months, the child showed poor appetite and remained underweight. She was then admitted for pneumonia and was found to be underweight (weight: 6 kg, 5th percentile) and to have moderate splenomegaly and hard, smooth predominantly right-lobed hepatomegaly (4 and 10 cm below the costal margins respectively). There was rickets and right lobar pneumonia. Laboratory data included total and direct serum bilirubin of 89 and 80 μmol/l, and alanine transminase (ALT) of 530 U/l, aspartate transaminase (AST) of 1760 U/l, alpha-fetoprotein of 881 IU/l, alkaline phosphatase of 1000 U/l, and total serum protein and albumin of 73 and 43 g/l respectively. Serology of blood for hepatitis types A and B was negative. Urine chromatography for amino acids and reducing sugars in the urine were negative. PT and PTT were prolonged. The patient was discharged against medical advice. At the age of 13 1/2 months, she was readmitted and treated for pneumonia and found to have persistent hepatosplenomegaly and abnormal liver function tests. A percutaneous liver needle biopsy was interpreted as showing active micronodular cirrhosis resembling ICC. The patient was discharged







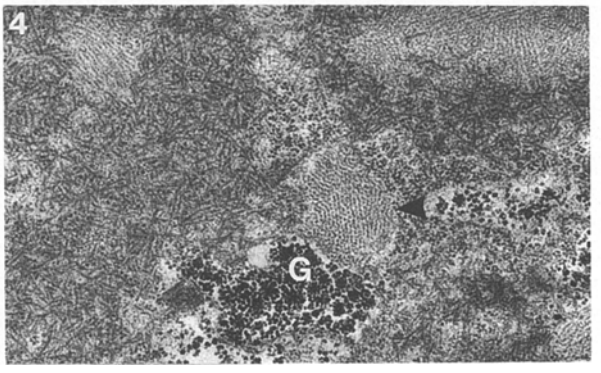


Fig. 1 Light microscopy of liver needle biopsy showing portal and diffuse pericellular "creeping" fibrosis, generalized liver cell ballooning, and irregular limiting plates. Masson-trichrome, × 62

Fig. 2 Light microscopy of Mallory bodies. Crescentic (*large arrow head*) and irregular lumpy (*small arrows*) forms are shown. Also notice a focus of liver cell necrosis (left lower corner), a psuedoacinus (right upper corner) and diffuse liver cell ballooning and pericellular fibrosis. Haematoxylin/eosin, × 369

Fig. 3 Ultrastructure of a ballooned hepatocyte. Dilated RER (*R*) and glycogen rosetts make up the bulk of this hepatocyte cytoplasm. Also shown are clumps of intracisternal glycogen rosetts, pericellular collagen (*C*), and inflammatory cells (*L*). Uranyl acetate/Reynold's lead citrate, × 4450

Fig. 4 Higher power view of the Mallory body shown in Fig. 3 featuring abundant type II (MB) and a small collection of type I (*arrowhead*) filaments and admixed glycogen (*G*). Uranyl acetate/Reynold's lead citrate, × 15 000

on 5 mg of prednisone twice daily. She was admitted for the fourth time at the age of 14 1/2 months. She was comatose and jaundiced and had anasarca and pneumonia. She expired at the age of 15 months and no post-mortem examination was permitted.

Materials and methods

A 1.3 × 0.05 cm core of liver tissue was received fresh in normal saline in two pieces within 5 min of the biopsy procedure. Half of larger segment was fixed in absolute alcohol and the other was left overnight in 10% neutral buffered formalin and routinely processed for paraffin embedding. Sections were stained with haematoxylin eosin, periodic acid Schiff (PAS) with and without diastase digestion, Pearl's, Shikata's orcein, and rhodanine stains. The smaller piece was fixed in 3% gluteraldehyde in Millonig phosphate buffer (pH 7.2) and post-fixed in buffered osmium tetroxide (pH 7.2), dehydrated in ethanol, and embedded in araldite. Ultrathin sections were cut on an LKB ultramicrotome, stained with uranyl acetate and lead citrate, and viewed and photographed in Jeol 100CX and 1200EX electron microscopes. For quantitative copper measurement, the paraffin block containing the liver tissue, which was originally fixed in absolute alcohol, was melted and passed through xylene to absolute alcohol. Three paraffin-embedded liver needle biopsies from children matched for the patient's age and of equivalent sample size, were assayed simultaneously as low and high tissue controls. They represented cases of glycogenosis, non-specific hepatitis and typical ICC. The graphite furnace atomic absorption spectrophotometric method was used.

Results

Sections showed panacinar liver plate disarray and marked liver cell swelling (Fig. 1), focal giant cell and pseudoglandular transformation, focal liver cell necrosis (Fig. 2), mild panacinar lymphocytic infiltration, moder-

ate portal inflammation with mononuclear cells slightly outnumbering polymorphomuclear leukocytes, prominent piece-meal necrosis, mild to moderate portal fibrosis extending diffusely into surrounding acini in the form of thin strands isolating individual and small groups of hepatocytes and bridging portal with central areas, and mild lymphocytic infiltration and sclerosis of central veins without any appreciable luminal compromise. Mallory bodies (MB) were found in hepatocytes throughout the acinar zones (Fig. 2). Most of the portal tracts contained one or more cross sections of interlobular bile ducts (ILBD). Almost all of the ILBDs showed mild to moderate changes consisting of epithelial cell swelling with resultant luminal compromise, cell dropour, acidophilic shrinkage, and lymphocytic and neutrophilic infiltration. All portal areas showed mild to moderate ductular proliferation. Canalicular cholestasis was seen mainly in the centre of the pseudoglands. No significant brown pigment granules were seen. Orcein and rhodanine stains were repeatedly negative while sections from a typical control case of ICC were strongly positive. No large diastase-resistent PAS positive hepatocellular cytoplasmic globules were seen. Masson-trichrome stain highlighted the portal and peri-cellular fibrosis. Electron microscopy demonstrated large amounts of cytoplasmic glycogen and dilated rough endo-plasmic reticulum (RER) (Fig. 3) and frequent aggregates of two types of filaments that matched Mallory bodies (MB) types I and II (Roy et al. 1971; Yokoo et al. 1972) (Fig. 4). Hepatic copper concentration was 425 ± 10 μg/g of dry weight compared to 4.6 ± 0.2 μg/g, 75 ± 5 μg/g, and 1180 ± 20 μg/g in the control tissue samples representing cases of glycogenosis, reactive non-specific hepatitis, and typical ICC respectively.

Discussion

The temporal profile of the liver disease in this case was characterized by an apparent uneventful neonatal period, questionable mild hepatomegaly at the age of 40 days, poor weight gain therafter, apparent acute onset of severe liver disease at the age of 1 year, and a progressive steroid-resistant course that culminated in death due to liver failure in 4 months.

Prolonged intrahepatic and extrahepatic bilary obstruction were dismissed as potential diagnoses because of the lack of characteristic morphological changes of obstruction, the presence of adequate number of ILBDs, and since cholestasis was both mild and focal, failing to account for both the severity and diffuseness of the liver cell damage. Alpha-1-antitrypsin deficiency could not be diagnosed in the absence of specific fuidings. Metabolical conditions having hepatocellular fatty change as an essential finding, including galactosaemia and tyrosinaemia were deemed improbable and toxic and virological causes were excluded although serological assays for Epstein-Barr virus and delta and C types of hepatitis viruses were not done.

The clinicopathological and biochemical profile of this patient shows most of the typical features of ICC. This includes young age, parental consanguinity, rapid fatal outcome, panlobular hepatitis with diffuse pericellular fibrosis, hepatocellular ballooning, MBs and no steatosis, and increased hepatocellular copper concentration. The negative staining reactions for copper and copper-associated protein was surprising. However, Mehrotra et al. (1981) found negative rhodanine and orcein staining reactions in 2 of 43 liver biopsies which otherwise showed classical ICC. In our case, the negative histochemical findings are explained by the limited sensitivity of such methods since the quantitative assay revealed a significant increase in the hepatic copper concentration (425 ± 10 μg/g). The latter level, although high, is much less than those encountered in the classical ICC reported thusfar and which is above 1000 μg/g. (Tanner et al. 1979). However, two of the four American siblings with ICC reported by Lefkowitch (1982) had hepatic copper concentration less than 1000 μg/g (708 and 992 μg/g).

In summary, we present a case of fatal ICC-like disease in a non-Indian and the first in an Arab child. The hepatic copper overload was moderate and was not detectable by the histochemical methods.

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References

Adamson M, Reiner B, Olson JL, Goodman Z, Plotnick L, Bernardini I, Gahl WA (1992) ICC in an American child Gastroenterology 102:1771–1777

Anthony PP, Ishak KG, Nayak NC, Poulsen HE, Scheuer PJ, Sobin LH (1977) The morphology of cirrhosis: definition nomenclature, and classification. Bulletin of the World Health Organization 155:521–524

Lefkowitch JH, Honig C, King M, Hagstrom JWC (1982) Hepatic copper overload and features of Indian childhood cirrhosis in an American sibship. N Engl J Med 307:271–277

Maggiore G, De Giacomo C, Sessa F, Burgio GR (1987) Idiopathic hepatic copper toxicosis in an Italian child. J Pediatr Gastroenerol Nutr 6(6): 980–983

Mehrotra R, Pandey RK, Nath P (1981) Hepatic copper in Indian childhood cirrhosis. Histopathology 5:659–665

Muller-Hocker J, Weiss MM, Meyer U, Schramel P, Wiebecke B, Belohradsky BH, Hubner G (1987) Fatal copper liver storage disease in German infant resembling Indian childhood cirrhosis. Virchows Arch [A] 411:379–385

Muller-Hocker J, Meyer U, Wiebecke B, Hubner G, Eife R, Kellner M, Schramel P (1988) Copper storage disease of the liver and chronic dietary copper intoxication in two further German infants mimicking Indian childhood cirrhosis. Pathol Res Pract 183(1): 39–45

Nayak NC (1987) Indian childhood cirrhosis. In: MacSween RNM, Anthony PP, Scheuer PJ (eds). Pathology of the liver. Churchill Livingstone, New York, pp. 358–360

Roy S, Ramalingaswami V, Nayak NC (1971) An ultrastructural study of the liver in Indian childhood cirrhosis with particular reference to the structure of cytoplasmic hyaline. Gut 12:693–701

Tanner MS, Portman B, Mowat AP, Williams R, Pandit AM, Mills CF, Bremner I (1979) Increased hepatic copper concentration in Indian childhood cirrhosis. Lancet II: 1203–1205

Walker-Smith JA, Blomfield J (1973) Wilson's disease or chronic copper poisoning? Arch Dis Child 49:476–479

Yokoo H, Minick OT, Batti F, Kent G (1972) Morphologic variants of alcoholic hyaline. Am J Pathol 69:25–40