Baltic Journal of CLINICAL MEDICINE and RESEARCH • 2025/01 • 019–022
https://doi.org/10.25143/rsu-bjcmr.2025.01.019-022
BJCMR

Recurrent Hyperbilirubinemia: The Diagnostic Challenge of Benign Recurrent Intrahepatic Cholestasis

Ieva Tolmane[1, 2], **Seda Arutjunana**[1], **Karīna Elza Stiģe**[2, 3]

Affiliation: [1] Riga East University Hospital, Latvian Centre of Infectious Diseases;
[2] University of Latvia, Faculty of Medicine;
[3] Children Clinical University Hospital, Latvia

E-mail: karinastige@gmail.com

Summary

Benign recurrent intrahepatic cholestasis (BRIC) is an autosomal recessive disorder characterized by mutations in genes encoding hepatocyte bile duct membrane proteins, most often in a homozygous form; only 30% of cases exhibit multiple heterozygous mutations. This case presents an unusual instance of BRIC with heterozygous mutations in a single gene encoding a hepatocyte bile duct membrane protein, accompanied by prominent clinical symptoms. Typically, multiple heterozygous mutations are thought to intensify clinical manifestations, but this case suggests otherwise.

Keywords: benign recurrent intrahepatic cholestasis, conjugated hyperbilirubinemia.

Aim of demonstration

The aim of this study was to highlight the complex and time-consuming diagnostic pathway and challenges associated with rare diseases exhibiting recurrent patterns.

Case report

In 2013, a 19-year-old woman was hospitalized with symptoms of jaundice, pruritus, body rash, dark urine, and minor dyspeptic complaints. Three weeks prior, she experienced pharyngitis and a dry cough; a week later, a rash appeared on her arms, legs, and abdomen. The patient reported no other symptoms, illnesses, or allergies and denied taking medications or supplements regularly. She also reported no sexual activity and had been vaccinated according to the mandatory vaccination schedule. On examination, her physical condition was moderate, with clear consciousness and orientation to time, place, and person. Notable findings included severe jaundice affecting the skin, sclera, and mucosa, a maculopapular rash on her arms, legs, and abdomen, and herpes labialis lesions. Lymph nodes were unremarkable. Abdominal examination revealed a soft, non-tender abdomen, with the liver palpable along the rib margin without tenderness.

Laboratory examination showed leucocytosis 10.26 x 10^3/Ml (4.0–9.8 x 10^3/Ml), total bilirubin 168.3 µM/L (1.1–19.0 µM/L), conjugated bilirubin 129.1 µM/L (<3.4 µM/L), unconjugated bilirubin 39.2 µM/L (<13.7 µM/L), alanine aminotransferase 54 U/L (<31 U/L), aspartate aminotransferase 44 U/L (<31 U/L), gamma-glutamyl transferase 10 U/L (<30 U/L), alkaline phosphatase 105 U/L (<117 U/L), alfa amylase 105 U/L (28–100 U/L), copper 27.9 µM/L (12.5–24 µM/L), ceruloplasmin 0.315g/L (0.18–0.45 g/L). Serology was negative for viral hepatitis (HBsAg, anti-HCV, anti-HAV IgM), Epstein-Barr virus (EBV:EA IgG, EBV:EBNA IgG, EBV

VCA IgM), cytomegalovirus (CMV IgM, IgG), HIV (HIV 1 antigen, anti-HIV1/2), and syphilis (*Treponema pallidum* IgM, IgG). The liver appeared normal on ultrasonography and magnetic resonance imaging with non – dilated intrahepatic and extrahepatic ducts, gall bladder also appeared normal with smooth walls and anechogenic fluid. A liver biopsy guided by ultrasound indicated acute hepatic injury with pericentrolobular and intracanalicular cholestasis, and the portal fields appeared unaffected by acute injury or inflammatory cell infiltration, suggesting possible toxic etiology.

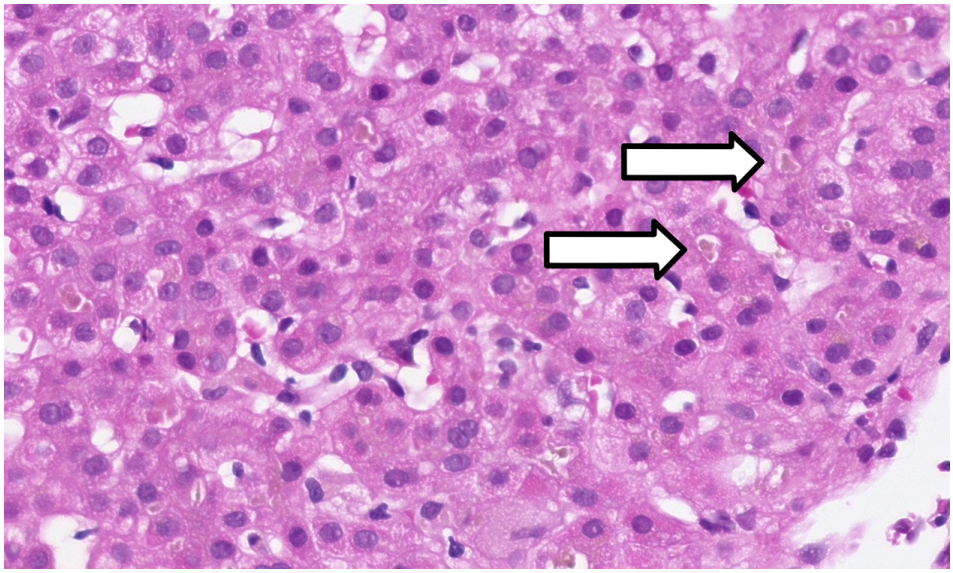

Figure 1. Hematoxylin-eosin-stained liver biopsy showing cholestasis (arrows).

The patient received intravenous 0.9% NaCl solution, oral ursodeoxycholic acid (cholelitholytic agent, 250 mg three times daily), and omeprazole (proton pump inhibitor, 20 mg twice daily). Despite these treatments, her bilirubin levels continued to rise, necessitating plasmapheresis with absorbent BS330, which was well-tolerated. The procedure produced positive results, with total bilirubin levels dropping from 321 μM/L to 109 μM/L, accompanied by a reduction in jaundice and pruritus. The patient was discharged with recommendations to continue ursodeoxycholic acid (250 mg three times daily) and loratadine (antihistamine, 10 mg once daily). Liver markers normalized within a few weeks, and she reported no further symptoms.

Between 2013 and 2022, the patient experienced 14 similar episodes of conjugated hyperbilirubinemia without specific triggers. A definitive diagnosis was not made until 2016 when genetic testing, polymerase chain reaction, and gene sequencing confirmed BRIC type 2 with single heterozygous mutation in the ABCB11 gene.

Discussion

BRIC is an autosomal recessive disorder with mutations in genes encoding hepatocyte bile duct membrane proteins, primarily occurring in a homozygous form; approximately 30% of patients present heterozygous mutations (1, 2). The precise global prevalence of BRIC remains undetermined; however, the incidence is estimated to be 1 in 50,000 to 100,000 individuals. The first documented case dates to 1959 in the United Kingdom. There is no clinically significant data to demonstrate a gender prevalence for BRIC. BRIC is classified into two subtypes, BRIC1 and BRIC2, based on the specific genetic mutations involved. BRIC1 is associated with mutations in the ATP8B1 gene, whereas BRIC2 results from mutations in the ABCB11 gene. Despite these distinct genetic etiologies, the clinical presentations of both subtypes are virtually indistinguishable. (3, 4, 5) The initial cholestasis episode typically appears before the second decade of life, with

known triggers including oral contraceptives, infections, and pregnancy. Clinical episodes are marked by intermittent jaundice, pruritus, dark urine, and pale stools, with severity varying significantly between individuals. Episodes can last for weeks to months, followed by complete clinical, biochemical, and histological remission. (1) Clinical diagnosis of BRIC requires three criteria: at least two episodes of jaundice with symptom-free intervals of several months to years; laboratory findings indicating intrahepatic cholestasis with elevated gamma-glutamyl transferase (GGT) and bilirubin; severe pruritus; and normal intrahepatic and extrahepatic bile ducts on cholangiography. (7) Histologic findings resemble drug-induced liver injury, particularly due to estrogens, anabolic steroids, and parenteral nutrition, which can also cause intrahepatic cholestasis. (1) Therefore, patients with jaundice should be thoroughly questioned about drug and supplement use. Currently, there is no specific treatment to prevent recurrence; symptomatic therapy, including ursodeoxycholic acid, can significantly alleviate pruritus. Other options, such as rifampin, cholestyramine, and plasmapheresis, have shown some success, and endoscopic nasobiliary drainage may benefit patients unresponsive to standard therapies. (7) Liver transplantation is not considered due to the non-progressive nature of BRIC. (6) Patients should be monitored through follow-up visits 1 to 2 times per year if no exacerbations; however, pregnancy in BRIC2 patients warrants more aggressive management and closer follow-up, as it may act as a catalyst for the progression of BRIC2 to progressive familial cholestasis type II (PFIC2). The ABCB11 mutation, associated with BRIC2, is also linked to PFIC2, a severe autosomal recessive liver disorder characterized by early onset, progressive liver damage due to impaired bile flow, and the absence of bile salts in the bile, often leading to cirrhosis and liver failure in childhood if untreated. (8)

Conclusions

BRIC is a rare, autosomal recessive disorder that presents significant diagnostic challenges due to its recurrent nature and the necessity to exclude other hepatic and non-hepatic causes of jaundice. This case underscores the importance of thorough clinical, biochemical, imaging, and histopathological evaluation over multiple episodes to establish a definitive diagnosis. Genetic testing, as demonstrated in this case, plays a pivotal role in confirming the diagnosis, particularly when heterozygous mutations are detected in a gene encoding hepatocyte bile duct membrane proteins. While BRIC is classically associated with homozygous or compound heterozygous mutations, cases involving heterozygous mutations, such as the one presented here, offer new insights into the phenotypic variability of this condition.

The genetic landscape of BRIC is centered around two primary genes: ABCB11, encoding the bile salt export pump (BSEP), and ATP8B1, encoding a P-type ATPase involved in bile canalicular membrane maintenance. Mutations in these genes underlie two subtypes of BRIC:

- BRIC1, associated with ATP8B1 mutations, and
- BRIC2, caused by ABCB11 mutations.

The presented case highlights the complexity of BRIC, where heterozygous mutations in the ABCB11 gene were sufficient to produce significant clinical manifestations, challenging the conventional understanding that multiple heterozygous or homozygous mutations are typically necessary for severe symptomatology. Notably, ABCB11 mutations account for a significant subset of BRIC cases, with missense, nonsense, frameshift, and splice site mutations being the most commonly reported. These mutations often impair BSEP function, leading to cholestasis due to disrupted bile acid excretion. The phenotypic expression of BRIC may depend on the severity of the functional impairment caused by these mutations, contributing to the wide spectrum of disease presentations.

The recurrent episodes of conjugated hyperbilirubinemia, severe jaundice, pruritus, and biochemical abnormalities emphasize the chronic but benign course of this condition. Although BRIC episodes are self-limiting, the associated symptoms significantly impact the quality of life,

necessitating effective symptomatic management. Currently, there is no curative or preventive therapy for BRIC; however, treatment strategies such as ursodeoxycholic acid, plasmapheresis, and symptomatic relief measures, including antihistamines, play a crucial role in improving patient comfort and reducing bilirubin levels. The efficacy of plasmapheresis, as observed in this case, demonstrates its utility in managing severe episodes and highlights its role as an adjunctive therapy in resistant cases.

This case further emphasizes the need for heightened clinical suspicion and genetic evaluation in patients presenting with recurrent, unexplained intrahepatic cholestasis. Early recognition and appropriate management can prevent unnecessary interventions, improve patient outcomes, and reduce the diagnostic burden. Importantly, despite the chronic and relapsing nature of BRIC, it remains a non-progressive condition with no risk of long-term liver damage, differentiating it from other cholestatic liver disorders. This distinction is vital for providing accurate prognostic information and reassurance to patients and their families.

References

1. Feldman, M., Friedman, L.S. and Brandt, L.J., 2013. *Sleisenger and Fordtran's gastrointestinal and liver disease*. 11th ed. Philadelphia: W.B. Saunders Company, pp. 313–323.
2. van Mil, S.W.C., Klomp, L.W.J., Houwen, R.H.J. and Bull, L.N., 2004. Benign recurrent intrahepatic cholestasis type 2 is caused by mutations in ABCB11. *Gastroenterology*, 127(2), pp. 379–384. doi: 10.1053/j.gastro.2004.04.065
3. Salyani, A., Barasa, L., Rajula, A. and Ali, S.K., 2020. Benign recurrent intrahepatic cholestasis (BRIC): An African case report. *Case Reports in Gastrointestinal Medicine*, 2020, Article ID 2894293. doi: 10.1155/2020/2894293
4. Sohn, M.J., Woo, M.H., Seong, M.W., Park, S.S., Kang, G.H., Moon, J.S. and Ko, J.S., 2019. Benign recurrent intrahepatic cholestasis type 2 in siblings with novel ABCB11 mutations. *Pediatric Gastroenterology, Hepatology & Nutrition*, 22(2), pp. 201–206. doi: 10.5223/pghn.2019.22.2.201
5. Luketic, V.A. and Shiffman, M.L., 1999. Benign recurrent intrahepatic cholestasis. *Clinics in Liver Disease*, 3(3), pp. 509–528. doi: 10.1016/s1089-3261(05)70083-0
6. Chowdhury, J.R., Wolkoff, A.W. and Cohen, D.E., 2022. Inherited disorders associated with conjugated hyperbilirubinemia. *UpToDate*. https://www.uptodate.com
7. Burt, A.D., Ferrell, L.D. and Hübscher, S.G., 2017. *MacSween's pathology of the liver*. 8th ed. Philadelphia: Elsevier, pp. 122–294.
8. Kuwelker, S., Kumar, M., Saatchi, M. and Hussain, M., 2021. Benign recurrent intrahepatic cholestasis type 2 presenting with worse outcome during pregnancy. *The American Journal of Gastroenterology*, 116(Suppl), p. S1123. doi: 10.14309/01.ajg.0000784244.20861.30