Case report

Benign recurrent intrahepatic cholestasis

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Summary:

A case of benign recurrent intrahepatic cholestasis (BRIC) in a 42 year old female, who had 3 episodes of jaundice and pruritus, each attack lasted about 6 months, resolved clinically and biochemically without permanent liver damage. The clinical features, biochemical tests, diagnostic criteria, etiopathogenesis and treatment are reviewed.

Introduction

Benign Recurrent Intrahepatic Cholestasis (BRIC) is an idiopathic syndrome characterized by recurrent, self-limited episodes of intra-hepatic cholestasis . Elevation of the alkaline phosphatase and bilirubin and near-normal aminotransferases and Gamma glutamyl transferace (GGT) are typical . The gene responsible for BRIC has been localized to chromosome 18.[1] The reason for the normal GGT and for the defect in bile acid synthesis is unknown, but failure of the hepatocytes to secrete bile acid into canaliculus may be involved.[2]

Case report

A 42-year-old Iraqi female patient presented in 1989 with jaundice, itching, malaise, anorexia, nausea, vomiting and low grade fever. Physical examination revealed jaundice and hepatomegaly. The TSB was 13 mg\dl, alkaline phosphatase18 K.A.U\dl, aminotransferases were normal and the liver biopsy showed intra-hepatic cholestasis. Her condition resolved on symptomatic treatment after 6 months.

The second attack occurred in 1995 during pregnancy in the first trimester as jaundice, pruritus and malaise. TSB was 9mg\dl, direct 6.3mg\dl, alkaline phosphatase 20 K.A.U\dl, aminotransferase were normal ,prothrombin time (PT) 17 second, (control 14 second), virology for HBV,HCV,HAV,HEV, immunology (ANA,AMA, ASMA) and ultrasound were normal. The attack persisted during pregnancy and subsided one month after delivery.

The third attack occurred in 2001 as jaundice, malaise, pruritus and low grade fever. Physical examination showed jaundice and hepatomegally. Laboratory Investigation: TSB 3.3mg\dl,direct 2.5mg\dl, alkaline phosphatase 17 KAU\dl, total serum protien.8.6 gm\dl. GGT , aminotransferase, PT, complete blood count, virology, immunology, s.iron, total iron binding capacity, s.copper, ceruloplasmin, 24 hr urine copper were all are normal MRI ;MRCP : the length of the liver is increased due to presence of Reidl's of normal homogenous signal intensity ,no intrahepatic biliary dilatation ,normal common bile duct & pancreatic duct .Liver biopsy reveled intra-hepatic cholestasis, mild mononuclear inflammatory cell infilrate of the portal tract, no evidence of piecemeal necrosis or increased fibrosis , no granuloma ,no malignancy. Uneventful recovery after 6 months on symptomatic treatment.

Discussion

BRIC is a rare disorder, first described in 1959 by Summerskill and Walshe, is characterized by recurrent attacks of cholestasis. Generally, there is a pre-icteric phase lasting 2-4 weeks during which the patient complaine of malaise, anorexia and pruritus.[3] subsequently, clinicl jaundice occur and may have an enlarged tender liver. There is no

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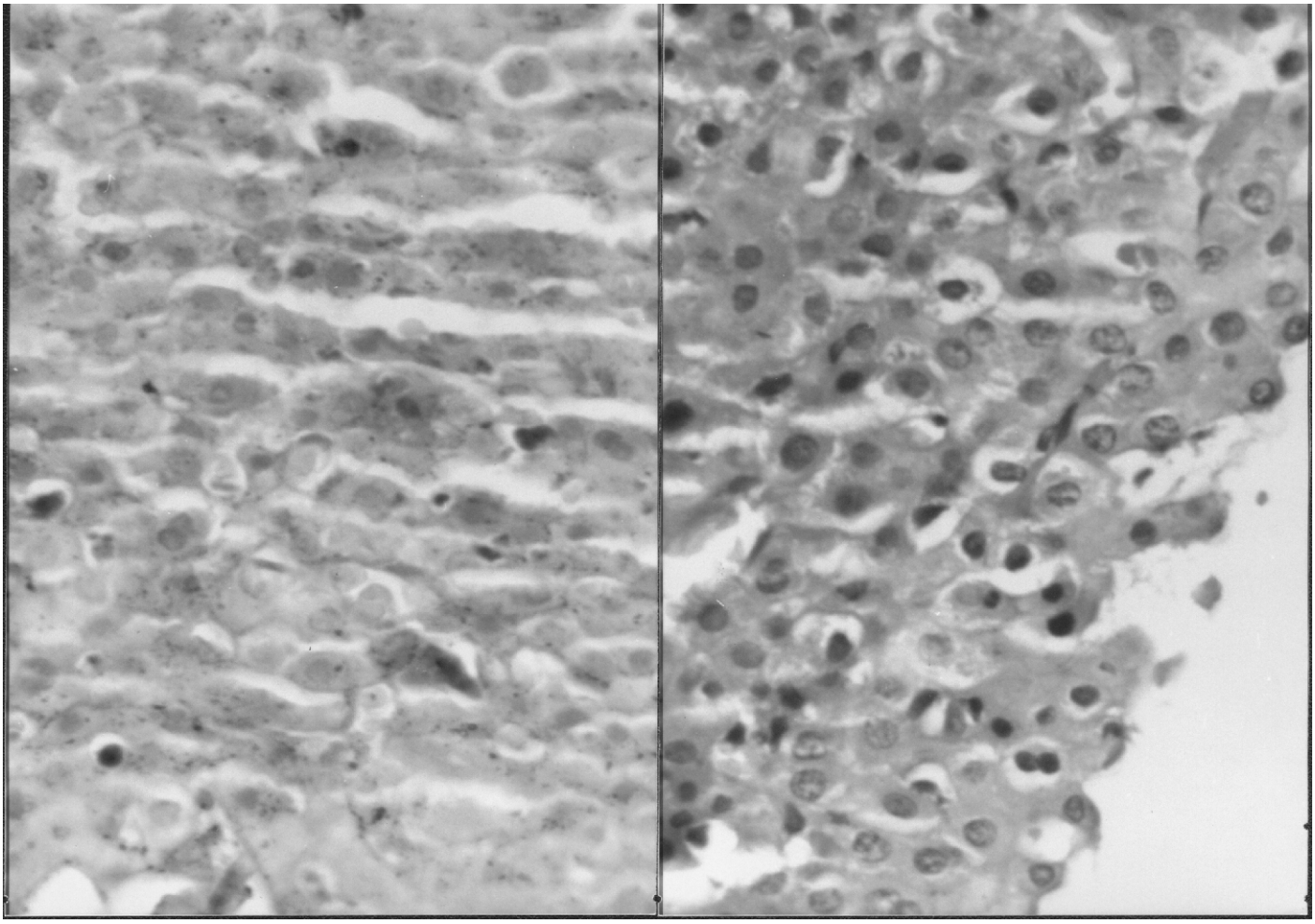
splenomegaly and patients are usually afebrile.[4] The majority are diagnosed in adolescence or early adulthood, [5] although it his been presented in infancy [6] as well as in middle age. [7]

The cholestatic episode last from a few weeks to several months, following which complete clinical and biochemical resolution, and may recur at intervals of several months to years. In a given patient , recurrent attacks resemble each other regarding symptoms and duration.[8] The attacks are clinically suggestive of biliary obstruction and may be accompanied by malabsorption and weight loss secondary to steatorrhoea, which may required parenteral fat soluble vitamins . The first one or two episodes may be misdiagnosed as acute viral hepatitis. In the pre-icteric phase, serum bile acids rise to abnormal level. Serum alkaline phosphatase activity is elevated. During the icteric phase, conjugated bilirubin accumulate in the serum. There is marked dissociatoion between bilirubin and bile acid level bilirubin accumulate in the serum. There is marked dissociatoion between bilirubin and bile acid level[9].The serum transaminases may be mildly elevated. The prothrombin time may be prolonged because of malabsorption of vit. K; light microscopic examination of the liver during cholestatic episode reveales features of intra-hepatic cholestasis. Electron microscopy shows marked alteration of bile canaliculi with distorted and reduced microvilli.[10]

The pathogenesis of this disorder is unknown, both familial and sporadic forms has been described, the familial form has an autosomal recessive pattern of inheritance, a gene termed FIC1 was recently identified and found to be mutated in patient with BRIC. The protein encoded by FIC1 show little similarity to gene that have been shown to play a role in bile canalicular excreation of various compounds. Rather it appear to be a member of a p-type ATPase family that transport aminophospholipid from the outer to the inner leaflet of a variety of cell membrane,



To be a member of a p-type ATPase family that transport aminophospholipid from the outer to the inner leaflet of a variety of cell membrane, it play an essential role in the enterohepatic circulation of bile acids. (11)

For the diagnosis of BRIC; The following criteria were proposed :

(1) At least three episodes of severe jaundice and pruritus, (2) Biochemical evidence of cholestsais, (3) Normal intra-and extra-hepatic bile duct on cholangiography, (4) Absence of a factor known to produce cholestasis and

(5) Symptome-free interval of several months or years.

The disease is very rare and both clinical and pathological features are necessary for the right diagnosis. The value of liver biopsy in excluding other icteric diseases is stressed; clinical and serological findings are also important for the diagnosis and management. (12)

BRIC is considered a benign disorder in that it does not lead to cirrhosis or end stage liver disease. However the episode of jaundice and pruritus can be prolonged and debilitating, and some patients have undergone liver transplantation to relief the intractable and disabling symptoms . Treatment during cholestatic episode is symptomatic ;proposed treatment have included cholestyramin, steroid, phenobarbital, 5-adenosylmethionine, ursodeoxycholic acid (urso); There is no specific treatment to prevent or shorten the occurrence of episodes.

References

1- Carlton, V. F., Knisely, A. S., Mapping of locus the benign recurrent intrahepatic cholestasis region Hum. Mol. Genet. n: long, 1995.

2- Jacquemin, et al; Evidence for defective primary bile acid secretion in children with progressive familial intrahepatic cholestasis. Eur. J. Pediatr. 153: 424,1994.

3- Williams R, et al ; ideopathic recurrent cholestasis: A study of Function and pathological Lesions in four cases. QJ Med 33 : 382 ,1964.

4- Summerskill WHJ. Walshe JM. Benign recurrent intrahepatic obstructive jaundice, Lancet 2: 686, 1959 .

5- Ruymann FB, Takeuchi A, Boyce HW. idiopathic, recurrent cholestosis. Pediatrics US : 812, 1970.

6- Tygstrup N. Intermittent possibly familial intrahepatic cholestatic jaundice. Lancet 1: 1171, 812, 1970.

6- Tygstrup N. Intermittent possibly familial intrahepatic cholestatic jaundice. Lancet 1: 1171, 1960.

7- Summerskill WHJ. The syndrome of benign intrahepatic cholestasis. Am J Med 38: 298, 1982.

8- De Pagter AGF, et al; familial benign intrahepatic cholostasis. Gastroenterology 71: 202,1976.

9- Summer Field, J. A; et al: A distinctive pattern of serum bile acid and bilirubin concentration in benign recurrent intrahepatic cholestasis. Hepatogastroenterol., 28 : 139, 1981.

10- Biempica L, Gutstein S, Arias I M. Morphological and biochemical studies of benign recurrent cholestasis. Gastroenter-ology 52 : 521 ,1967.

11- Iyantagi T, et al; Biochemical and molecular of genetic disorders of bilirubin metabolism Biochom Biophys Acta 1407: 173 , 1998.

12- Cissaret T, et al; follow up of benign recurrent intrahepatic cholestasis. Z. Gastroenterol. 1998 May; 36 (s) : 379-83.