Benign recurrent intrahepatic cholestasis – case series and literature review

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ABSTRACT

Benign recurrent intrahepatic cholestasis (BRIC) is a rare form of intrahepatic cholestasis seen in patients with genetic predispositions. It is a rare disease of unknown prevalence and is transmitted as an autosomal recessive pattern of inheritance. The available literature for BRIC is limited. It is hard to formulate the true prevalence of the disorder. Often precipitated by a trigger like viral infections and drugs, this condition results in a self-limiting episode of cholestasis. We present a case series of three patients with the clinical picture of BRIC. All three cases were fully evaluated for the cause of cholestasis and thereafter treated with ursodeoxycholic acid and rifampicin, which showed complete recovery.

Key words: BRIC, Cholestasis liver disease, Genetics, Self-limiting

Benign recurrent intrahepatic cholestasis (BRIC) was first described by Summerskill and Walshe in 1959 [1]. BRIC represents a milder form of a much more severe disease called progressive familial intrahepatic cholestasis (PFIC). Based on the genetic defects, BRIC is further divided into types 1, 2, and 3 [2]. Both PFIC and BRIC share common genes, which is the ATPase phospholipid transporting 8B1 gene responsible for BRIC 1 and PFIC 1, while the ATP-binding cassette, sub-family B member 11, gene is associated with BRIC 2 and PFIC 2, and the ATP-binding cassette, subfamily B member 4, also called Multidrug Resistance Protein 3, is associated with BRIC 3 and PFIC 3 [3]. Unlike PFIC, which is present in early childhood and leads to end-stage liver disease, BRIC usually causes benign attacks of cholestasis pruritus with complete recovery in between attacks [4]. Because of the rarity of the condition, it is often misdiagnosed, overtreated, or has the added insult of drug-induced liver injury (DILI) superimposed over BRIC.

CASE SERIES

Case 1

A 20-year-old male patient presented with a complaint of jaundice and pruritus for 20 days. Jaundice was not associated with pain in the abdomen, vomiting, fever, or preceded by any prodromal symptoms. The patient had no history of drug intake, including conventional, complementary, and alternative medicine. The patient had three similar episodes in the past, separated by 2–4 years each (first episode age of 12 years, 16 years, and 18 years old); each episode lasted for 4–6 weeks and was resolved completely by treatment. The general physical examination was positive for icterus and scratch marks, with a blood pressure of 110/72 mmHg and a pulse of 68 beats/min with unremarkable systemic examination. On investigation, the patient had direct hyperbilirubinemia with a total bilirubin level of 21.98, a direct fraction of 10.56, aspartate aminotransferase of 78 IU/L, and alanine aminotransferase (ALT) of 86 IU/L. Serum alkaline phosphatase (ALP) was 460 IU/L, and gamma-glutamyl transferase (GGT) was 58 IU (Table 1). The patient tested negative for viral hepatitis B, C, A, and E. The patient had normal ceruloplasmin and ferritin levels. The autoimmune hepatic profile was negative for antinuclear antibody (ANA), anti-mitochondrial antibody test (AMA), and anti-smooth muscle antibody test (ASMA). On further investigation, the size, shape, and echotexture of the liver were normal, with no intrahepatic biliary radicals (IHBRD) on ultrasonography (USG) of the abdomen and normal magnetic resonance cholangiopancreatography (MRCP).

The patient underwent a liver biopsy and was advised for genetic testing, keeping the possibility of BRIC. The liver biopsy showed preserved liver architecture with hepatocellular and canalicular cholestasis, mild lobular inflammation, and no steatosis or fibrosis (Fig. 1). The patient was diagnosed with potential BRIC and was started on ursodeoxycholic acid (UDCA) (15 mg/kg/day), rifampicin (5 mg/kg/day), and anti-histaminic. The patient gradually improved in condition.

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Table 1: Hematological and biochemical parameters of cases

Investigation	Case 1		Case 2		Case 3		Normal range
	Baseline	@4 weeks	Baseline	@6 weeks	Baseline	@8 weeks	
Hb (g/dL)	14.3	14.7	14.2	13.8	14.9	14.1	12.5–15.5 g/dL
White blood cell (per mm^3)	8300	5780	5670	4210	4410	4960	4000–11000/mm^3
Platelets ($10^3/mm^3$)	410	350	1.89	230	306	310	150–450×$10^3/mm^3$
Urea (mg/dL)	20	26	34	40	18	18	14–40 mg/dL
Creatinine (mg/dL)	0.98	0.86	0.9	0.82	0.72	0.6	0.80–1.40 mg/dL
Bil (total) (mg/dL)	21.98	4.2	30.46	3.2	14.46	2.8	0.1–1.2 mg/dL
Bil (direct)	10.58	2.6	18	1.1	8.39	1.3	
Aspartate aminotransferase (IU/L)	78	56	79	45	42	28	<37 IU/L
Alanine aminotransferase (IU/L)	85	44	102	52	40	24	<40 IU/L
Alkaline phosphatase (U/L)	460	310	277	249	161	149	70–306 U/L
Gamma-glutamyl transferase (IU/L)	58				38		5–40 IU
Total protein (gm/dL)	6.8	7.2	6.8	7.1	6.8	7.2	6.2–8.5 g/dl
Albumin (gm/dL)	3.5	3.8	3.2	3.7	4.1	3.8	3.5–5.3 g/dL
PT INR	1.03		1.06		0.93	0.98	

Hb=Hemoglobin, Bil=Bilirubin

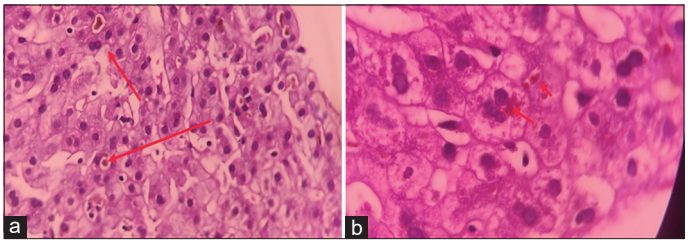

Figure 1: (a and b) Photomicrograph of case 1 showing cholestasis inside hepatocytes part and canalicular cholestasis

Case 2

A 24-year-old male presented with features of intrahepatic cholestasis for 30 days with no history of pain in the abdomen, fever, vomiting, or prodromal symptoms. In history, the patient had two similar episodes of jaundice with pruritus in 2012 and 2018, which lasted for 4 weeks each. The examination was positive for icterus and scratch marks with a blood pressure of 112/74 mmHg and a pulse of 72/min; the rest of the examination, including systemic, was unremarkable. There were no hepatosplenomegaly, lymphadenopathy, or features of malnutrition. The investigation is summarized in Table 1. The etiology workup was negative for viral hepatitis (Hepatitis B, C, A, and E), Wilson disease (ceruloplasmin level 34 mg/dL), and an autoimmune liver disease panel including ANA and AMA, and there was no history suggestive of DILI. On imaging, the MRCP and CECT abdomen revealed multiple gall bladder, calculi normal CBD, and no IHBRD. This patient has had a normal ALP level on repeated occasions. The patient underwent a liver biopsy, which was suggestive of canalicular cholestasis. A possible diagnosis of BRIC type 2 was made and treated on similar lines with UDCA and antihistamine medications.

Case 3

A 24-year-old male presented with a history of yellowish discoloration of the eyes with mild pruritus with no features of liver failure for 15 days. Recently, the patient had an episode of upper respiratory tract infection about 20 days ago. He also had two similar episodes in the past spread over 5 years; both of those episodes were also precipitated by an upper respiratory tract infection. The general and systemic examinations were unremarkable except for scratch marks with a blood pressure of 110/68 mmHg and a pulse of 68/min. He has direct hyperbilirubinemia and mildly raised transaminases; the rest of the liver function parameters were normal (Table 1). The patient tested negative for viral hepatitis (Hepatitis B, C, A, and E), Wilson disease (serum ceruloplasmin 30 mg/dL), and hemochromatosis (serum ferritin 394). ANA, as measured by IFA, AMA, and ASMA, has an IgG level of 15 (<16gm/L). Imaging including both USG and MRCP were normal. The liver biopsy revealed a moderate degree of cholestasis, both intrahepatic and canalicular, with mild focal inflammation. With two episodes in the past, the patient was diagnosed with a possible case of BRIC. The patient was started on symptomatic treatment, UDCA, and rifampicin, and gradually made a full recovery.

DISCUSSION

The clinical presentation of BRIC is made on the basis of a recurrent episode of self-limiting episode of cholestasis, which is usually precipitated by triggers. The common triggers are viral infections and DILI [5]. The common age of presentation is in the 1^{st}–2^{nd} decade of life, but one can present at any time in their lifetime. The frequency of these attacks can vary from many attacks a year to once every 10 years or more attacks of similar character, and the severity and frequency of these attacks decrease with age [6]. In addition to the typical presentation of conjugated hyperbilirubinemia, itching, weakness, malabsorption, and weight loss, the patient might also develop steatorrhea and features of fat-soluble vitamin deficiency. Type 1 BRIC often has associated features of hearing loss and pancreatitis, while BRIC type 2 has

more chances of cholelithiasis and a theoretically higher risk of hepatobiliary malignancy. Diagnosing BRIC is clinical by ruling out both intra- and extra-hepatic causes of cholestasis with the help of Luketic and Shiffman [7] criteria (Table 2).

Biochemistry reveals direct hyperbilirubinemia, a mildly raised liver enzyme level, normal ALP, and normal or mildly raised GGT, often called a classic of BRIC. A liver biopsy is often performed in this clinical setting. The presence of centrilobular cholestasis (described as canalicular and intracellular cholestasis) is often considered a pathognomic of BRIC. Other findings include pericentral hepatocellular degeneration, focal lobular mononuclear infiltration, portal inflammation, no ductal loss, and no fibrosis [7]. Genetic analysis can diagnose and subtype BRIC.

In this case series, three patients were diagnosed over a period of 2 years at a tertiary care hospital in western Rajasthan during the time period of 2020–2022, and all three presented as self-limiting intra-hepatic cholestasis with multiple episodes in the past. The most frequently cited triggers are viral illness, or DILI. Only a third of patients could recall the trigger in the form of URTI (upper respiratory tract infection), leading to the precipitation of symptoms. As BRIC is self-limiting, all three cases in our case series made a full recovery on UDCA and rifampicin only. Covid-19 has been suggested as a potential trigger for BRIC precipitation for clinical presentation, [8] along with other viral infections and drugs, including OCP [5]. All our patients were clustered during the COVID-19 peak in India, so the potential role of Covid-19 can be suggested; however, no definitive history of COVID is available in our patients for COVID-related hospitalization.

Treatment of BRIC includes symptomatic treatment with antihistamines and oral UDCA, which works to enhance the hepatobiliary secretion of bile salts, or rifampicin. Refractory pruritus to medical treatment might need measures like short-term nasobiliary drainage [9]. The postulated mechanisms behind the effectiveness of endoscopic naso-biliary drainage for BRIC include forced bile drainage, blockage in the enterohepatic circulation, and subsequent reduction in the hydrophobic bile acid pool, which improves pruritus in cholestatic jaundice. Extracorporeal albumin dialysis in a molecular absorbent recycling system removes bile acids from the body and causes rapid improvement in pruritus, [10] and liver transplants have rarely been tried. A review of the literature of cases from the last 10 years is documented in Table 3 [11–15].

Table 2: Clinical criteria for benign recurrent intrahepatic cholestasis

I. At least 2 attacks of jaundice separated by a symptom free interval lasting several months to years.
II. Laboratory values consistent with intrahepatic cholestasis.
III. Normal or mildly elevated gamma-glutamyl transferase
IV. Pruritus because of cholestasis
V. Liver histology suggestive of centrilobular cholestasis
VI. Normal intra and extrahepatic bile duct (magnetic resonance cholangiopancreatography)
VII. Absence of other causes of cholestasis (drugs, pregnancy)

Table 3: Recent Literature from India for last 10 years

Authors	Findings	Management
Kumar *et al*. 2016 [11]	27 year old with cholestasis, liver biopsy	UDCA Cholestyramine
Choudhury *et al*. 2017 [12]	23 year old severe refractory pruritus of 2 years, liver biopsy	ENBD
Ganesh *et al*. 2021 [13]	7 patient case series over 20 years 2000–2020 2 cases diagnosed ATPB8B1 positive, rest clinically.	UDCA, Rifampicin One patient succumbed to superimposed CAM induced liver injury. 2 girls developed ICP during pregnancy
Kalaranjini *et al*. 2021 [14]	12 year old, diagnosed by genetic testing ABCB11 deficiency	UDCA, antihistamine
Acharya *et al*. 2023 [15]	28 year old male, liver biopsy	UDCA, antihistamine

UDCA: Ursodeoxycholic acid

CONCLUSION

BRIC is a rare, self-limiting episodic illness that gets precipitated by a variety of triggers, including COVID-19. It has a benign course of illness with a complete recovery unless complicated by the use of alternative medicine, leading to a superimposed liver injury. Diagnosis is clinical; genetic testing can be done. The most important step after diagnosing BRIC in a patient is educating the patient regarding the benign nature of the illness's potential triggers and avoiding CAM.

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