CASE REPORT

Endoscopic nasobiliary drainage: an effective treatment option for benign recurrent intrahepatic cholestasis (BRIC)

Ashok Choudhury,¹ Anand V Kulkarni,¹ Bishnupriya Sahoo,² Chhagan Bihari³

¹Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

²Pediatrics, Shree Guru Gobind Singh Tricentenary University Faculty of Medicine and Health Sciences, Gurgaon, India

³Institute of Liver and Biliary Sciences, New Delhi, India

Correspondence to
Dr Anand V Kulkarni;
anandvk90@gmail.com

Accepted 19 April 2017

SUMMARY

Benign recurrent intrahepatic cholestasis (BRIC) is characterised by recurrent episodes of jaundice, severe pruritus and low or normal serum γ -glutamyltransferase activity lasting from several weeks to months. BRIC is an autosomal recessive disorder caused by the mutation in either of the two hepatic transporter genes—ATP8B1 or *ABCB11* gene. The disease is very well known for episodic flare of jaundice with cholestatic symptoms that are spontaneous or perpetuated by acute insults, followed by self-recovery. There is no proven medical therapy and rarely does it progress to progressive familial intrahepatic cholestasis (PFIC) or biliary cirrhosis. BRIC may be associated with nephrolithiasis, diabetes or pancreatitis. Here, we report a case of BRIC with spontaneous flare and further complicated by drug-induced liver injury with disabling cholestatic symptoms, who underwent endoscopic nasobiliary drainage and was completely relieved of the distressing symptoms.

BACKGROUND

Benign recurrent intrahepatic cholestasis (BRIC) is a rare disease with frequent exacerbations which cause distressing symptoms. Endoscopic nasobiliary drainage (ENBD) is a novel therapy which can lead to permanent resolution of the symptoms and can be the treatment of choice.

CASE PRESENTATION

A 23-year-old male with no family history of jaundice presented with complains of intermittent jaundice associated with severe pruritus and clay coloured stools since 2 years. He also complained of steatorrhoea and night blindness during the episodes. The symptoms would exacerbate during periods of stress or minor illness. His symptoms would last for 4–5 months and then would be asymptomatic for 2–3 months before recurrence. He visited multiple hospitals and was treated with ursodeoxycholic acid, cholestyramine, high dose of hydroxyzine, rifampicin, naltrexone, but all failed to improve his symptoms. He then received complementary alternative medicine for 15 days leading to aggravation of the above symptoms and presented to our hospital.

On examination, there were excoriation marks all over the body but predominantly distributed over palms and lower limbs. There were no signs of liver cell failure and there was no organomegaly.

INVESTIGATIONS

Investigations revealed serum bilirubin of 11.9 mg/dL with a predominant direct fraction of 6.7 mg/dL. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were mildly elevated with AST being 77 IU/L (normal ~5–40 IU/L) and ALT of 58 IU/L (normal ~10–40 IU/L). High alkaline phosphatase of 213 IU/L (normal ~32–92 IU/L) and normal γ -glutamyltransferase (γ -GT) of 57 (normal ~7–64 IU/L) were seen. Hypoalbuminaemia (2.8 g/L (normal ~3.5–5.5 g/L)) and prolonged INR (2.03) secondary to anorexia and steatorrhoea were seen (figure 1).

Autoimmune markers, typical (HAV, HBV, HCV, HEV) and atypical hepatotropic (EBV, HSV and CMV) viral markers were negative. Serum copper and ceruloplasmin were normal. Ultrasonography revealed a normal liver echo texture and non-dilated biliary system. Magnetic resonance cholangiopancreatography confirmed the normal intrahepatic and extrahepatic bile ducts (figure 2). Liver biopsy showed centrilobular cholestasis with mild inflammation and mild periportal fibrosis (figure 3).

DIAGNOSIS

After ruling out all the causes of cholestatic jaundice and based on history of recurring jaundice and histopathology showing intrahepatic cholestasis with preserved architecture, he was suspected to have BRIC based on Tygstrup *et al*¹ criteria.

TREATMENT

In view of protracted course and failure of medical therapy and on the basis of limited literature, we undertook a trial of ENBD to hasten the bile drainage (figure 2). He was supplemented with vitamin K for raised INR and vitamin A orally for the symptoms.

OUTCOME AND FOLLOW-UP

Patient showed improvement in jaundice, itching and night blindness. Nasobiliary drainage was removed after 7 days. Patient has been asymptomatic for five consecutive months.

DISCUSSION

BRIC and progressive familial intrahepatic cholestasis (PFIC) form a part of spectrum of familial intrahepatic cholestatic disorders. The prevalence of BRIC is largely unknown but is said

CrossMark

To cite: Choudhury A, Kulkarni AV, Sahoo B, *et al*. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2016-218874

Figure 1 The laboratory parameters and clinical features in relation to endoscopic nasobiliary drainage (ENBD) placement. (A) Total serum bilirubin (mg/dL). (B) Serum alkaline phosphatase (SAP-32-92 IU/L), gamma glutamyl transferase (GGT-7-64 IU/L). (C) Prothrombin time-International normalised ratio (PT-INR). (D) ENBD placement, improvement in itching, night blindness and stool colour. Dotted line indicates—ENBD removed.

to be rarer than PFIC which occurs in 1/50 000–1/100 000 births.² BRIC is a rare autosomal recessive disorder characterised by repeated self-limiting episodes of severe pruritus and jaundice lasting from several weeks to months. The disease may begin in childhood or adulthood.² It usually begins with malaise, cholestatic jaundice with mild transaminitis and hence can be misdiagnosed as acute viral hepatitis. The episodes can be preceded by influenza-like illness or viral gastroenteritis or drugs which act as precipitants.² It is a benign disease as it does not lead to progressive liver dysfunction or cirrhosis but is the cause for high morbidity. The patients can be severely jaundiced and can have pruritus, steatorrhoea and weight loss. Even in the presence

Figure 2 Imaging in benign recurrent intrahepatic cholestasis. (A, B) Magnetic resonance cholangiopancreatography imaging of the abdomen showing normal intrahepatic and extrahepatic ducts. (C) Fluoroscopic image showing nasobiliary drain.

Figure 3 H&E stained section of core biopsy specimen obtained from the liver lesion. Liver biopsy showing (A and B) portal areas with mild inflammatory infiltrate and liver parenchyma showing cholestatic features. $\times 200$. (C) Mild portal fibrosis highlighted by Masson's trichrome, 200.

of cholestasis the serum γ -glutamyltransferase activity is not elevated. The diagnostic criteria suggested by Tygstrup was the presence of episodes of pruritus and jaundice with biochemical and histological evidence of cholestasis, symptom-free intervals lasting months to years, absence of known cause of cholestasis and normal bile ducts on cholangiography, all of which were seen in our patient.¹

Minuk and Shaffer³ showed that BRIC is not mediated by a circulating cholestatic agent, but rather is secondary to an intrinsic abnormality in hepatocyte bile salt secretion. BRIC can be caused by the mutation in either of the two hepatic transporter genes: the *ATP8B1* gene, coding for familial intrahepatic cholestasis-1 (FIC1; BRIC type 1), or the *ABCB11* gene, coding for the bile salt export pump (BSEP; BRIC type 2).^{2,3} *ATP8B1* acts as an aminophospholipid flippase. Thus, the defect in *ATP8B1* reduces transport of bile acids in the liver and the gut, which results in cholestasis and watery diarrhoea. Missense mutations in *ATP8B1* leads to BRIC and non-sense frameshift mutations lead to PFIC-1. BSEP is a P-glycoprotein, defect of which leads to impaired bile salt secretion, accumulation of bile salts in hepatocytes and subsequent hepatocellular injury, apoptosis or necrosis.

Histopathology in BRIC-2 shows intrahepatic cholestasis with mild inflammation but otherwise preserved normal liver architecture and no ductular reaction. In contrast, PFIC shows intracanalicular cholestasis, giant cell transformation and varying degree of fibrosis and frank cirrhosis in advanced disease. On immunohistochemistry, loss of BSEP staining is noted. However, there is substantial polymorphism in BSEP noted and hence it is not pathognomonic hallmark feature of BRIC-2 or PFIC-2.²

There is no proven treatment for this disease. Various medical approaches have been tried which include ursodeoxycholic acid, corticosteroids and bile acid-binding resins but without much success.⁴ Rifampicin and colestimide have been reported to be successful in few cases. Refractory cases

of jaundice with pruritus (for BRIC exacerbation) have been treated with albumin dialysis.^{5 6}

Surgical approach to this disabling disease includes partial biliary diversion similar to PFIC. It is effective in improving the jaundice and pruritus, but may be associated with a high incidence of stoma-related complications. Minimally invasive laparoscopic external biliary diversion is an innovative method and showed good long-term benefit without complication in paediatric patients as case report.⁷

Endoscopic nasobiliary drainage is a type of transpapillary external drainage wherein the distal end of the long tube is left in the bile duct and the proximal end emerges out through the nose. It is a well-established way of biliary decompression which is most often used in acute cholangitis.⁸ The main advantage of ENBD is the real-time monitoring of drainage status. Report of ENBD as an effective therapy has been shown in few case series and is encouraging. Some series even showed the effects to be long lasting without any further attack of jaundice even though the nasobiliary drainage is one time and usually for 1 week, for which the exact mechanism is unknown. Stapelbroek *et al*⁹ demonstrated a reduction in the total bile acid levels (100–200 $\mu\text{mol/L}$ pretreatment) that get normalised by day 3 along with resolution of pruritus. The postulated mechanism behind effectiveness of ENBD for BRIC includes forced bile drainage, block in the enterohepatic circulation and subsequent reduction in the hydrophobic bile acid pool. But the same thing could be achieved by placing a stent as well; advantage of ENBD over a stent is not known. Plausible explanation is that the stent-mediated biliary drainage is internal where there can be reabsorption of bile acids while ENBD is external leading to rapid decline in bile acid pool. This is supported by the fact that increased levels of phospholipids other than phosphatidylcholine, particularly sphingomyelin, in the bile drained by ENBD and disruption of the phospholipid gradient.⁹

Our patient did not undergo any genetic testing; however the long-standing history, recurrent cholestatic jaundice episode, no imaging or histological abnormality is in favour of BRIC. He had acute worsening probably due to drug-induced liver injury. He was diagnosed based on classical clinical features, liver function tests and histology. ENBD improved the symptoms as well as the quality of life. There are hardly few cases of BRIC reported from

Learning points

- Benign recurrent intrahepatic cholestasis, though referred as benign can lead to distraught for the patient and needs early clinical suspicion.
- Medical management may not be successful in all.
- Endoscopic nasobiliary drainage can be the treatment of choice for patients with refractory symptoms

South-East Asia to achieve a successful cure of this highly morbid disease with ENBD.

Contributors AC did the ENBD procedure. Framework and idea by AVK and AC. Manuscript by AVK with inputs from BS. CB provided the histopathology images. All the authors have read the manuscript and approved the final manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Tygstrup N, Jensen B. Intermittent intrahepatic cholestasis of unknown etiology in five young males from the Faroe Islands. *Acta Med Scand* 1969;185:523–30.
- 2 Luketic VA, Shiffman ML. Benign recurrent intrahepatic cholestasis. *Clin Liver Dis* 2004;8:133–49.
- 3 Minuk GY, Shaffer EA. Benign recurrent intrahepatic cholestasis. evidence for an intrinsic abnormality in hepatocyte secretion. *Gastroenterology* 1987;93:1187–93.
- 4 Folvik G, Hilde O, Helge GO. Benign recurrent intrahepatic cholestasis: review and long-term follow-up of five cases. *Scand J Gastroenterol* 2012;47:482–8.
- 5 Oldakowska-Jedynak U, Jankowska I, Hartleb M, *et al*. Treatment of pruritus with Prometheus dialysis and absorption system in a patient with benign recurrent intrahepatic cholestasis. *Hepatol Res* 2014;44:E304–E308.
- 6 Huster D, Schubert C, Achenbach H, *et al*. Successful clinical application of extracorporeal albumin dialysis in a patient with benign recurrent intrahepatic cholestasis (BRIC). *Z Gastroenterol* 2001;39(Suppl 2):13–14.
- 7 Metzelder ML, Petersen C, Melter M, *et al*. Modified laparoscopic external biliary diversion for benign recurrent intrahepatic cholestasis in obese adolescents. *Pediatr Surg Int* 2006;22:551–3.
- 8 Leung JW, Chung SC, Sung JJ, *et al*. Urgent endoscopic drainage for acute suppurative cholangitis. *Lancet* 1989;1:1307–9.
- 9 Stapelbroek JM, van Erpecum KJ, Klomp LW, *et al*. Nasobiliary drainage induces long-lasting remission in benign recurrent intrahepatic cholestasis. *Hepatology* 2006;43:51–3.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow