Benign recurrent intrahepatic cholestasis

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Abstract:
Benign recurrent intrahepatic cholestasis (BRIC) is a rare cause of cholestatic jaundice in children and young adults. Jaundice recur throughout life but does not lead to chronic liver disease or cirrhosis. It is an autosomal recessive disorder characterised by profound elevation of alkaline phosphatase with normal gamma glutamyl transferase activity. Gene responsible for BRIC is located in chromosome 18. Genetic studies have demonstrated that this disorder is a result of mutation of ATP8B1, which is involved in the transport of bile in the biliary canaliculi. Treatment is mostly symptomatic. Very few cases have been reported till date. Here we report a 24 year old female, who had recurrent episodes of jaundice since 2 years of age.

Keyword:
BRIC, cholestasis, jaundice, cirrhosis

Case report
24 years old female presented with history of yellowish discolouration of sclera, intense pruritus and hyperpigmentation of skin all over the body 3 months. Patient had first episode of jaundice at the age of 2 years which lasted for one month. Second episode at the age of 14 years which lasted for two months. During each episode patient was admitted in hospital and discharged. She was asymptomatic in between the episodes. No family history of liver disease. No history of ingestion of toxins or drugs.

Physical examination:
Icteric, diffuse excoriations due to severe itching. No signs of hepatocellular failure in the form of spider angioma, palmar erythema, thenar atrophy. No pallor/significant lymphadenopathy/pedal edema. No KF ring. No hepatomegaly/splenomegaly. Other systems clinically normal.

Lab Investigations:
Total Bilirubin 31.8mg/dl; Direct - 23mg/dl; Liver Enzymes: AST-89 IU/L(5-40); ALT-140 IU/L(5-40); ALP-896 IU/L(100); GGT-21 IU/L(5-85); Total Protein-6.0gms%; Albmin 3.0 gms%; Globulin 3.0 gms%; BT-2 min 30 sec; CT-5 min 30 sec; PT-15 sec(13sec). Blood Urea, creatinine, Serum electrolytes, cholesterol, calcium, phosphorus,.
Serum bilirubin, Thyroid profiles were normal.

**Serological tests:** Viral markers HAV, HBV, HCV were all negative.

**Antibody profile:**
Negative for ANA, AMA, Anti-SMA, Anti-LKM1 antibody.

**Abdominal ultrasonography** revealed a normal Liver with non dilated Intra-Hepatic & Extra Hepatic Bile Duct Obstruction. Spleen was Normal in size. There was no Ascites. **CT-Abdomen** revealed Normal study. **Liver Biopsy** showed Normal architecture of Liver, marked Intra-Hepatic Cholestasis with Hepatocellular Cholestasis with Bile Thrombi formation in Bile Duct. No evidence of Intralobular & Periportal necrosis. No evidence of Chronic Active Hepatitis, Fibrosis or Cirrhosis. No Black Pigmentation as in Dubin-Johnson Syndrome.

Patient was followed up for 12 weeks, symptoms resolved & Liver Biopsy taken at the end of 12th week. Biopsy revealed normal Liver parenchyma, complete absence of Hepatocellular Cholestasis, no Liver cell necrosis or Inflammatory reactions.

**fig. a.** shows Intrahepatic cholestasis
**fig. b.** shows normal liver architecture without evidence of cirrhosis

**fig. c.** On admission, patient with hyperpigmentation

**fig. d.** At the time of discharge, hyperpigmentation resolved

**Discussion:**
BRIC was first described by Summerskill and Walsh in 1959. This disorder was characterised by repeated self limited episodes of severe pruritus and jaundice lasting for several weeks to months.

Generally there is preicteric phase 2-4 weeks during which patient complaints of malaise, anorexia and pruritus, subsequently clinical jaundice occurs. Patient may have enlarged tender liver. There is no splenomegaly. Patient generally afebrile.
The majority are diagnosed in adolescence or early adulthood. Liver function test shows profound elevation of alkaline phosphatase with normal gamma glutamyl transferase activity. Cholestatic episode lasts from a few weeks to several months, following which complete clinical and biochemical resolution occur and may recur at intervals of several months to years\(^2\). The attacks are clinically suggestive of biliary obstruction and may be accompanied by malabsorption, weight loss secondary to steatorrhoea, which may require parenteral fat soluble vitamins.

Pathogenesis of this disorder is unknown. Both sporadic and familial cases have been described. Familial form has an autosomal recessive pattern of inheritance, gene FIC1 recently identified and found to be mutated in patients with BRIC\(^2\). Protein that encode appears to be a member of P-type ATPase family that transports aminophospholipids from the outer to inner leaflet of a variety of cell membrane\(^3\). Hence play a essential role in the enterohepatic circulation of bile acids.

BRIC considered to have a benign disorder and does not lead to cirrhosis or end stage liver disease\(^4\). However the episodes of jaundice and pruritus can be prolonged and debilitating.

**Diagnostic criteria: (Tygstrup 1969)**\(^5\)

(a) At least two episodes of jaundice separated by a symptom-free interval lasting several 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 extrahepatic bile ducts confirmed by cholangiography.
(f) Absence of factors known to be associated with cholestasis.

This disease is very rare. Both clinical and pathological features are necessary for diagnosis. The value of liver biopsy in excluding other icteric diseases is stressed.

Treatment during cholestatic episodes includes cholestyramine, ursodeoxycholic acid\(^6\), phenobarbitone. Some recent reports have shown a beneficial role of rifampicin in remission of cholestasis\(^7\).

In the present case, she was given a trial of ursodeoxycholic acid which provided symptomatic relief with decrease in pruritus and hyperpigmentation. She made an uneventful recovery within 10 weeks. She is on regular follow up for 6 months and has not suffered another attack.

**References:**


