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Case Report

Internal Medicine Section

Benign Recurrent Intrahepatic Cholestasis: A Rare Diagnostic Challenge

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ABSTRACT

Benign Recurrent Intrahepatic Cholestasis (BRIC) is a rare liver disorder that occurs sporadically or via autosomal recessive inheritance. It is characterised by recurrent episodes of cholestasis with pruritus and jaundice in the absence of chronic liver disease. It typically first presents in childhood or adolescence; however, adult-onset forms may occur and can be difficult to diagnose. The present case report involves a 23-year-old male who presented with recurrent episodes of jaundice, pruritus and pale stools. A thorough evaluation, including autoimmune, infectious and metabolic workup, was negative. Imaging studies showed no evidence of extrahepatic biliary obstruction, and liver biopsy indicated a cholestatic pattern consistent with intrahepatic cholestasis. Whole-exome sequencing, a form of genetic testing, identified a mutation in the ATP8B1 gene, confirming the diagnosis of BRIC. Whole-exome sequencing revealed a pathogenic mutation in ATP8B1, which encodes the Familial Intrahepatic Cholestasis 1 (FIC1) protein responsible for bile salt homeostasis. Mutations in ATP8B1 are associated with BRIC type 1 and are essential to confirm the diagnosis, particularly in atypical or late-onset presentations. The patient was managed conservatively, with resolution of symptoms, and experienced no further attacks during follow-up. The present case illustrates the need to consider BRIC in the differential diagnosis of recurrent cholestatic jaundice in young adults when other common aetiologies have been excluded. Timely recognition allows appropriate supportive management and reduces the burden of unnecessary investigations.

Keywords: Familial intrahepatic cholestasis 1, Mutations, Pruritis, Ursodeoxycholic acid

CASE REPORT

A 23-year-old male presented to the Outpatient Division of Medical Gastroenterology with a one-month history of yellowing of the eyes, progressively worsening itchiness, pale stools and right upper abdominal pain that began the day prior to the visit. The patient's abdominal pain was described as dull, constant and intermittent, without obvious aggravating or relieving factors. There were no associated fevers, and the symptoms developed spontaneously without any preceding illness.

The patient reported two previous episodes of jaundice within the past year. The first episode occurred 10 months earlier and lasted one month, while the second episode occurred four months earlier and lasted 20 days. On both occasions, the jaundice resolved spontaneously. These prior episodes were not associated with medication use, high-risk behaviours, or complementary and alternative therapies. There was no family history of liver disease. The patient denied alcohol consumption, drug use or blood transfusions. No other significant co-morbidities were noted.

On physical examination, the patient appeared icteric, with skin excoriations secondary to severe pruritus. There were no signs of hepatosplenomegaly or clinical features of chronic liver disease, including spider angiomas, palmar erythema or gynaecomastia. The abdomen was soft and non-tender, with no organomegaly.

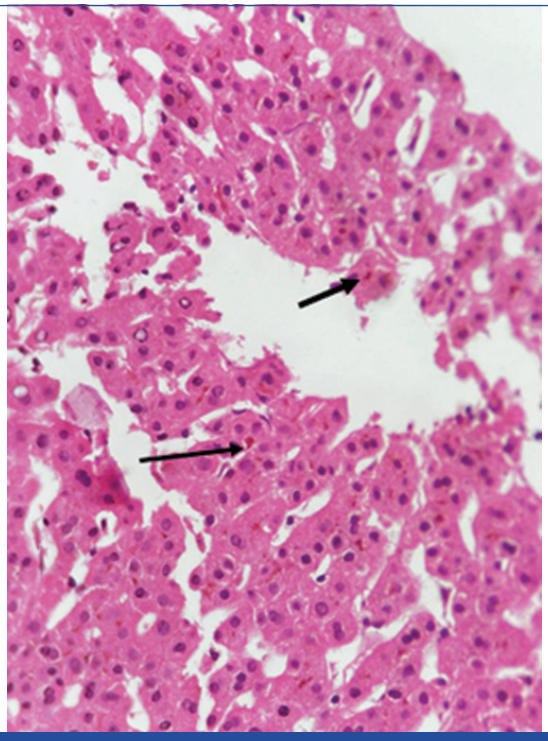
Initial laboratory tests showed significant direct hyperbilirubinaemia with normal liver transaminases. Alkaline phosphatase was mildly elevated at 200 IU/L, while Gamma-Glutamyl Transferase (GGT) was normal. Albumin and prothrombin time were within normal limits, and complete blood count, renal function and electrolytes were unremarkable. Serological testing for hepatitis A, B and C was negative [Table/Fig-1].

Autoimmune markers including Antinuclear Antibodies (ANA), Smooth Muscle Antibody (SMA), Antimitochondrial Antibodies (AMA) and anti-Liver Kidney Microsomal (anti-LKM) antibodies were all negative. Metabolic screening, including serum caeruloplasmin and 24-hour urinary copper, was performed to rule out Wilson disease and was non-diagnostic. Abdominal ultrasound and Magnetic Resonance Cholangiopancreatography (MRCP) did not reveal biliary dilatation, gallstones or masses. The liver and spleen were normal in size and echotexture.

Tests	Observed values	Reference range
Total Bilirubin (TB)	17 mg/dL	0.3-1.2
Direct Bilirubin (DB)	9 mg/dL	-0.2
Indirect Bilirubin (IB)	8 mg/dL	0.2-0.8
Aspartate Transaminase (AST)	43 U/L	<40 U/L
Alanine Transaminase (ALT)	40 U/L	<41 U/L
Alkaline Phosphatase (ALP)	200 U/L	<120 U/L
Gamma Glutamyl Transferase (GGT)	17 U/L	<60 U/L
Total protein	7 g/dL	6-8 g/dL
Albumin	4g/dL	3-5 g/dL
Globulin	3g/dL	2-3 g/dL
Albumin/Globulin (A/G) ratio	1.3	1.2-1.5: 1
Haemoglobin	14 g/dL	12-15 g/dL
Total leukocyte count	6200 cells/mm^3	4000-11000 cells/m^3
Platelets	290000/ul	150000-400000 /uL
Prothrombin time	12 sec	11-13.5 seconds
International Normalised Ratio (INR)	1.1	0.8-1.2
Blood urea	15 mg/dL	15-40 mg/dL
Serum creatinine	1.1 mg/dL	0.6-1.2 mg/dL
Lactate Dehydrogenase (LDH)	200 U/L	140-280 U/L
HBsAg	Non-reactive	
Anti HCV	Non-reactive	
Anti HBc total	Non-reactive	

[Table/Fig-1]: Showing initial investigations done on admission.
HBsAg: Hepatitis B surface antigen; Anti HCV: Antibody to Hepatitis C virus; Anti HBc: Antibody to Hepatitis B core antigen

Given the persistent hyperbilirubinaemia and previously unremarkable imaging and laboratory results, a liver biopsy was performed. Histopathology showed preserved liver architecture with canalicular and intracellular cholestasis, mild portal inflammatory infiltrates and no fibrosis, duct loss, steatosis or Mallory bodies [Table/Fig-2]. These findings were consistent with a cholestatic process without features of advanced liver disease.



[Table/Fig-2]: Haematoxylin and Eosin stain 400x magnification, Showing preserved hepatic parenchyma with canalicular and intrahepatic cholestasis.

Given the pathological findings and absence of an identifiable cause, the overall results supported a diagnosis of idiopathic intrahepatic cholestasis, with BRIC being the most likely possibility.

Genetic testing and diagnosis: Given that the episodes were recurrent, self-limiting, and had no identifiable acquired causes-with a cholestatic pattern on histology-a congenital cholestatic disorder was suspected. Whole-exome sequencing revealed a mutation in the ATP8B1 gene, confirming a diagnosis of BRIC type 1.

Management and follow-up: The patient was started on Ursodeoxycholic Acid (UDCA) (15 mg/kg/day) and cholestyramine (4 g twice daily) to manage pruritus. He was hospitalised for 21 days, during which he showed mild clinical improvement in the form of slightly reduced pruritus and improved general well-being, although bilirubin levels remained high (22.1 mg/dL). Upon discharge, he continued both medications and was advised to attend regular follow-up visits.

He returned three weeks later for review, reporting significant improvement in pruritus and overall well-being. Liver function tests at that visit showed a marked drop in bilirubin to a near-normal value (1.2 mg/dL). The patient received treatment for a total of 45 days [Table/Fig-3]. He has remained stable, with no recurrence thus far. Follow-up is ongoing, and liver function tests are being monitored regularly. Psychological support and education regarding the relapsing nature of the condition were provided to the patient and his relatives.

DISCUSSION

BRIC is a rare autosomal-recessive liver disorder characterised by episodes of cholestasis that resolve spontaneously. The resulting symptoms include jaundice, pruritus, and cholestatic biochemical abnormalities; however, the condition does not progress to chronic liver disease. First described by W.H.J. Summerskill and Walshe in 1959, BRIC remains a rare diagnosis, with only a few hundred cases reported in the medical literature [1,2].

The episodic, unpredictable nature of BRIC with long symptom-free intervals presents a unique diagnostic challenge. This difficulty is compounded by early-stage, non-specific biochemical findings and typically normal biliary imaging [3,4].

In the present case, the patient demonstrated biochemical evidence of cholestasis and had typical BRIC symptoms of intermittent jaundice, significant pruritus, and pale stools in the absence of an obstructive process. The most notable laboratory finding was the normal GGT level during episodes. A normal GGT is a characteristic finding in BRIC and an important diagnostic clue, as it is not seen in most other cholestatic liver disorders. The diagnosis was further supported by exclusion of cholestatic, metabolic, structural, autoimmune, and viral causes for these episodes. Whole-exome sequencing identified a mutation in ATP8B1, consistent with BRIC type 1, following liver biopsy.

Diagnostic challenges in the current case: The present case highlights several major diagnostic challenges associated with BRIC:

- Intermittent disease course: Long, asymptomatic periods often result in testing being performed during quiescent phases, when results are normal, thereby delaying diagnosis.
- Normal or low GGT: While marked cholestasis with normal GGT is typical of BRIC, it can be misleading for clinicians accustomed to elevated GGT in cholestatic disorders.
- Normal biliary imaging: Ultrasound and MRCP findings are typically normal, which may divert attention from defects in hepatocanalicular transport and lead to unnecessary testing for infectious, autoimmune, or drug-induced aetiologies.
- Limited access to genetic testing: In resource-limited settings, lack of timely genetic confirmation forces reliance solely on clinical and histopathological correlation.
- Overlap with Progressive Familial Intrahepatic Cholestasis (PFIC): Shared genetic features necessitate long-term follow-up to ensure the disease does not progress.

In this case, whole-exome sequencing provided definitive molecular confirmation of an ATP8B1 mutation, eliminating diagnostic uncertainty and avoiding unnecessary interventions [5,6].

Comparative review of reported BRIC cases: In this case, a 23-year-old male presented with recurrent episodes of jaundice and severe pruritus, separated by symptom-free periods characteristic of BRIC. Each episode resolved spontaneously over 3-4 weeks,

Day	Total Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)	Aspartate Bransaminase (U/L)	Alanine Transaminase (U/L)	Alkaline Phosphatase (U/L)	Gamma Glutamyl Transferase (U/L)
Day 1	17.0	9.0	43	40	200	17
Day 7	24.2	15.3	36	48	226	20
Day 15	34.5	22.1	44	39	240	19
Day 21	22.1	15.8	36	38	233	25
Day 28	14.4	8.1	44	42	180	17
Day 45	1.2	0.8	40	38	120	20

[Table/Fig-3]: Liver Function Tests pattern during hospitalisation and on follow-ups.

without identifiable precipitating factors such as infection, drug exposure, or alcohol intake.

The present episodic and self-limited clinical course has been consistently documented in previously published cases. Chen H et al., reported a 39-year-old Chinese man with BRIC type 1 who experienced recurrent jaundice and pruritus lasting weeks, with complete inter-episode resolution [7]. Similarly, Piazzolla M et al., described a 29-year-old man with intermittent jaundice and severe pruritus, without progression to chronic liver disease [8]. Bing H et al., reported a 17-year-old girl with recurrent, self-limiting jaundice [9], and Suzuki et al., documented a 20-year-old female with repeated cholestatic episodes over two years [6]. Vo VH et al., described a 25-year-old female with jaundice and pruritus since adolescence [10].

The recurrent cholestatic attacks with complete resolution between episodes are a consistent clinical pattern in all these reports, emphasising that BRIC typically affects young individuals with normal development and no clinical evidence of chronic liver injury between episodes.

In the present case report, the patient showed pronounced direct hyperbilirubinemia with almost normal liver enzymes, slightly elevated ALP (200 IU/L) and normal GGT, which are characteristic laboratory features of BRIC type 1. The liver biopsy exhibited preserved architecture with canalicular and intracellular cholestasis, mild portal inflammation, and no fibrosis or duct loss, consistent with a cholestatic process without chronic liver disease.

Similar laboratory and histological findings have been described in earlier reports. For example, Chen H et al., reported markedly elevated conjugated bilirubin with normal GGT and mild elevation of ALP during acute attacks; liver biopsy showed canalicular cholestasis with preserved hepatic architecture [7]. Bing H et al., noted a similar laboratory and biopsy pattern (elevated direct bilirubin, mildly elevated transaminases, normal GGT, and centrilobular cholestasis on liver biopsy) [9]. Suzuki et al., [6] and Piazzolla M et al., also highlighted normal GGT despite significant cholestasis, emphasising that this finding may help distinguish BRIC from other cholestatic disorders [8]. Vo VH et al., reported that liver histology during an acute attack revealed canalicular cholestasis, while the lobular architecture remained intact, which is typical of BRIC patients [10]. Collectively, these cases illustrate that normal or mildly elevated GGT in the setting of profound conjugated hyperbilirubinemia, coupled with liver biopsy evidence of canalicular cholestasis and preserved architecture, is characteristic of BRIC type 1.

Genetic analysis of this patient identified a pathogenic mutation in the ATP8B1 gene, supporting a diagnosis of BRIC type 1. This finding is consistent with the known genetic characteristics of BRIC1, which typically results from autosomal recessive mutations in ATP8B1, although both homozygous and heterozygous variants have been described. Previous reports have demonstrated a spectrum of ATP8B1 mutations associated with BRIC. Chen H et al., reported a homozygous variant in a patient with classical BRIC1 who experienced recurrent jaundice and pruritus, similar to the present case [7]. Conversely, Piazzolla et al., [8] and Bing H et al., [9] described heterozygous variants, suggesting that haploinsufficiency and/or additional genetic or environmental factors may contribute to clinical episodes even in patients with a single allele variant. Suzuki et al., also reported a heterozygous mutation resulting in a BRIC1 phenotype, and Vo VH et al., underscored variability in expressivity and age of onset [6,10], indicating that patients without severe acute cholestatic episodes may have similar genetic findings.

The authors conclude that both homozygous and heterozygous ATP8B1 mutations are significant in producing the characteristic episodic cholestasis that defines BRIC1. However, more severe or conventional episodes tend to occur in patients with homozygous mutations. Therefore, confirmation of a BRIC1-related genetic mutation in this patient firmly supports this continuum of clinical expression.

In the present case, the patient was treated with UDCA (15 mg/kg/day) and cholestyramine, resulting in gradual improvement in pruritus and general well-being over a six-week period, with a reduction in bilirubin from 22.1 mg/dL to 1.2 mg/dL (near normal). During follow-up visits, the patient remained stable, demonstrating the benign, self-limiting natural history of BRIC type 1 when managed supportively.

Other examples of similar therapeutic responses have been documented. In one case report, Chen H et al., [7] described rapid symptomatic improvement with UDCA during an acute episode. In the case reported by Bing H et al., [9], the patient demonstrated partial response to UDCA and cholestyramine, although some episodes required rifampicin and/or extracorporeal therapy for severe pruritus. Likewise, case studies by Piazzolla et al., [8] and Suzuki H et al., [6] agreed that UDCA and cholestyramine alone were adequate for symptomatic improvement, consistent with mild to moderate episodes that resolve spontaneously. Vo VH et al., noted that severe or prolonged attacks may warrant consideration of plasma exchange or rifampicin; however, the prognosis remained favourable [10]. Collectively, these cases demonstrate that symptomatic management with bile-acid-modulating and antipruritic agents is generally safe and effective for the majority of BRIC patients, while highlighting the importance of safety monitoring and escalation strategies for severe episodes.

In the present case, the patient remained clinically stable after the acute episode, without indications of chronic liver disease, portal hypertension, or extrahepatic complications. Such a benign course is common in BRIC type 1, as recurrent episodes typically do not lead to progressive liver injury. Regular follow-up with monitoring of liver function and psychological support regarding the relapsing nature of the disease were recommended.

Comparable outcomes have been reported in the literature, with Suzuki H et al., and Chen H et al., reporting patients with multiple recurrent episodes who maintained normal liver function between attacks, emphasising the non-progressive nature of BRIC1 [6,7]. On the other hand, Vo VH et al., described a patient who developed distal renal tubular acidosis as a complication, indicating that extrahepatic manifestations may occasionally occur and stressing the importance of early recognition [10]. Additionally, Bing H et al., [9] and Piazzolla et al., [8] emphasised the need for genetic counselling and family screening due to the hereditary nature and variable expressivity of ATP8B1 mutations.

Collectively, these reports indicate that while BRIC type 1 generally has a favourable prognosis, careful long-term follow-up, patient and family education, and awareness of potential complications are essential. Counselling regarding the episodic and unpredictable nature of attacks helps patients and families cope with the condition and promotes understanding and vigilance. Various cases of BRIC are summarised along with the present case in [Table/Fig-4] [6-10].

Prognosis and follow-up: The prognosis of BRIC is excellent, with most patients achieving complete remission between episodes, and none progressing to cirrhosis or chronic liver disease. Nevertheless, follow-up is important to identify recurrences, promote medication compliance, and screen family members where applicable. In this case report, management with UDCA and cholestyramine led to complete resolution of symptoms and normalisation of biochemistry. The absence of fibrosis on biopsy and the benign clinical course at follow-up are consistent with the good prognosis associated with BRIC.

The present case reinforces the importance of recognising BRIC as a rare but challenging diagnosis, and of confirming its molecular basis to differentiate it from other causes of recurrent cholestasis. The addition of genetic testing, even in resource-limited settings where appropriate, may eliminate delays in diagnosis, permit

Author (Year)	Age/Sex	Gene Affected	Key Symptoms	GGT	Treatment	Outcome
Suzuki H et al., (2022) [6]	20 / M	ATP8B1 (heterozygous)	Pruritus, jaundice	Normal	Rifampicin ± UDCA	Rapid symptom resolution
Chen H et al., (2021) [7]	39 / M	ATP8B1 (homozygous)	Recurrent cholestasis	Low	UDCA	Symptomatic improvement
Bing H et al., (2022) [9]	17 / F	ATP8B1 (rare missense)	Cholestasis, pruritus	Normal	UDCA, rifampicin	No progression
Vo VH et al., (2019) [10]	25 / M	ATP8B1	Cholestasis	Normal	Plasmapheresis, rifampicin	Controlled episodes
Piazzolla M et al., (2020) [8]	29/M	ATP8B1	Recurrent jaundice	Normal/Low	UDCA, cholestyramine	Good control
Present case	22 / M	ATP8B1 (homozygous)	Recurrent jaundice, pruritus	Normal	UDCA + cholestyramine	Symptomatic improvement

[Table/Fig-4]: Comparison of various cases of BRIC with current case [6-10].

appropriate management by discontinuing unnecessary invasive procedures, and provide significant prognostic information and genetic counselling.

CONCLUSION(S)

Although uncommon, BRIC can significantly impact patients due to recurrent jaundice and severe pruritus. Subtle clues, such as normal GGT levels in the setting of cholestasis, when combined with histology and genetic testing, can lead to the correct diagnosis. Supportive therapy with UDCA and cholestyramine often provides symptom relief, while newer treatments may be beneficial for individuals with refractory episodes. Clinician awareness is key to avoiding unnecessary workups and reassuring patients that the course is benign. An evidence-based, patient-centered approach ensures that patients are managed safely while maintaining their quality of life.

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