

Benign Recurrent Intrahepatic Cholestasis: A Case Report

Prapun Aanpreung, M.D.*, Ananya Pongpaibul, M.D.**

*Department of Pediatrics, **Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Benign recurrent intrahepatic cholestasis (BRIC) is an autosomal recessive cholestatic liver disease. Recurrent self-limited episodes of jaundice and severe pruritus are leading clinical manifestations. We report a 16-year-old Thai boy with three recurrent episodes of cholestasis. The first episode occurred at 30 months old. The subsequent recurrent episodes were at 13 and 16 years, respectively. Investigations including viral study, autoimmune hepatitis markers, abdominal ultrasound and magnetic resonance cholangiopancreatography (MRCP) were negative. Diagnosis of BRIC was made based on specific criteria. He was treated with cholestyramine and ursodeoxycholic acid when the first and second episodes occurred which resulted in good recovery. However, for the last recurrent episode, treatment with ursodeoxycholic acid failed to improve his condition, so his treatment was changed to rifampicin, which resulted in dramatic response. Although BRIC is a rare disease, it should be taken into account in all cases with recurrent cholestasis with normal or minimally elevated GGT level. Currently, genetic study for the mutation of *ATP8B1* and *ABCB11* genes are crucial for making a definite diagnosis.

Keywords: Cholestasis, severe pruritus, *ATP8B1*, *ABCB11*, gene mutation

Siriraj Med J 2015;67:296-300

E-journal: <http://www.sirirajmedj.co>

INTRODUCTION

Benign recurrent intrahepatic cholestasis (BRIC) is a rare disease characterized by recurrent self-limited episodes of jaundice and intense pruritus lasting from weeks to months. It is an inherited disease with autosomal recessive transmission.¹ BRIC was first described by Summerskill and Walsh in 1959.² Within 10 years after that report, Tygstrup N reported 5 patients from the Faroe Islands with intermittent intrahepatic cholestasis and proposed a diagnostic guideline of BRIC.³ Before making the diagnosis of BRIC, other diseases, including infection,

biliary tract obstruction, autoimmune disease and other metabolic disorders should first be excluded. BRIC were previously reported in Europe, Africa, North America and Asia. We report a case of a 16-year-old Thai boy with a diagnosis of BRIC who had three recurrent episodes of cholestasis. Pathogenesis, proper investigations and managements of this disease were reviewed.

CASE REPORT

A 16-year-old Thai boy presented with recurrent episodes of jaundice. The first episode of cholestatic jaundice occurred at the age of 30 months. He was treated with cholestylamine for one month and his jaundice was completely resolved. Following the first episode, he remained healthy with normal growth, up until the age of 13.

Correspondence to: Prapun Aanpreung
E-mail: prapun.aan@mahidol.ac.th

He presented with the second episode of apparent jaundice for one month, which was preceded by two-week history of pruritus and malaise. There appeared to be neither associated clinical symptoms nor changing of stool color at that time. Two months prior to this episode, he reported taking ciprofloxacin and doxycycline as acne treatment for three weeks. There was no history of chronic liver disease or consanguinity in his family. His 17-year-old elder sister was healthy. On examination, marked jaundice without pallor was noted. There were scratch marks and excoriations from generalized itching on his body and face. There was mild hepatomegaly without splenomegaly. There were no other signs of chronic liver disease. Liver function tests revealed TB18 mg/dL, DB 14 mg/dL, SGOT 46 U/L, SGPT 46 U/L, and ALP 381 U/L. Viral hepatitis study yielded negative results for HBsAg, anti-HBsAg, anti-HCV, CMV IgG, and EBV IgG. Only anti-HAV IgG was positive. Autoimmune liver profiles, including antinuclear antibody (ANA), anti-smooth muscle antibody (Anti SMA), and anti-liver kidney microsomal antibody (Anti LKM) were negative. Serum copper, serum ceruloplasmin and urine copper results were normal. Abdominal ultrasound showed mild hepatomegaly. MRCP was negative for biliary tract obstruction or inflammation. At that time, there was a suspicion of drug hypersensitivity being the etiology of jaundice. After treatment with ursodeoxycholic acid and vitamin E for two months, liver function tests were normalized.

In the third episode, he presented again with similar symptoms at 16 years old. He was then treated with ursodeoxycholic acid 500 mg three times daily for 2 weeks. There was no improvement for jaundice and intense pruritus from the laboratory results. Percutaneous liver biopsy was carried out and demonstrated mild lobular disarray with moderate centrilobular cholestasis. Mostly, canalicular cholestasis with cholestatic rosettes and occasional hepatocellular cholestasis were observed. The portal areas showed minimal or no inflammation. Interlobular bile ducts were unremarkable and present in all portal tracts. (Fig 1, 2)

Due to failure to achieve clinical improvement with ursodeoxycholic acid, it was discontinued and changed to oral rifampicin 300 mg per day, which resulted in dramatic improvement of jaundice and pruritus. The liver function tests were normalized after 3 months of treatment, and then rifampicin was discontinued. Following this last episode, he has been symptom free. Results of laboratory testing during the recurrent episodes of cholestasis are shown in Table 1.

DISCUSSION

Our patient was diagnosed as BRIC by using the following criteria 1) At least two episodes of jaundice separated by symptom free interval lasting several months to years 2) Laboratory data were consistent with intrahepatic cholestasis

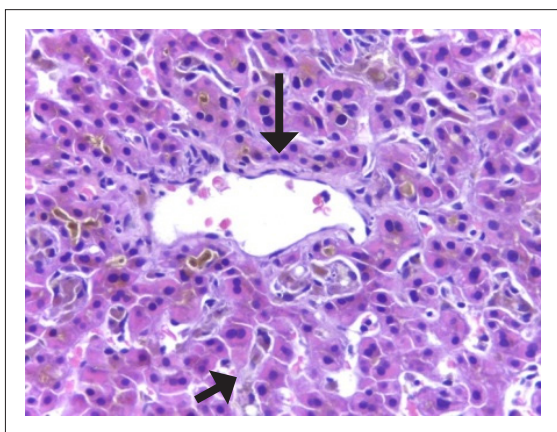


Fig 1. Bland centrilobular cholestasis with cholestatic rosettes (arrows).

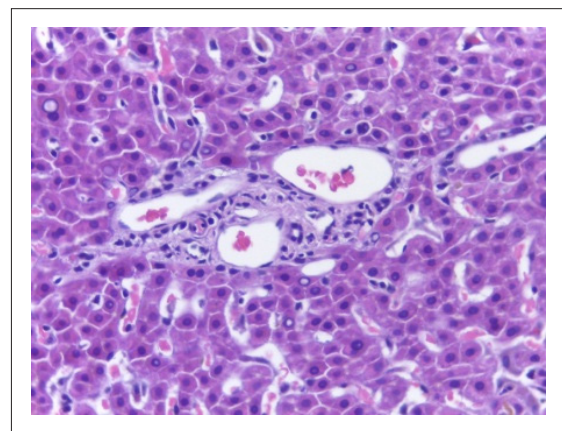


Fig 2. Minimal inflammatory infiltrate in portal tracts, unremarkable interlobular bile duct and no ductular reaction.

TABLE 1. Results of laboratory testing during the recurrent episodes of cholestasis.

Day	Second episode (age of 13)				Third episode (age of 16)						
	D1	D14	D30	D60	D1	D7	D14	D21	D35	D60	D90
TB (mg/dL)	18	15.2	2.7	1	17	19	25	20.8	5.1	1	0.5
DB (mg/dL)	14	11.8	1.7	0.2	12.2	14	22	19	4.74	0.8	0.2
SGOT (U/L)	46	68	31	27	61		48	61	90	22	24
SGPT (U/L)	46	50	25	17	85		42	59	120	16	27
ALP (U/L)	381	299	199		447		374	364	252	140	121
GGT (U/L)		13					9		17	17	13
Alb (g/dL)		4	4.4								
Glo (g/dL)		2.9	2.6								
PT (sec)		11.1			10						
PTT (sec)		27.9			25						

3) GGT level was either normal or minimally elevated 4) Severe pruritus secondary to cholestasis 5) Liver biopsy demonstrated centrilobular cholestasis 6) Normal intra and extra hepatic bile duct by cholangiography and 7) absence of factors known to be associated with cholestasis.¹ BRIC is a rare disease that is more common in European people. Jaundice and pruritus typically occur during the teenage and twenties.^{4,5} Each attack can last from 2 weeks to 18 months with mean duration 3 months before the symptoms resolve spontaneously. Most of patients are asymptomatic between attacks. Pruritus can be a prodromal symptom that precedes jaundice by 2-4 weeks. Other associated symptoms were malaise, irritability, nausea, and vomiting. The most common precipitants reported were influenza and gastroenteritis.^{4,6} Liver function tests usually show marked elevation of conjugated bilirubin, alkaline phosphatase, and mildly increased transaminase. Low or normal GGT level was a significant clue to support the diagnosis of BRIC and help to exclude biliary obstruction. Liver histopathology in BRIC showed prominent centrilobular cholestasis during the attack. Bile was present in dilated canaliculi, hepatocytes and Kupffer cells.^{4,6,7}

In our patient, all investigations were repeated for every attack to exclude other diseases causing cholestasis. Recently, finding of gene mutation has been a significant tool to establish a diagnosis of BRIC. Familial intrahepatic cholestasis (FIC) is a genetic liver disease, which is

classified into 3 groups based on phenotypical difference: progressive familial intrahepatic cholestasis (PFIC), BRIC and intrahepatic cholestasis of pregnancy (ICP).⁸ FIC has 3 type gene mutations, including *ATP8B1*, *ABCB11* and *ABCB4*. Each of these genes encodes a hepatocellular transporter, which are all important for the bile formation. *ATP8B1* deficiency is an autosomal recessive disorder with defect gene located on the chromosome 18q21 encoding for *ATP8B1* protein. The interference of this protein cause impaired inward translocation of aminophospholipids over hepatocyte and cholangiocyte membranes, causing impaired bile salt excretion. It can present as chronic and severe cholestasis in infants (PFIC type 1), and recurrent less severe cholestasis with spontaneous resolution in older children and adults (BRIC type 1) and ICP. *ABCB11* deficiency is an autosomal recessive disorder caused by mutation in *ABCB11* on chromosome 2q24 resulting in impaired canaliculi bile salt export pump in PFIC type 2, BRIC type 2 and ICP. *ABCB4* deficiency has a mutation on chromosome 7q21 causing increased toxic bile, which will destroy bile ducts in PFIC type 3 and ICP. Occasionally, BRIC will progress to the more severe and permanent form of PFIC, indicative of a clinical continuum with intermediate phenotypes between mild and severe disease. Our patient did not undergo genetic testing due to the lack of availability in our hospital. There have been reports of clinical presentations and genetic studies in Asian patients.⁹⁻¹¹ Mizuochi T,

et al reported a 7-year-old Japanese girl presenting with an episode of progressive jaundice and pruritus. BRIC 1 was confirmed by demonstrating 2 novel mutations (1226delA/2210delA) in the *ATP8B1* gene.¹⁰ The patient received rifampicin treatment resulting in increased bile acid excretion in urine. Lee YS, et al presented the case of 7-year-old Korean boy with multiple episodes of severe cholestasis. BRIC 1 was confirmed by discovering a single heterozygote novel mutation in the *ATP8B1* gene.¹¹

Our patient was treated with cholestyramine for the first attack and ursodeoxycholic acid for the second attack, which resulted in a good response. For the third attack, he did not respond to ursodeoxycholic acid, but responded to rifampicin. Currently, there is no effective treatment to prevent recurrence or minimize the duration of each attack. Therefore, treatment to relieve the symptom is still the mainstay. The cause of pruritus is not well understood. The anti-pruritic medications include antihistamine, phenobarbital, cholestyramine, ursodeoxycholic acid and rifampicin can be used, but the results are variable. Cholestyramine acts by sequestering bile acid within the intestinal lumen, increasing bile acid loss and a compensatory increase in bile acid synthesis exists in BRIC patients.¹² Ursodeoxycholic acid is a tertiary hydrophilic bile acid, which is used in chronic cholestatic liver diseases, especially primary biliary cirrhosis. Among patients with BRIC, ursodeoxycholic acid was given to treat pruritus, and was reported to reduce duration of attack.¹³ Rifampicin is a potent inducer of various cytochromes, enhances the hepatic uptake of various organic ions and partly interferes with hepatic uptake of bile acid and decreases hepatocyte bile concentration.¹⁴ It reduces bilirubin, alkaline phosphatase and pruritus in patients with various forms of cholestasis including BRIC. The efficacy of this medication has been shown to shorten the duration of cholestasis.¹⁵ Our patient had good responses to cholestyramine, ursodeoxycholic acid and rifampicin in each attack. If there is going to be a further recurrent episode, rifampicin may be the drug of choice to be used for our patient.

Some patients may not respond to pharmacological therapy alone, therefore other alterna-

tives such as plasmapheresis, Prometheus dialysis, intermittent nasobiliary drainage, partial external biliary diversion and liver transplantation can be the other options of therapy.¹⁶⁻¹⁹ In case of prolonged cholestasis, a patient will need nutritional support to prevent fat malabsorption and fat-soluble vitamin deficiency. As mentioned earlier, there has been no reported medication to prevent future attack. The long-term prognosis is still good. However, regular follow-up is needed, because BRIC may progress to PFIC, which has a poor prognosis.²⁰

In conclusion, we report a Thai boy who had recurrent cholestasis. Clinical course and laboratory data supported the diagnosis of BRIC. Cholestyramine, ursodeoxycholic acid and rifampicin successfully alleviated jaundice and pruritus. Patient and family counseling regarding his disease were given and long-term follow up is needed.

REFERENCES

1. Luketic VA, Shiffman ML. Benign recurrent intrahepatic cholestasis. *Clin Liver Dis.* 2004 Feb; 8(1):133-49.
2. Summerskill WH, Walshe JM. Benign recurrent intrahepatic "obstructive" jaundice. *Lancet.* 1959 Oct; 2(7105): 686-90.
3. Tygstrup N, Jensen B. Intermittent intrahepatic cholestasis of unknown etiology in five young males from the Faroe Islands. *Acta Med Scand.* 1969 Jun; 185(6):523-30.
4. Brenard R, Geubel AP, Benhamou JP. Benign recurrent intrahepatic cholestasis. A report of 26 cases. *J Clin Gastroenterol.* 1989 Oct; 11(5):546-51.
5. Lesser PB. Benign familial recurrent intrahepatic cholestasis. *Am J Dig Dis.* 1973 Apr; 18(4):259-64.
6. Tygstrup N. Intermittent possibly familial intrahepatic cholestatic jaundice. *Lancet.* 1960 May; 1:1171-2.
7. Williams R, Cartter MA, Sherlock S, Scheuer PJ, Hill KR. Idiopathic recurrent cholestasis: A study of functional and pathological lesions in four cases. *Q J Med.* 1964 Jul; 33: 387-99.
8. van der Woerd WL, van Mil SW, Stapelbroek JM, Klomp LW, van de Graaf SF, Houwen RH. Familial cholestasis: progressive familial intrahepatic cholestasis, benign recurrent intrahepatic cholestasis and intrahepatic cholestasis of pregnancy. *Best Pract Res Clin Gastroenterol.* 2010 Oct; 24(5):541-53.
9. Gupta V, Kumar M, Bhatia BD. Benign recurrent intrahepatic cholestasis. *Indian J Pediatr.* 2005 Sep; 72(9):793-4.

10. Mizuochi T, Kimura A, Tanaka A, Muto A, Nittono H, Seki Y, et al. Characterization of urinary bile acids in a pediatric BRIC-1 patient: effect of rifampicin treatment. *Clin Chim Acta*. 2012 Aug; 413(15-16):1301-4
11. Lee YS, Kim MJ, Ki CS, Lee YM, Lee Y, Choe YH. Benign recurrent intrahepatic cholestasis with a single heterozygote mutation in the ATP8B1 gene. *Pediatr Gastroenterol Hepatol Nutr*. 2012 Jun; 15(2):122-6.
12. Spiegel EL, Schubert W, Perrin E, Schiff L. Benign recurrent intrahepatic cholestasis, with response to cholestyramine. *Am J Med*. 1965 Oct; 39(4):682-8.
13. Maggiore G, de Giacomo C. Efficacy of ursodeoxycholic acid in preventing cholestatic episodes in a patient with benign recurrent intrahepatic cholestasis. *Hepatology*. 1992 Aug; 16(2):504.
14. Bachs L, Parés A, Elena M, Píera C, Rodés J. Effects of long-term rifampicin administration in primary biliary cirrhosis. *Gastroenterology*. 1992 Jun; 102(6):2077-80.
15. Cançado EL, Leitão RM, Carrilho FJ, Laudanna AA. Unexpected clinical remission of cholestasis after rifampicin therapy in patients with normal or slightly increased levels of gamma-glutamyltranspeptidase. *Am J Gastroenterol*. 1998 Sep; 93(9):1510-7.
16. Mezey E, Burns C, Burdick JF, Braine HG. A case of severe benign intrahepatic cholestasis treated with liver transplantation. *Am J Gastroenterol*. 2002 Feb; 97(2):475-7.
17. Oldakowska-Jedynak U, Jankowska I, Hartleb M, Jirsa M, Pawłowska J, Czubkowski P, et al. Treatment of pruritus with Prometheus dialysis and absorption system in a patient with benign recurrent intrahepatic cholestasis. *Hepatol Res*. 2014 Oct; 44(10):E304-8.
18. Saich R, Collins P, Ala A, Standish R, Hodgson H. Benign recurrent intrahepatic cholestasis with secondary renal impairment treated with extracorporeal albumin dialysis. *Eur J Gastroenterol Hepatol*. 2005 May; 17(5):585-8.
19. Stapelbroek JM, van Erpecum KJ, Klomp LW, Venneman NG, Schwartz TP, van Berge Henegouwen GP, et al. Nasobiliary drainage induces long-lasting remission in benign recurrent intrahepatic cholestasis. *Hepatology*. 2006 Jan; 43(1):51-3.
20. Van Ooteghem NA, Klomp LW, van Berge-Henegouwen GP, Houwen RH. Benign recurrent intrahepatic cholestasis progressing to progressive familial intrahepatic cholestasis: low GGT cholestasis is a clinical continuum. *J Hepatol*. 2002 Mar; 36(3):439-43.