BRIC Type 3? A Case of Benign Recurrent Intrahepatic Cholestasis unlinked to *ATP8B1* and *ABCB11*

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ABSTRACT

Benign Recurrent Intrahepatic Cholestasis (BRIC) is a rare genetic disorder characterized by recurring episodes of jaundice. Two subtypes of BRIC have been well-characterized in the literature: BRIC I, caused by mutations in *ATP8B1* gene, and BRIC II, triggered by mutations in *ABCB11* gene. There are exceedingly rare cases of BRIC in which individuals do not have mutations in either of the associated genes, suggesting the possibility additional loci implicated in this disorder. Herein, we present a case of BRIC in a 21-year-old male who demonstrated clinical, biochemical and histological evidence of disease but lacked both of the associated mutations in ATP8B1 and ABCB11.

INTRODUCTION

Benign Recurrent Intrahepatic Cholestasis (BRIC)
- Autosomal Recessive genetic disorder
- Recurring episodes of jaundice due to poor biliary flow

Average age of onset: infancy to young adulthood (1).

Diagnosis by liver biopsy during episodes and genetic testing
- Histology: noninflammatory hepatocanalicular cholestasis without fibrosis

Two subtypes of BRIC have been well-characterized
- BRIC I (mutation: *ATP8B1* gene)
- BRIC II (mutation: *ABCB11* gene) (3-4).

- There are exceedingly rare cases of BRIC without mutations in either of the associated genes.

CASE

A 17-year-old male presented with intermittent yellowing of his skin and eyes for one year

HPI
- (+) Pruritus, acholic stools, dark brown urine. Intermittent sharp, peri-umbilical abdominal pain lasting minutes.
- (-) No triggering illness or stress. No new medications, supplements, or vitamins. No oral ulcers, fevers, nausea, vomiting, diarrhea, constipation, or GI bleeding.

Pertinent Medical, Family, and Social History
- No other medical conditions. No family history of liver disease.
- No tattoos. No blood transfusions. No known allergies. No alcohol use, smoking, or recreational drug use.

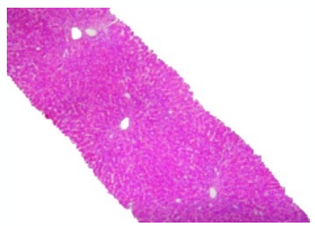
Physical Examination
- Vital Signs – Normal
- General – Icteric. BMI - 25
- Abdomen was soft, non-tender, non-distended, and without hepatomegaly.

Hepatic Function Panel on Initial Presentation	
ALT	370 U/L
AST	96 U/L
Alkaline Phosphatase	66 U/L
Total Bilirubin	7.7 mg/dL
Conjugated Bilirubin	6.7 mg/dL

Further Diagnostic Testing			
Hepatitis B Surface Ab	7.7 mg/dL	**C28Y/H63D**	Negative
Hepatitis C Antibody	6.7 mg/dL	**Serum tissue transglutaminase**	Negative
CMV Serology	Negative	**Serum Ceruloplasmin**	44 (H)
EBV Serology	Negative	**Alpha-1 Antitrypsin Phenotype**	MM
HSV-1 Viral Load	Negative	**Anti-Mitochondrial Antibody**	Negative
HIV antibody	Negative	**Antinuclear Antibody**	Negative
TSH	2.15 (nl)	**Anti-Smooth Muscle Antibody**	Negative
		Anti-Liver Kidney Microsomal Antibody	Negative

Liver Ultrasound
Mildly enlarged liver without any focal abnormality or biliary dilation.

Non-Focal Liver Biopsy
Bland centrilobular cholestasis with coarse granular biliary material within dilated bile canaliculi, without any significant inflammation, bile duct damage, or ductular reaction



DISCUSSION

We report a case of BRIC in the absence of mutations in ATP8B1 and ABCB11. Such cases are exceedingly rare in the literature.

A set of diagnostic criteria established in 1969 are still applicable today (6-7).

- (1) multiple episodes of jaundice separated by a symptom-free interval of at least 6 months
- (2) laboratory evidence of intrahepatic cholestasis
- (3) histological evidence of non-inflammatory cholestasis
- (4) non-dilated biliary ducts
- (5) absence of other known risk factors for cholestasis.

Our patient satisfied these diagnostic criteria.
- ✓ Age of onset and history of symptoms
- ✓ Cholestatic liver enzyme elevation
- ✓ Conjugated bilirubinemia
- ✓ No biliary dilation
- ✓ No other clinical factors to explain clinical presentation.
- ✓ Pathology interpretation of the liver biopsy - coarse granular biliary material within dilated bile canaliculi with morphologically similarities to biopsies seen in BRIC.

Some evidence suggests the existence of additional disease loci for low γ-GT BRIC (3, 8-9), explaining why some individuals diagnosed with BRIC on clinical and histopathologic evidence do not have an association with either *ATP8B1* or *ABCB11*.

This disorder has been informally termed “BRIC 3. Further studies are needed.

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