Adult onset Benign Recurrent Intra Hepatic Cholestasis type 2 - a case report

Senthamizh Selvan K
Senior resident, Department of Medical Gastroenterology, JIPMER, Puducherry, India, Post graduate, Department of Medical gastroenterology, Madras Medical College, Chennai, India

Pugazhendhi T
Professor, Department of Medical Gastroenterology, Madras Medical College, Chennai, India

ABSTRACT
Benign Recurrent Intrahepatic Cholestasis (BRIC) is a disease characterized by recurrent episodes of pruritus and jaundice, which are self limiting. It presents usually in the second decade of life. First presentation of BRIC in adulthood is rare. Here we present a case of 36 year old male with recurrent episodes of pruritus and jaundice. His liver function test showed elevated direct bilirubin and a normal gamma glutamyl transferase level, Magnetic resonance cholangiogram (MRC) showed normal bile ducts, viral markers and autoimmune markers were negative. Liver biopsy was suggestive of chronic intrahepatic cholestasis. He was treated with ursodeoxycholic acid and supportive measures. He showed rapid improvement in his symptoms and had no further attacks as on date.

KEYWORDS:
Cholestasis, Gamma glutamyl transferase, Ursodeoxycholic acid

INTRODUCTION
Benign Recurrent Intrahepatic Cholestasis (BRIC) is a rare disorder characterized by recurrent episodes of intense pruritus and jaundice that resolves spontaneously. The disease is thought to be benign in nature without progression to liver dysfunction. However, development of biliary cirrhosis has been documented. [1] Approximately 100 cases have been reported till now worldwide [2] and less than 10 cases have been reported from India. We report BRIC in an adult patient, from our institution.

CASE REPORT
A 36 years old male was admitted with jaundice of 3 months duration associated with pruritus, pale stools and high colored urine. Jaundice was not accompanied by fever, prodrome, abdominal pain or mass. He did not manifest with other features such as abdominal distension, swelling of legs, altered sensorium or GI bleeding. He had not received previous blood transfusion and there were no risk factors for viral hepatitis. He had five similar episodes in the past 2 1/2 years, each lasting for approximately 3-4 weeks and subsided spontaneously. He is the elder of the two siblings with no family history of liver disease.

On examination, he was icteric and had shiny nails, excoriations and scratch marks. There was no hepatomegaly, splenomegaly or ascites. There were no signs of hepatocellular failure. Investigations showed a hemoglobin of 11.3 g/dl, normal total and differential counts, serum bilirubin of 6.8 mg/dl, alkaline phosphatase (ALP) of 181 IU/L, γ-glutamyl transferase (GGT) of 10 IU/L, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of 31 and 20 units IU/L respectively, and prothrombin time of 16 seconds. He was negative for hepatitis B surface antigen, antibodies to hepatitis C virus, IgM antibodies to hepatitis A virus and hepatitis E virus, antinuclear antibodies, anti-smooth muscle antibodies, anti-mitochondrial antibodies and anti-liver kidney microsomal antibodies. Magnetic resonance cholangio-pancreatography (MRCP) showed normal intra- and extra-hepatic biliary system. (fig 1&2)

Liver biopsy revealed polyhedral hepatocytes showing feathery degeneration with intracytoplasmic bile pigments and foci of lymphocytes within lobules. There was no definite fibrosis. (fig 3)

DISCUSSION
Based on the clinical presentation, laboratory tests, imaging and histology, a diagnosis of BRIC-2 was made in this patient. Patient was treated with ursodeoxycholic acid (UDCA) 300mg three times a day along with supplementation of fat soluble vitamins (A, D, E, and K). Patient’s symptoms improved after a month and liver function tests were normalized. He is on regular follow up as on date without recurrence of symptoms.

Fig-1 MRCP image

Fig-2 MRI image

Fig-3 Liver biopsy image
1959 characterized by recurrent bouts of jaundice and pruritus.[3] There are 2 types, BRIC 1 and 2 both are autosomal recessive disorders. Mutations of the FIC1 (familial intrahepatic cholestasis 1) gene on chromosome 18q21-22 have been identified as the pathogenetic basis of the two hereditary cholestasis syndromes, benign recurrent intrahepatic cholestasis (BRIC-1) and PFIC-1 (progressive familial intrahepatic cholestasis-1).

BSEP (Bile Salt Export Pump) is expressed in the liver canicular membrane, and functions as an ATP-dependent bile acid transporter. The mutations in the FIC 2 (also called BSEP, ABC B1) gene, located on chromosome 2q24 results in accumulation of bile salts and hepatocellular damage leading to PFIC-2 (progressive familial intrahepatic cholestasis-2) within the first decade of life. Pruritus and jaundice are hallmarks of the disease. Other rare manifestations include fever, headache, arthralgia, anorexia, nausea and malaise. The cholestatic episodes are preceded by influenza-like illness or gastroenteritis. During the periods of prolonged cholestasis, fat malabsorption and vitamin K malabsorption occur leading to coagulopathy and hemorrhagic complications. Clinical features of chronic cholestatic liver diseases are absent. Each episode of jaundice lasts for 3-4 months, then spontaneously subsides, and usually recurs in approximately yearly intervals. FIC 1 (ATP8B1) is also expressed in the membrane of cells of small intestine, lung, kidney and pancreas. Hence both syndromes (PFIC-1 and BRIC-1) are associated with extrahepatic manifestations such as diarrhea, bile acid malabsorption, pneumonia, pancreatitis and nephrolithiasis. Such manifestations are not present in PFIC-2 and BRIC-2 as in our patient.

Biochemically, conjugated hyper-bilirubinemia with a moderate elevation of ALP levels is observed. Serum AST and ALT levels are either normal or only mildly elevated (up to 3 times of normal). The characteristic hallmark of BRIC and other forms of familial intrahepatic cholestasis (Type 1 and 2) that separates these disorders from other cholestatic disorders is the GGT level, which remains normal. As an attack resolves patients are totally asymptomatic and all these laboratory abnormalities normalize. On liver biopsy the liver architecture is normal. A bland cholestasis (without inflammatory changes) with presence of bile in dilated canaliculi, hepatocytes, and Kupffer cells is present. On cholangiography (MRCP or ERCP) the bile ducts are normal. The diagnostic criterion for BRIC is suggested by Luketic and Schiffman (Box -1)

- At least two episodes of jaundice separated by a symptom free interval lasting several months to years
- Laboratory values consistent with intrahepatic cholestasis
- GGT either normal or only minimally elevated
- Severe pruritus secondary to cholestasis
- Liver histology demonstrating centriflobular cholestasis
- Normal intra- and extra-hepatic bile ducts by cholangiography
- Absence of factors known to be associated with cholestasis (ie, drugs, pregnancy)

Box-1 Diagnostic criteria for BRIC

Our patient fulfilled all the above criteria. [4] Hence the diagnosis of BRIC (type 2) was made. The absence of onset in the first decade, pancreatitis, malabsorption and hearing loss distinguish type 2 from type 1.

Long term follow-up of BRIC patients has shown that the disease follows a benign course and that there is no progression to chronic liver disease. However a recent report suggested that few patients of BRIC may progress to PFIC-1.[5] Treatment is purely symptomatic. Anthistaminics, bile acid binding resins, centrally acting opioid antagonists[6], enzyme inducers like rifampicin and phenobarbital, UV phototherapy and plasmapheresis [7] have been tried for pruritis. Anecdotal reports have suggested that UDCA may improve pruritis, shorten duration of attacks and prevent recurrence in these patients.[8] Molecular adsorbent recirculating system (MARS) has been shown useful[9]. Liver transplantation has been carried out in a patient with BRIC for intractable pruritus.[10]

References: