

AN IRANIAN GIRL WITH BENIGN RECURRENT INTRAHEPATIC CHOLESTASIS

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Abstract: This report presents an 11 year-old girl with benign recurrent cholestasis (BRIC) who developed episodes of severe jaundice and pruritus at the ages of 2.5 and 10 years. Each episode lasted for 3-4 months. The peak level of serum bilirubin reached 33-37 mg/dL.

Liver function tests were all normal during the attack except for increased alkaline phosphatase and prolonged prothrombin time responsive to vitamin K injection. All laboratory tests were normal between attacks. Other causes of liver diseases and cholestatic disorders were excluded. Imaging studies performed during the second attack all were normal.

So, diagnosis of BRIC should be kept in mind in pediatric patients with cholestasis.

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Key words: Benign recurrent intrahepatic cholestasis, jaundice, cholestasis, icterus

CASE REPORT

An 11-year-old girl, who is the first child of her healthy consanguineous parents, developed two clinical attacks of deep jaundice and pruritus at the ages of 2.5 and 10 years. She was completely well with normal growth and developmental milestones between attacks. There was no history of febrile illness or ingestion of toxin or drugs. These attacks were preceded by two weeks of pruritus. The attacks lasted for 3-4 months. The peak level of serum bilirubin was 33-37 mg/dL. She had normal physical examination but obvious jaundice and itching. She also suffered from mild abdominal pain, malaise, dark urine and intermittent pale stools. There was no family history of liver diseases. Results of liver function tests in these two attacks are shown in table 1. Prolonged PT responded to vitamin K injection. Blood cholesterol and triglycerides were increased. Results of other laboratory investigations (complete blood count, erythrocyte sedimentation rate, serum electrolytes, calcium, phosphorus, total protein and albumin) were normal. Screening for hepatitis A, B and C, cytomegalovirus and Epstein-Barr virus yielded negative results. Serum immunoglobulines, and serology for antinuclear antibodies, anti-smooth muscle antibodies were negative. Serum and 24-hr urine copper were normal (serum copper: 85&100 µg/dL and urinary copper: 17 & 30 µg/day). Serum ceruloplasmin was slightly elevated (56-62 mg/dL). Ultrasonography of the liver, biliary tree and kidneys yielded normal results except for mild hepatomegaly with homogenous echogenicity. Abdominal MRI and ERCP done in the second attack were normal. Percutaneous liver biopsy performed in the first episode had mild infiltration of chronic inflammatory cells in portal area and some bile pigments in hepatocytes. In the second episode liver biopsy showed no significant abnormality except slight canalicular cholestasis in central areas (Fig.1, Fig. 2). All abnormal test results were normal between attacks (Table 1). Total bilirubin of 1.5 mg/dL with direct bilirubin of 0.5 mg/dL, ALKP of 350 IU/dL,

INTRODUCTION

Benign recurrent intrahepatic cholestasis (BRIC) is a form of relapsing cholestasis that was reported in 1959 (1). The disorder is uncommon but well described in literature. It is associated with normal life expectancy. This rare disorder with unknown etiology is said to be autosomal recessive. It's characterized by repeated episodes of intense pruritus and jaundice (2-4).

The onset of the disease may be at any age, but it usually starts in the first decade (4). It's rare in infancy (1). The intensity and duration of cholestatic episodes, and the length of the intervening periods, vary unpredictably (5). The number of attacks varies in different patients (1-27). Each attack lasts from months to weeks before resolving spontaneously (6).

The disorder does not lead to progressive liver disease (3).

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An Iranian girl with benign ...,

with normal serum cholestrol and triglycerides were found.

Treatment was supportive to relieve of pruritus

and supplement fat-soluble vitamins. In the second attack rifampin was tried with no benefit. The episodes resolved spontaneously.

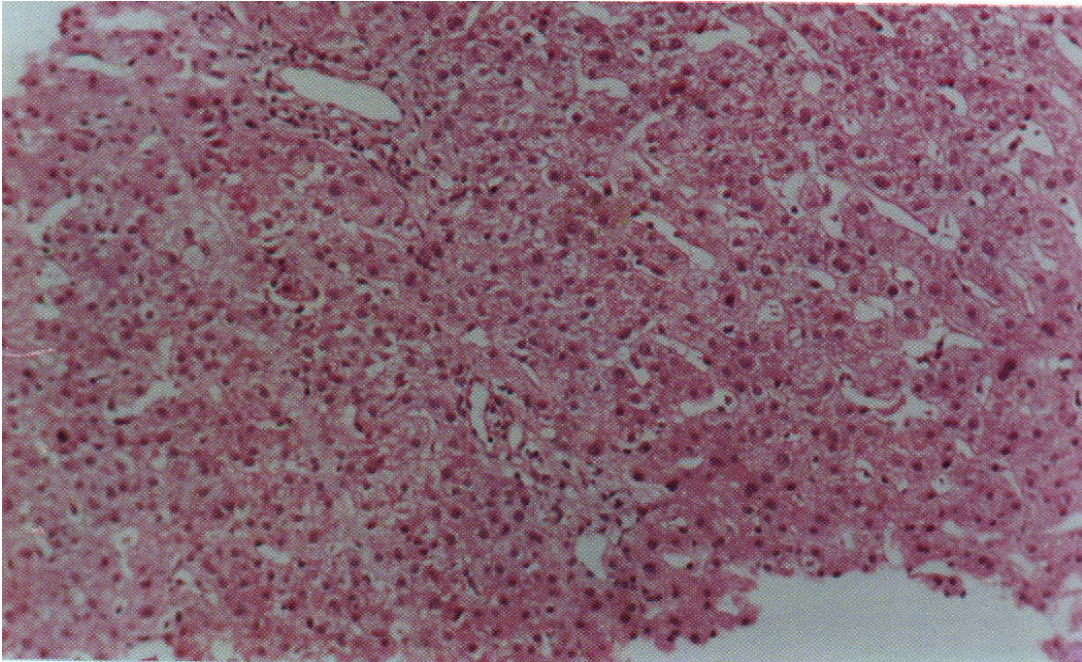


Fig. 1. Photograph of liver tissue with essentially normal portal spaces (Hematoxylin and Eosin $\times 160$)

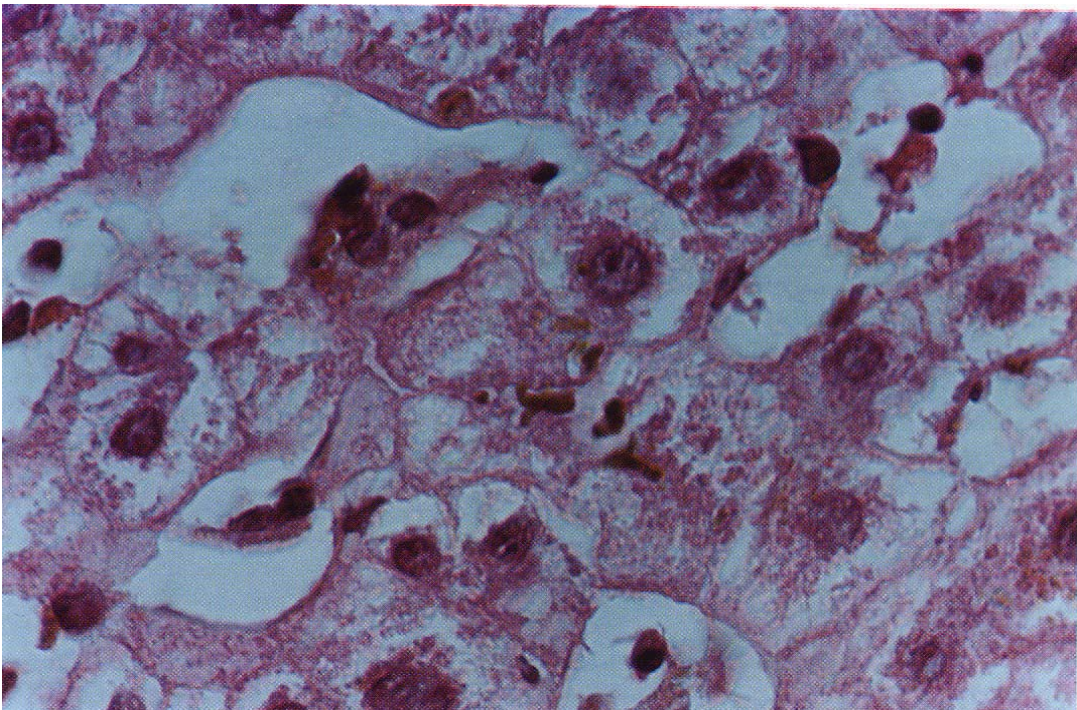


Fig. 2. Rare focus of canalicular cholestasis (Hematoxylin and Eosin $\times 400$)

Table 1. Liver function tests in the patient

Test	1st episode	2nd episode	Between attacks	Normal
Total bilirubin	33	37	1.5	1-1.5
Direct bilirubin	27.5	30	0.5	0.5
ALKP*	1280	1512	350	150-400
AST	32	27	30	15-35
ALT	19	25	22	25-42
GGTP**	NA****	20	18	5-32
PT***	42%	40%	100%	100%

* Alkaline phosphatase

** gamma glutamyl transpeptidase

*** prothrombin time

**** not available

DISCUSSION

Diagnosis of BRIC has been based on the following criteria: (a) several attacks of jaundice, pruritus and biochemical disorders indicating cholestasis; (b) bile plugs in the liver specimen; (c) normal intrahepatic and extrahepatic bile ducts at cholangiography; (d) absence of factors known to produce intrahepatic cholestasis; and (e) symptom-free intervals of several months to years (7). This patient fulfilled these criteria.

The episodes may be associated with febrile diseases (3) which was not apparent in this patient. The episodes may be related to pregnancy or oral contraceptive use (7).

The associated symptoms could be anorexia, weight loss, vomiting, fatigue, malaise, dark urine and pale stools(1,2,8). In one series of patients, pruritus was not accompanied by cholestasis in 15%. Gallstones have been reported in few patients (7). In one report there was intractable cough during the attack, which subsided when cholestasis was resolved (5).

Laboratory findings are non-specific. Serum conjugated bilirubin is elevated 3-10 fold. Serum transaminases are usually normal or slightly increased. Serum gamma glutamyl transpeptidase (GGTP) is normal. A persistent normal serum level of GGTP would suggest cellular or canalicular cholestasis rather than bile duct inflammation (9). Serum bile acids are elevated just before and during the attack, but the specimen was not available to measure. Serum ceruloplasmin is usually normal. But in this patient it was slightly elevated during the attacks, which may be as an acute phase reactant.

Results of light microscopic examination of liver in the icteric period are normal or show minimal reactive changes similar to that observed in this patient. It may also show centrilobular cholestasis

with mild inflammatory infiltration of portal spaces with mononuclear cells (4,6).

It has been suggested that BRIC inheritance is either autosomal recessive or dominant with incomplete penetrance. Genetic studies have mapped the defect of this disorder to the long arm of chromosome 18q21-22 (3,4,6,10).

Treatment is supportive and seems to have no effect in disease process. Although there are some reports of beneficial effects of ursodeoxycholic acid, cholestyramine or rifampin, but in this patient none of them resulted recovery (4,6,11). But cholestyramine seemed most effective in relief of pruritus.

The patient's clinical and para-clinical data are consistent with BRIC diagnostic criteria. So, the disease should be kept in mind as a differential diagnosis of recurrent cholestasis in Iranian children.

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