Case Report

Benign Recurrent Intrahepatic Cholestasis: A Rare Case Report

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Abstract

One of the very rarely encountered causes of cholestasis is benign recurrent intrahepatic cholestasis (BRIC). It is, usually, inherited and occasionally sporadic. It presents as recurrent relapsing and remitting cholestatic type of jaundice with normal intra and extrahepatic biliary tree. This condition, usually, benign can very rarely progress onto cirrhosis. We report an interesting case of an 18-year-old male who presented with recurrent episodes of cholestatic jaundice and pruritus, first episode beginning at 6 years of age. Imaging and liver biopsy confirmed the diagnosis of BRIC. He was managed with Rifampicin in addition to cholerectics and anti histaminics due to the initial failure in treatment response.

Keywords: Benign recurrent intrahepatic cholestasis, Cholestasis, Cirrhosis, Magnetic resonance cholangiopancreatogram

INTRODUCTION

Benign recurrent intrahepatic cholestasis (BRIC) is a rare inherited disease characterized by recurrent attacks of jaundice and pruritus which resolve spontaneously without ensuing liver damage.[1] In between the attacks, patients are completely symptom-free. The diagnosis is, usually, made after excluding other causes of primary and secondary cholestasis along with a confirmatory liver biopsy. Treatment is purely symptomatic ranging from bile acid binding resins, centrally acting opioid antagonists, enzyme inducers like rifampicin and phenobarbital, ultraviolet phototherapy and plasmapheresis to relieve pruritus.[2] Approximately 100 cases have been reported till now worldwide.[3] This disorder forms part of a continuum.[4] At one end of the spectrum, lies progressive familial intrahepatic cholestasis (PFIC) and on the other end is BRIC. To the best of our knowledge till 2010, only five cases have been reported from India with only a single case from Southern India.

CASE REPORT

An 18-year-old male presented to us with insidious onset, gradually progressive jaundice, pruritus, intermittent pale stools, and high colored urine for 3 months. He gave a history of similar episodes in the past. First episode began at 6 years of age, wherein an insidious onset jaundice and pruritus lasted for about 2 months and then gradually reduced over a period of 3 months. Following this episode, he was asymptomatic for next 6 months. He again suffered from a similar episode of jaundice and pruritus which resolved slowly again over a period of about 3 months. During the above episodes, he was treated at a local practitioner with cholerectics which offered some temporary relief. He was then apparently asymptomatic for the next 9 years. The cycles again began at 15 years of age with increased frequency and severity with an episode lasting for about more than 5 months at a rate of 1-2 cycles per year. During these episodes, there was no abdominal pain, distension, bleeding tendencies or loss of weight. There is no history of febrile illness prior to or along with jaundice. There were no involuntary movements, irritable behavior or history suggestive of similar illness in the family.

On examination he had a short stature, (height - 142 cm, weight - 40 kg, body mass index -20.4). He was icteric, had generalized hyperpigmentation, scratch marks. There were no signs of vitamin deficiencies or ecchymosis. He had a regular pulse rate of 88/min with a blood

pressure of about 110/80 mm Hg. His abdominal examination was normal with no localized tenderness, organomegaly or free fluid. Rest of the systemic examination was normal. His investigations (Table 1) revealed a normocytic normochromic anemia, prominent conjugated hyperbilirubinemia, markedly elevated alkaline phosphatase with normal levels of hepatic transaminases and gamma glutamyl transpeptidase. An abdominal ultrasonogram revealed normal study of intra-abdominal organs. Magnetic resonance cholangiopancreatogram (Figure 1) was normal and did not reveal any features suggestive of obstruction. Viral markers for hepatitis A, B, and C were negative. Serum ceruloplasmin (8 mg) was within normal range. Workup for autoantibodies like anti-nuclear, anti-mitochondrial and anti-smooth muscle antibodies was negative. Based on clinical and laboratory findings, the possibility of recurrent intrahepatic cholestasis was considered, and liver biopsy was performed.

Liver biopsy (Figure 2) showed minimal expansion of portal tracts with parenchyma showing accentuated hepatocanalicular cholestasis with rosette formation, preserved lobular architecture and mild increase in inflammatory cell infiltrates. Based on history of cyclical episodes of cholestatic jaundice, clinical features, biochemical values, imaging studies, and biopsy findings, a diagnosis of BRIC was made. We explained the condition to the patient and then started him on anti histaminics and ursodeoxy cholic acid 500 mg QID. Even with 14 days of treatment, there was no improvement in clinical or laboratory parameters. Hence, tablet rifampicin 300 mg was added. Icterus and pruritus both began to reduce and alkaline phosphatase and bilirubin slowly normalized over a period of 3 weeks.

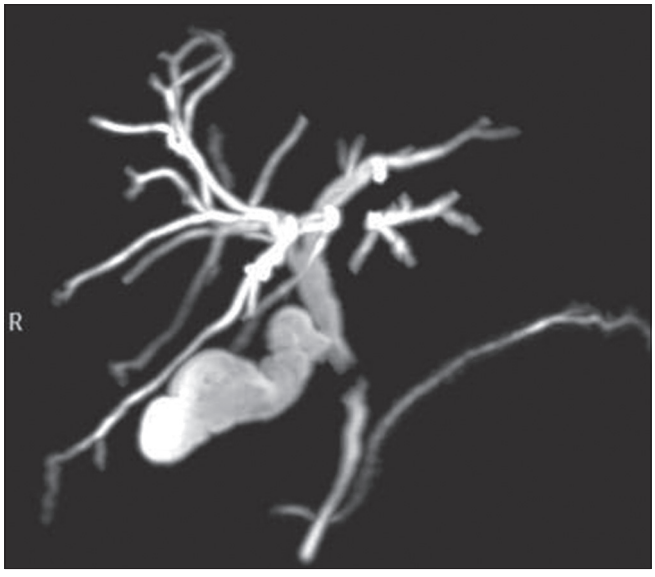

Figure 1: Magnetic resonance cholangio pancreatogram showing normal undilated intra and extrahepatic bile ducts

DISCUSSION

BRIC is a rare disorder first described by Summerskill and Walshe in 1959 characterised by recurrent bouts of jaundice and pruritus.[2] The exact prevalence of BRIC remains unknown, but estimated incidence varies between 1/50,000 and 1/100,000 births. It is a benign hereditary form of cholestasis.[4] But progression to PFIC and liver failure have also been described. It occurs due to abnormalities in cannalicular excretion of bile acids and phospholipids. There are 3 types. BRIC 1 and 2 are both autosomal recessive disorders while BRIC 3 is autosomal dominant. BRIC 1 is due to mutation in ATP8B1 gene on chromosome 18q21. BRIC 2 is due to mutation in bile salt export pump (ABCB11) on chromosome 2q24. Defects in ABCB4 encoding the multidrug resistant protein 3 resulting in impaired biliary phospholipid secretion results in BRIC 3. All the 3 subtypes are phenotypically similar. This disease is distributed worldwide with both sexes being

Table 1: Investigations

Hemoglobin	12.2 g/dl (13-16 g/dl)
Total count	6600 cells/mm^3 (4000-11,000)
Platelet	385,000 (1.5 lakhs-4 lakhs)
Total bilirubin	16.3 mg (0.3-1.3 mg/dl)
Direct bilirubin	10.8 mg (0.1-0.4 mg/dl)
Alkaline phosphatase	688 IU (33-96 U/L)
Gamma glutamyl transferase	28 IU (9-58 U/L)
Prothrombin time	Control 12-15 s Test 14 s
APTT	Control 26 s Test 26 s
INR	1.0
Total protein	6.4 g (6-8 g/dl)
Serum albumin	4.3 g (4-5 g/dl)
Aspartate transaminase	100 IU (12-38 U/L)
Alanine transaminase	97 IU (7-41 U/L)

APTT: Activated partial thromboplastin time, INR: International normalized ratio

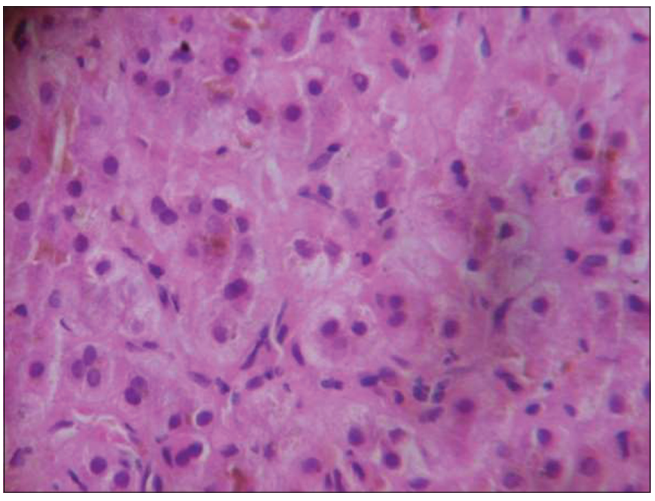

Figure 2: Liver biopsy showing bland intrahepatic cholestasis and inflammatory cell infiltrates

equally affected. It manifests early in life with the onset in the first decade. Duration of cholestasis varies from 2 to 24 weeks. Between the attacks, patients are completely asymptomatic. Associated symptoms include anorexia, steatorrhea, and deficiency of fat-soluble vitamins. BRIC 2 is at times associated with cholelithiasis.

Conditions like Wilson's disease, alpha-1 antitrypsin deficiency, autoimmune hepatitis, and chronic viral hepatitis are to be considered in the differential diagnosis. In our patient, the liver biopsy did not show ductopenia or florid ductular reaction. There was no bridging or peri ductal concentric fibrosis. Periodic acid Schiff-diastase stain was negative for intracytoplasmic inclusions. Iron staining was negative for increased deposits. In 1999, Luketic and Schiffman proposed a diagnostic criteria for BRIC which includes (a) At least two episodes of jaundice separated by an asymptomatic interval of months to years, (b) laboratory values consistent with intrahepatic cholestasis, (c) severe pruritus secondary to cholestasis, (d) liver histology demonstrating centrilobular cholestasis, (e) normal intrahepatic and extra-hepatic bile ducts confirmed by cholangiography, (f) absence of factors associated with cholestasis.[5] Our patient fulfilled all the above-mentioned criteria.

The main goal of treatment initially is to relieve pruritus till spontaneous resolution of attacks occurred.[1] The various options include anti histamines, cholerectic agents like cholestyramine and ursodeoxycholic acid and rifampicin.[6] Rifampicin has also been shown to reduce and prevent relapses in patients with BRIC.[7] Successful treatment with colestimide for preventing attack of jaundice in a BRIC patient has been reported from Japan.[8] Molecular adsorbent recirculation system and partial biliary diversion have been tried in refractory cases.[9] A case report from Netherlands suggesting the use of endoscopic retrograde cholangiopancreatography mediated nasobiliary drainage for long term relief from jaundice and pruritus has been reported. Liver transplantation is indicated when BRIC progresses to PFIC.

CONCLUSION

BRIC is a rare disease with initial case reports suggesting its benign nature. But recent reports have shown instances where the patient initially diagnosed as BRIC progresses to cirrhosis namely PFIC. Hence, the patient should be under regular follow-up for monitoring the course and progression of this disease. Gene therapies are under trial which may succeed in the near future.[3] Furthermore, BRIC should be included in the list of differentials in evaluating such a patient with recurrent cholestasis.

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