Case Report

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Role of Biopsy in Benign Recurrent Intrahepatic Cholestasis –Report of Two Rare Cases

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ABSTRACT

Benign recurrent intrahepatic cholestasis (BRIC) is an inherited self limiting cholestatic disorder. It is very rare and less common than its severe form, Progressive familial intrahepatic cholestasis (PFIC). Due to impaired canalicular biliary excretion, patients develop recurrent episodes of jaundice and intense pruritus with characteristic symptom free intervals. Most of the cases have a benign course and are managed symptomatically. Histopathological examination of liver biopsy is essential in cases of recurrent intrahepatic cholestasis to confirm the diagnosis. Here we report two cases of biopsy confirmed Benign recurrent intrahepatic cholestasis for its rarity.

Keywords: *Benign Recurrent Intrahepatic Cholestasis, Canalicular Cholestasis, Gamma Glutamyl Transferase, Jaundice.*

Introduction

Benign recurrent intrahepatic cholestasis (BRIC) is an inherited cholestatic disorder due to impaired canalicular biliary excretion. Patients present with recurrent attacks of jaundice and intense pruritus. Asymptomatic period between icteric episodes is classical of BRIC. Histopathological examination of liver biopsy shows centrizonal canalicular cholestasis without any inflammation or fibrosis. Due to its episodic and non progressive nature, patients are usually counseled and managed symptomatically. We report two cases of BRIC in a 23 years old male and a 15 years old female with histopathologic confirmation. Less than ten cases have only been reported so far in India with biopsy done in few cases.

Case Reports

Case report 1: 23 years old male presented with chief complaints of yellowish discolouration of urine and sclera and pruritus for 2 months and vomiting for 20 days. He had history of recurrent icteric episodes for past 2 years. Each episode started with pruritus and lasted for 1 to 1 ½ months. Upon evaluation, he was found to have elevated bilirubin which got completely resolved without intervention.. On general examination, he was icteric with no pallor and pedal edema. There were no features of liver cell failure. Ultrasonogram showed splenomegaly and normal liver. Magnetic resonance cholangiopancreatography revealed mild splenomegaly of about 13.79 cm. There was no evidence of intrahepatic biliary radicle dilatation. Common bile duct, liver and gall bladder were normal.

CASE REPORT: 2: 15 years old female presented with chief complaints of yellowish discolouration of urine and sclera for 20 days and pruritus for 20 days. She had her first episode at 4 years of age which lasted for 1 month, second episode at 12 years of age, third and fourth episodes at 15 years of age. Symptoms got completely resolved without intervention. On general examination, she was icteric with no pallor and pedal edema. There were no features of liver cell failure. Ultrasonogram showed hepatomegaly with mild coarse echoes and splenomegaly of 13 cm.

Routine hematological investigations and renal function tests were normal. Viral and autoimmune markers were negative. Serum ceruloplasmin and 24 hour urinary copper levels were normal in both cases. Both cases had normal ALT and AST levels. They had elevated serum direct bilirubin levels and alkaline phosphatase levels. Serum gamma glutamyl transferase (GGT) levels were 45U/L and 11U/L respectively.

Liver biopsy sections of first case showed hepatic parenchyma with maintained spatial arrangement and 2-4 portal tracts (Figure 1). Prominent centrilobular canalicular cholestasis and focal feathery degeneration of hepatocytes are seen (Figure 2). There is no significant interface hepatitis, portal tract changes or fibrosis.

Liver biopsy sections of second case showed liver tissue with preserved architecture (Figure 3). Lobules showed prominent canalicular cholestasis (Figure 4), ballooning of hepatocytes and prominent sinusoids.

In correlation with clinical history and histopathological findings of centrilobular canalicular cholestasis, final diagnosis of Benign Recurrent Intrahepatic Cholestasis (BRIC) is made in both cases. Molecular genetic analysis could not be done due to unavailability.

Patients were treated with Cholestyramine 4g 6th hourly and Ursodeoxycholic acid 300mg twice a day. One patient was added on Rifampicin and Sertraline for severe pruritus.

Discussion

Benign Recurrent Intrahepatic Cholestasis (BRIC) is characterized by recurrent episodes of intense pruritus and jaundice with intervening periods of normal health[1]. First case of BRIC was reported by Summerskill and Walshe in 1959[1,2]. BRIC is also known as Summerskill –Walshe - Tygstrup syndrome[2].

In 1969, Tygstrup and Jensen proposed the following criteria for defining BRIC[3,4].

a) Several episodes of jaundice and severe pruritus with symptom free intervals of months to years.
b) Absence of cholestatic factors like pregnancy, use of oral contraceptives and drugs.
c) Biochemical signs of obstructive jaundice but with normal bile ducts in cholangiography.
d) Histology showing bile plugs within ducts.

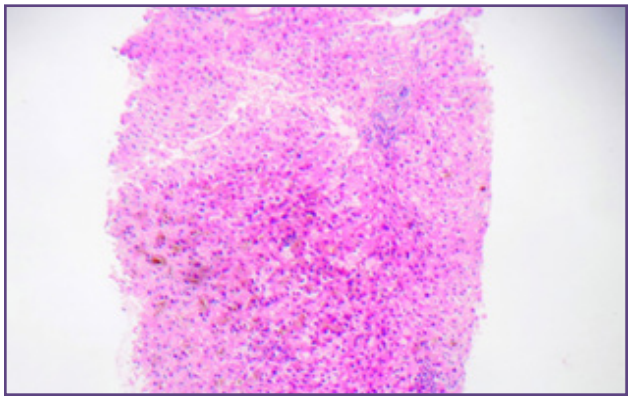

Fig. 1: Hepatic parenchyma with maintained lobular architecture (H&E, 100X).

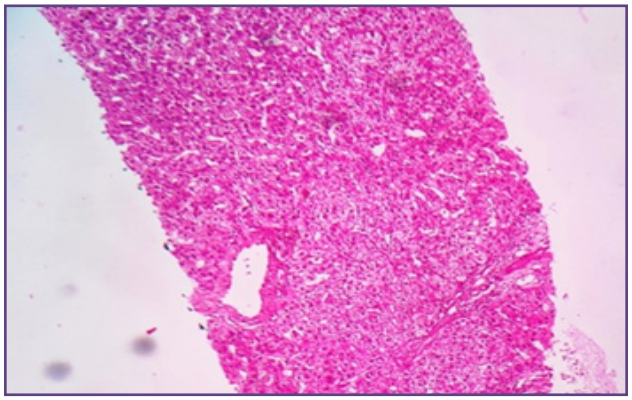

Fig. 3: Liver parenchyma with preserved architecture. (H&E, 100X).

Prevalence is unknown but the estimated incidence is 1 in 50,000 – 1,00,000 live births[5]. Both sexes are equally affected[5]. It is less common than Progressive Familial Intrahepatic Cholestasis (PFIC) which lies at the other end of the spectrum of hereditary cholestatic disorders. Most of the cases of BRIC originated in Europe and North America from a small village in Faroe islands[3,6]. Japan and Israel had the first incidence of BRIC in Asia. In India, first case of BRIC was documented by R.Kochhar et al in 1988 in association with Retinitis Pigmentosa[6].

Age at first presentation is usually seen within first two decades of life[7]. Symptomatic episode may last for days to weeks and may occur once in every month or once in a decade[5,7]. Frequency of attacks decreases with age[7].

There are 3 types of BRIC – 1, 2 and 3[7,8]. BRIC 1 and 2 are autosomal recessive disorders whereas BRIC 3 is an autosomal dominant disorder[7]. Progressive Familial Intrahepatic Cholestasis (PFIC) and BRIC represent two extreme ends of the spectrum of following mutational disorders[7,8].

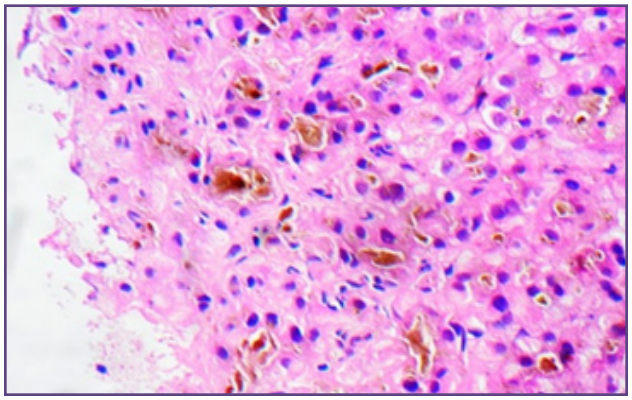

Fig. 2: Canalicular (bland) cholestasis in zone 3 and focal feathery degeneration (H&E, 400X).

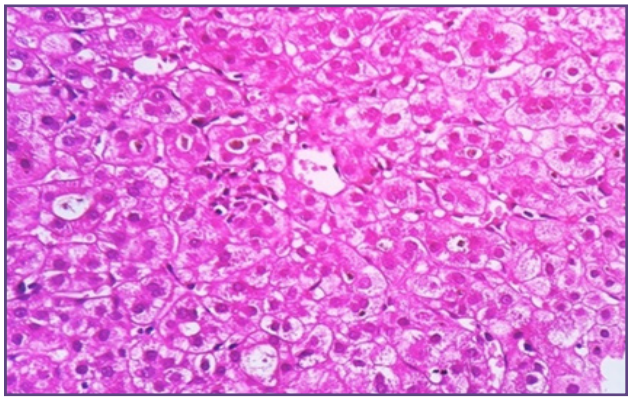

Fig. 4: Hepatic lobule showing canalicular cholestasis. (H&E, 400X).

a) BRIC 1 and PFIC 1 are due to mutations in ATP8B1 gene in chromosome 18q21 which encodes FIC1 protein on canalicular membrane of hepatocytes and other epithelia.

b) BRIC 2 and PFIC 2 are due to mutations in ABCB11 gene in chromosome 2q24 which encodes Bile salt export pump protein (BSEP).

c) BRIC 3 and PFIC 3 are due to mutations in ABCB4 gene which encodes Multidrug resistance protein 3 (MDR3).

Missense mutations leading to partial functional deficiency of FIC1 and BSEP occur in 50% cases of BRIC[7]. Nonsense mutations/frame shift mutations causing complete absence of protein occur in PFIC.

Amino-phospholipid flippase and phospholipid floppase are encoded by genes ATP8B1 and ABCB4 respectively. They translocate phospholipids along the membrane and protect from high bile salt concentration by neutralizing their detergent effect[7]. BSEP encoded by ABCB11 is the main exporter of hepatocyte bile acids to canaliculi[7,8].

Thus mutations in these genes cause impairment of canalicular excretion leading to intrahepatic cholestasis[7].

Episodes almost always clinically manifest in two phases[9].

i. Preicteric phase lasts for 2-4 weeks and is characterized by malaise, anorexia and intense pruritus leading to insomnia.

ii. Icteric phase is characterized by increasing jaundice without abdominal pain or fever.

The most common presentation is mild icteric phase with no signs of liver cell failure. Tygstrup in 1999 reported 36 episodes in a single patient in his study[3]. Very long symptom free interval of more than 15 years has been reported only thrice in the literature with the longest duration being 23 years[10]. There is no progression to cirrhosis in most of the cases and explains its benign nature[8]. C.Putterman et al in a followup of a case of BRIC over 25 years with repeated biopsies observed no evidence of chronic liver disease[10]. Extrahepatic manifestations such as acute pancreatitis and diabetes can be seen in BRIC 1 whereas gall stones can be seen in BRIC 2[4,5].

Jaundice is usually of obstructive type characterized by conjugated hyperbilirubinemia, increased serum bile acids and serum alkaline phosphatase levels[4]. Serum aminotransferases are either normal or mildly elevated. Serum GGT is characteriscally low or normal in BRIC types 1 and 2 but high in BRIC type 3[4,7].

Asymptomatic phase has biochemical resolution with normal liver function tests.

In 1999, Luketic and Schiffman[11] proposed the diagnostic criteria for BRIC which includes:

1. At least two episodes of jaundice separated by a symptom free interval lasting for several months to years.
2. Laboratory values suggestive of intrahepatic cholestasis.
3. Severe pruritus due to cholestasis.
4. Normal intra- and extrahepatic bile ducts confirmed by cholangiography.
5. Absence of factors associated with cholestasis, e.g. drugs, pregnancy.
6. Liver histology showing centrilobular cholestasis.

Our two patients have all the above features.

Ooteghem et al reported progression to PFIC with cirrhosis in four cases of BRIC[12]. Recent studies proposed the need of followup for monitoring the course and progression of disease.

BRIC is characterized by intrahepatic Centrilobular Canalicular Cholestasis in all patients[13]. Cholestasis is usually not accompanied by inflammation, duct damage, ductular reaction and fibrosis[13]. Liver biopsy is normal during remission. Drugs, pregnancy, oral contraceptives use, early large duct obstruction and coexistent malignancy must be excluded as causes of bland cholestasis. PFIC can be ruled out if there is no evidence of liver cell fibrosis.

In long term followup study of BRIC, C.Putterman et al observed mild lymphocytic infiltration, regression of previous thin fibrous bands and absence of fibrosis in repeated biopsies[10].

The main aim of treatment is to improve quality of life by controlling pruritus[7]. Patients are managed symptomatically with Ursodeooxycholic acid, Cholestyramine, Rifampin, Sertraline or Naltrexone. Other treatment modalities include endoscopic nasobiliary drainage, partial external ileal diversion, phototherapy and liver transplantation[8,13].

Liver transplantation can be done in cases with intractable pruritus[13]. There is a risk of progression to steatohepatitis and cirrhosis in these patients as the graft develops steatosis due to the continued expression of dysfuntional FIC1 in intestinal epithelium.

Conclusion

Benign recurrent intrahepatic cholestasis should be considered in the differential diagnosis of recurrent

intrahepatic cholestasis in young aged patients without signs of liver cell failure. It is a rare inherited cholestatic disorder with a good prognosis. Early diagnosis and confirmation with liver biopsy help to prevent other expensive investigations. Patients can be managed symptomatically and followed up.

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