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CASE REPORT

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Benign recurrent intrahepatic cholestasis: late initial diagnosis in adulthood

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ABSTRACT

Benign recurrent intrahepatic cholestasis (BRIC) is a rare autosomal recessive or sporadic disorder, characterized by recurrent episodes of intense pruritus and jaundice that resolve spontaneously without leaving considerable liver damage. The attacks can start at any age, but the first attack is usually seen before the second decade of life. We report the case of a young adult male patient with BRIC who presented with recurrent cholestatic jaundice and pruritus with negative work up for all possible etiologies and a liver biopsy consistent with intrahepatic cholestasis. He improved on treatment with rifampicin and has not suffered another attack on follow up. Although in adulthood, BRIC diagnosis should be kept in mind in patients with recurrent cholestatic attacks with symptom free intervals after main bile duct obstruction and other congenital or acquired causes of intrahepatic cholestasis excluded.

Key words. Benign recurrent intrahepatic cholestasis. Adulthood. Rifampicin.

INTRODUCTION

Benign recurrent intrahepatic cholestasis (BRIC) is a rare autosomal recessive or sporadic disorder characterized by recurrent episodes of intense pruritus and jaundice that resolve spontaneously without leaving considerable liver damage. The onset of the disease may be at any age, but it usually starts in the first decade, 80% of cases shows up before the age of 20. Each attack lasts from weeks to months before resolving spontaneously. Patients are completely asymptomatic for months to years between symptomatic periods. BRIC diagnosis can be only confirmed after exclusion of other possible congenital or acquired causes of intrahepatic cholestasis according to the recurrent character of the jaundice with hepatic biopsy.[1,2]

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CASE REPORT

A 23-year-old man was referred to emergency department of our hospital complaining of obvious jaundice and itching. He also suffered malaise, dark urine and intermittent pale stools. He recalled that his symptoms developed after an episode of upper respiratory tract infection. When he was 11 and 17 years old, he had two more self remitting jaundice attacks which lasted approximately 2 months. He had been initially diagnosed as infectious hepatitis at these occasions without an extensive investigation. There was no family history of liver disease. There was no history of ingestion of toxins or any other drugs, either. On physical examination he was icteric and he had diffuse excoriations all around in his body caused by severe itching. He had neither hepatomegaly nor splenomegaly. There were no signs of cirrhosis in the form of spider angiomas, palmar erythema or thenar atrophy. Laboratory examination revealed a sedimentation rate of 17 mm/hour, a white blood cell count of 8.4 x $10^3/\mu$L, a hemoglobin of 13.8 g/dL, a hematocrit of 41.7% and a platelet count of 318 x $10^3/\mu$L with a normal smear. Total bilirubin was 29.6 mg/dL with a direct component of 24.6 mg/dL. Serum total bile acids (TBA) concentration

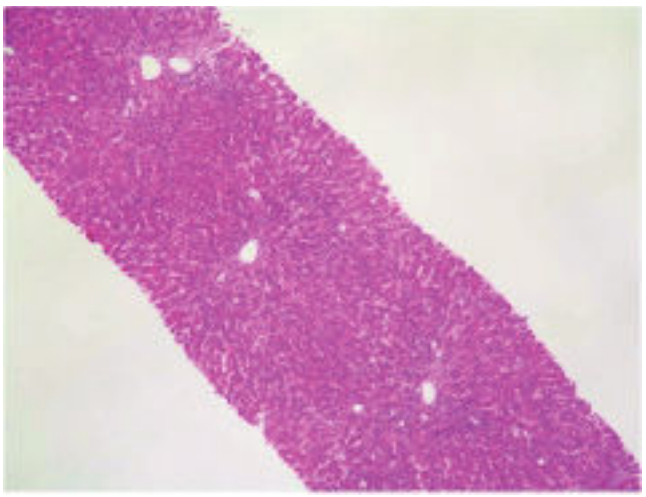

Figure 1. *Histologic appearence of the liver biopsy. Portal tracts and hepatic cords are preserved (H&E, x200).*

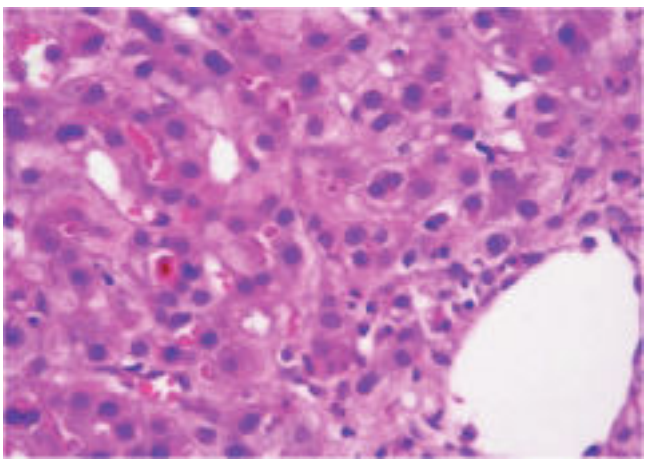

Figure 2. *In some areas, intracytoplasmic and intracanaliculer bile deposition is prominent. Focal inflammatory cells were also discernible (H&E, x400).*

was 735 μmol/L (< 15 μmol/L). Liver enzymes were increased as 2 folds of upper normal limits, alanine aminotransferase (ALT) was 92 IU/L (5-40), aspartate aminofransferase (AST) was 104 IU/L (5-40). Alkaline phosphatase (ALP) was elevated with a value of 331 IU/L (35-125), gamma glutamyl transpeptidase (GGT) was within normal limits, 29 IU/L (10-45). His coagulation parameters at admission include a prothrombin time of 12.8 s, an international normalized ratio of 1.03, and a partial thromboplastin time of 33.1 s. The patient's blood urea nitrogen, creatinine. serum electrolytes, cholesterol, calcium, phosphorus, uric acid, thyroid stimulating hormone, free thyroxine and free triiodothyronine were all normal. Serologic tests for viral hepatitis (HAV, HBV, and HCV), adenovirus, cytomegalovirus and Ebstein-Barr virus were all negative. He was also negative for anti-nuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody and anti-liver kidney microsome-1 antibody. The diagnosis of Wilson disease, α1-antitrypsin deficiency were excluded by normal plasma levels of copper, ceruloplasmin, and α1-antitrypsin. The liver appeared normal on ultrasonography with non dilated intrahepatic and extrahepatic bile ducts. There were neither gallstones nor intrahepatic or extrahepatic bile duct obstruction. Spleen was in normal size and there was no ascites or another abdominal abnormality. Bile ducts were also normal on magnetic resonance cholangiography. Since his bilirubin levels were persistently high, a liver biopsy was performed for further investigation. Tru-cut biopsy of the liver showed normal portal tracts and intact sinusoidal patern of hepatic cords (Figure 1) and revealed intracellular and canalicular cholestasis with some ballooning of heptocytes. Mild inflammatory cell infiltrates in occasional portal tracts and a few foci of parenchymal inflammation were also seen. There was no evidence of portal tract fibrosis or ductopenia. There were no Mallory or Councilman bodies, no siderosis and no steatosis (Figure 2).

Laboratory and pathology findings made it possible to exclude congenital or acquired causes of intrahepatic cholestasis for us and when the relapsing and benign feature of the disease was taken into account a diagnosis of "benign recurrent intrahepatic cholestasis" was made. We also looked for DNA analysis to verify our diagnosis and to find out the BRIC type. Our patient was homozygous for the IVS 26 + 2 T > A mutation in ATP8B1. In the course of the disease ursodeoxycholic acid 500 mg q.i.d, cholestyramine 4 g t.i.d and an antihistaminic tablet was commenced as a first line therapy. A 10-days ursodeoxycholic acid and cholestyramine treatment in adequate doses seemed to have no biochemical and clinic response. Then both of the drugs were ceased and rifampicin in a dose of 300 mg per day was commenced. Rifampicin treatment was accompanied with improvement of symptoms. Four weeks after initial rifampicin dosage laboratory findings changed as follows: total bilirubin was 3.4 mg/dL with a direct component of 2.8 mg/dL, TBA was 312 μmol/L, ALP was 185, AST was 26 IU/L, ALT was 25 IU/L. Eight weeks later, the patient was free of symptoms with all normal laboratory findings (Table 1). He is on regular follow up for 10 months and has not suffered another attack.

Table 1. Laboratory findings of the patient during the course of treatment.

Status	Baseline laboratory*	Ursodeoxycholic acid†	4th week‡	8th week§
Date	30 May 2009	10 April 2009	11 May 2009	12 June 2009
Total bilirubin (mg/dL)	29.6	28.2	3.4	0.9
Direct bilirubin (mg/dL)	24.6	23.9	2.8	0.3
Serum total bile acids (μmol/L)	735	705	312	13
ALP (IU/L)	331	325	185	110
GGT (IU/L)	29	31	33	27
AST (IU/L)	104	110	26	23
ALT (IU/L)	92	88	25	27

* Baseline laboratory results, ursodeoxycholic acid and cholestyramine treatment commenced. † Ursodeoxycholic acid and cholestyramine treatment ceased, rifampicin treatment commenced. ‡ 4th week of rifampicin treatment. § 8th week of rifampicin treatment.

DISCUSSION

BRIC is a rare autosomal recessively inherited or sporadic liver disease that is characterized by intermittent attacks of cholestasis. It was first described by Summerskill and Walshe in 1959.[3] Cholestatic attacks can last for several weeks to months. Symptom-free intervals can lead from several months to years. Liver biopsies are characterized by intrahepatic cholestasis with preservation of normal liver structure. There is no progression to liver cirrhosis.[1,4] Although attacks seem to be associated with a viral prodrome, an inciting viral agent or toxin has not been defined.[5] Mutations in a single gene, FIC1 (recently renamed ATP8B1) were found to be responsible for this disease in most families described to date,[6,7] although genetic heterogeneity is present.[8,9] Recently BRIC type 2 (BRIC 2) caused by another mutational change in ABCB11 gene has been demonstrated.[10] In comparison to patients with ATP8B1 mutations, patients with ABCB11 mutations lack extrahepatic symptoms such as pancreatitis and are more likely to exhibit cholestasis.[11]

The attacks can start at any age, but the first attack is usually seen before the second decade of life. In a large series of patients the age of presentation varied from 1 to 59 years and duration of icteric phase was also variable lasting from weeks to months.[1,3,12] In our patient, the first attack was seen at age 11 followed by another one when he was 17. Each episode lasted approximately for 2 months. He had been initially diagnosed as infectious hepatitis, but there are no documented causative agents in his history. It is most probable that the physician in charge at those occasions suspected an undetermined viral agent as the cause of the disease, without laboratory evidence.

In such cases, during icteric phase serum bilirubin, bile acids and ALP levels are elevated but GGT is characteristically low or normal. Occasionally ALT and AST levels may be markedly elevated but usually there is only a mild elevation.[13] In our patient, ALT and AST levels increased 2 times of upper normal limits and the clinical presentation, laboratory characteristics and the course of the disease were consistent with the diagnosis of sporadic BRIC. The pathologic findings in his liver biopsy were typical of this entity, as well. We also verified our diagnosis with mutational analysis and concluded as BRIC type 1.

To date no effective medical intervention to interrupt the cholestatic attacks in BRIC is available. Several treatment modalities have been described, such as cholestyramine, ursodeoxycholic acid.[14,15] However these interventions did not have a consistent effect on terminating cholestatic attack in our patient. Finally, rifampicin completely stopped the cholestatic episode in our patient. There are some reports that show beneficial role of rifampicin in remission of cholestasis. Rifampicin competes with bile acids for hepatic uptake, thereby lowering hepatocyte bile salt concentration.[16,17] Rifampicin also promotes the elimination of bile salts by inducing the 6-hydroxylation of secondary bile salts, this intervention warrants further investigation.[18] When medical therapy is not effective to interrupt the cholestatic attacks partial biliary diversion and nasobiliary drainage may be employed successfully. Partial biliary diversion is less advisable because of its permanent character in an episodic disease. Temporal endoscopic biliary diversion with nasobiliary drainage has also been shown effective in interrupting attacks in BRIC patients, recently.[19]

In the present case, rifampicin treatment provided laboratory improvement and symptomatic relief with

resolution of jaundice and pruritus. Our patient made an uneventful recovery within 8 weeks. He is on regular follow up for 10 months and has not suffered another attack.

We report here a case of BRIC initially diagnosed in adulthood, whose two previous attacks were undiagnosed in local hospitals. Although in adulthood, BRIC diagnosis should be kept in mind in patients with recurrent cholestatic attacks with symptom free intervals after main bile duct obstruction and other congenital or acquired causes of intrahepatic cholestasis excluded.

REFERENCES

1. Brenard R, Geubel AP, Benhamou JP. Benign recurrent intrahepatic cholestasis. A report of 26 cases. *J Clin Gastroenterol* 1989; 11: 546-51.
2. Lidofsky DS. Jaundice. in Feldman M, Friedman SL, Brandt JL. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 8th. Ed. Vol. 1. No.14. Philadelphia: Saunders-Elsevier; 2006, p. 301-16.
3. Summerskill WHJ, Walshe JM. Benign recurrent intrahepatic obstructive cholestasis. *Lancet* 1959; 2: 686-90.
4. Bijleveld CM, Vonk RJ, Kuipers F, Havinga R, Fernandes J. Benign recurrent intrahepatic cholestasis: a long-term follow-up study of two patients. *Hepatology* 1989; 9: 532-7.
5. Luketic VA, Shiffman ML. Benign recurrent intrahepatic cholestasis. *Clin Liver Dis* 1999; 3(3): 509-28.
6. 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; 36(3): 439-43.
7. Klomp LWJ, Bull LN, Juijn JA, Pabon-Pena CR, Mohkamsing S, Smith LB, et al. Characterization of multiple different mutations in FIC1 associated with hereditary cholestasis. *Hepatology* 1999; 30: 407A.
8. Sinke RJ, Carlton VE, Juijn JA, Delhaas T, Bull LN, van Berge-Henegouwen GP, et al. Benign recurrent intrahepatic cholestasis: evidence of genetic interval between D18S69 and D18S64.*Hum Genet* 1997; 100: 382-7.
9. Floreani A, Molaro M, Mottes M, Sangalli A, Baragiotta A, Roda A, et al. Autosomal dominant benign recurrent intrahepatic cholestasis (BRIC) unlinked to 18q21 and 2q24. *Am J Med Genet* 2000; 95: 450-3.
10. Luketic VA, Shiffman ML. Benign recurrent intrahepatic cholestasis. *Clin Liver Dis* 2004; 8: 133-49.
11. van Mil SW, van der Woerd WL, van der Brugge G, Sturm E, Jansen PL,Bull LN, et al. Benign recurrent intrahepatic cholestasis type 2 is caused by mutations in ABCB11. *Gastroenterology* 2004; 127: 379-84.
12. Houwen RHJ, Baharloo S, Blankenship K. Genome screening by searching for shared segments; mapping a gene for benign recurrent intrahepatic cholestasis. *Nature Genet* 1994; 8: 380-6.
13. Nakamuta M, Sakamoto S, Miyata Y, Sato M, Nawata H. Benign recurrent intrahepatic cholestasis: a long term follow up. Hepatogastroenterology 1994; 41: 287-9.
14. Crosignani A, Podda M, Bertolini E, Battezzati PM, Zuin M, Setchell KD. Failure of ursodeoxycholic acid to prevent a cholestatic episode in a patient with benign recurrent intrahepatic cholestasis: a study of bile acid metabolism. Hepatology 1991; 13:1076-83.
15. Bircher J. Correspondence: Treatment of patients with benign recurrent intrahepatic cholestasis. *Hepatology* 1989; 10: 1030-2.
16. Balsells F, Wyllie R, Steffen R, Kay M. Benign recurrent intrahepatic cholestasis: improvement of pruritus and shortening of symptomatic phase with rifampicin therapy: A case report. *Clin Pediatr* 1997; 36: 483-5.
17. Cancado EL, Leitao RM, Carrilho FJ, Laudanna AA. Unexpected clinical remission of cholestasis after rifampicin therapy in patients with normal or slightly increased levels of GGT. *Am J Gastroenterol* 1998; 93: 1510-17.
18. Lachaux A, Loras-Duclaux I, Bouvier R, Dumontet C, Hermier M. Benign recurrent cholestasis with normal gammagluamyl-transpeptidase activity. *J Pediatr* 1992; 121: 78-80.
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; 43: 51-3.