Benign Recurrent Intrahepatic Cholestasis

Femmy Nurul Akbar, Sjaifoellah Noer, LA Lesmana, Unggul Budi Husodo, Wirasmi Marwoto

Division of Gastroenterology, Department of Internal Medicine, Medical Faculty, University of Indonesia - Jakarta

ABSTRACT

Benign recurrent intrahepatic cholestasis (BRIC) or idiopathic recurrent intrahepatic cholestasis is a rare case. It is a familial and autosomal recessive. The etiology of BRIC is still unknown. We report the case of a patient with BRIC who suffered from recurrent jaundice 7 times in 7 years that occurred for 1-3 months with spontaneous resolutieon.

This patient received ursodeoxycholic acid, cholestiramine and prednisone. And within 2 months, the jaundice resolved together with other complaints.

***Key words**: Cholestasis, autosomal, familial.*

INTRODUCTION

Cholestasis refers to a condition of decreased or absence of bile flow into the duodenum due to intra-hepatic or extra-hepatic abnormalities. The intra-hepatic abnormalities are localized in the hepatocyte or intra-hepatic bile duct. Intra-hepatic cholestasis can be hereditary, as in the case of benign recurrent intra-hepatic cholestasis, Dubin-Johnson syndrome, Rotor syndrome, and porfiria; or acquired, such as in the case of drug-induced cholestasis, or that due to infection, alcohol, total parenteral nutrition, etc. The clinical cholestatic syndrome manifests in the form of jaundice, pruritus, increased blood bilirubin, and increased alkaline phosphatase and bile acid.[1,2]

Benign recurrent intrahepatic cholestasis (BRIC) or idiopathic recurrent intrahepatic cholestasis is a rare syndrome of recurring cholestasis that is usually familial and autosomal recessive. This disorder could be found in ages 8 months to 60 years, and 75% manifests in an age of less than 20 years. The male to female ratio is 1.7:1.[1,2,3,4]

The etiology of BRIC is still unknown. However, research shows that patients with a predisposition for BRIC have decreased primary bile acids cholate and chenodeoxycholate, and increased secondary bile acids lithocholate and deoxycholate, which are more cholestatic. A high fat diet and colon infection could cause increased toxic secondary bile acids due to fat malabsorption and bacterial metabolism in the colon. Environmental factors could also disturb bile acid metabolism and bile secretion through allergic or hypersensitivity reaction, even though the mechanism is still unclear.[3,4]

The clinical characteristic of BRIC is recurring cholestasis usually proceded by pruritus, constitutional symptoms such as weakness, decreased appetite, weight loss and influenza-like symptoms for 2 to 4 weeks.[1,3,4] The patient also commonly complains of nausea and vomiting, sometimes also abdominal discomfort and whitish defecation.[1,3] Attacks of jaundice usually last for 1 to 4 months and then resolve spontaneously. The next attack recurs within 1 month to 20 years, and between attacks the patient is normal and has no complaints.[1,3,4,5,6] Such attacks could recur for a lifetime. There has been a report of a patient who suffered from 27 attacks in 38 years.[3] The first attack of jaundice could be induced by pregnancy or the use of oral contraception such as methyl-testosteron or other steroids. However, in establishing the diagnosis of BRIC, the influence of drugs and pregnancy are annulled, since intrahepatic cholestasis of pregnancy and drug-induced intrahepatic cholestasis are separate diagnostic entities.[4]

Laboratory results demonstrate severely increased direct billirubin, increased indirect billirubin, positive uri-

nary billirubin, increased serum alkaline phosphatase, usually normal serum gamma-glutamil transferase (GT), and mildly increased or normal serum transaminase.[1,3] Liver biopsy demonstrates cholestasis in the form of accumulated bile pigment or bile plug Summerskill-Tygstrup in the hepatocytes and bile canals, infiltration of the portal ducts by mononuclear cells and sometimes eosinophils, and sometimes there is mild fibrosis in the peripheral and centrilobar zones (zone 1 and 3).[1,3,4,7] The morphology of liver biopsy is not patognomonic since it could resemble other intrahepatic cholestasis. Outside of attacks, laboratory and histologic findings of the liver are normal.

Cholangiography and ultrasonographic examination do not show signs of obstruction. Another supporting examination is the examination of the 18th chromosome, which demonstrate an abnormal locus on the q21-22 position of the long arm, as also found in Byler syndrome and progressive familial intrahepatic cholestasis 1 (PFIC1), which signifies a protein defect that disturbs bile acid transport.[1,8,9,10]

Summerskill-Tygstrup et al formulated the following criteria for benign recurrent intrahepatic cholestasis:[4]

1. Recurrent attacks of jaundice accompanied by severe pruritus and cholestasis based on biochemical examination.
2. The presence of bile plugs in liver biopsy.
3. Normal intra and extrahepatic bile duct based on cholangiography.
4. Absence of other factors that could cause intrahepatic cholestasis, such as pregnancy and drugs.
5. Periods of absence of symptoms for months or years.

Intrahepatic cholestasis is called benign because long-term examination does not reveal fibrosis, cirrhocis or liver failure.[4,7]

Therapy for BRIC is still unclear. Therapy is usually symptomatic, such as to alleviate the itch and combat infection with antibiotics. Several medications in research to deal with pruritus are as follows:[1,3]

- Cholestiramine: 12-16 g/day
- Ursodeoxycholic acid: 13-15 mg/kg bodyweight/day
- Antihistamine: hydroxyzine and difenhydramine, especially for nocturnal pruritus.
- Rifampisin: 300-600 mg/day

There is yet a sure therapy for the cholestasis itself. A medication commonly used is ursodeoxycholic acid, which reduces destruction of hepatic cells due to accumulation of toxic bile acid that obstructs the secretion of bile acids. The process of bile secretion and intrahepatic cholestasis also involves cellular mechanisms such as cellular immunity, which could explain how corticosteroid therapy may be able to help reduce cholestasis.[3] Other medications that could reduce intrahepatic cholestasis but still require further research are azatioprin, chlorambucyl, cholchicine, cyclosporine, S-adenosylmethionine, FK 506 and methotrexate.

CASE ILLUSTRATION

Mrs. N, 35 years, a middle-class housewife, was hospitalized on the fifth floor of IRNA B (B ward) of the Cipto Mangunkusumo Hospital from the 23rd to the 29th of August 2000, with a chief complaint of yellowish color all over the body from 3 weeks prior to admission. The yellowish color occurred suddenly, preceded by severe continuous itching and weakness of the whole body. The patient did not complain of fever nausea, vomiting, abdominal discomfort, gassiness or diarrhea, and her appetite was still normal. Her urine was tea-colored, her defecation was white color. The patient was admitted to Koja hospital for 10 days, and underwent ultrasound examination, which proved to be normal, and the patient was referred to Cipto Mangunkusumo Hospital. For 3 days prior to admission the patient complained of a sore throat and cough without sputum.

For 7 years prior to admission, the patient had suffered from similar attacks of jaundice 7 times, and the complaints usually resolve spontaneously after 1 to 3 months. The first attack of jaundice occurred 6 months after the patient gave birth to her second child and received oral contraception. The patient used Microgynon and stopped taking it every time she suffered from jaundice. The patient had been hospitalized in the Islamic Hospital of North Jakarta 4 times and twice at the Koja Hospital, and during three hospitalizations was diagnosed with cholecystitis and hepatitis, and the rest of the time no abnormality was found. During hospitalization the patient usually received Urdafalk, Methicol, Cursil, and Antacid. The patient also underwent frequent ultrasound examination and has undergone barium meal and ERCP examination during attacks, without any abnormal findings. History of other medications was denied. Prior to attacks the patient often ate fatty foods such as liver, spleen, etc, but the patient has ceased to do so. The attacks were not induced by fatty foods. The patient had a history of transfusion during her third hospitalization. The patient suffered from jaundice and fever at the age of approximately 12 years.

History of bile stone, renal stone, hypertension, dia-

betes mellitus and pulmonary disease was eliminated. The patient's mother has also suffered from jaundice.

Physical examination revealed the patient to be in good health, soundly alert, with a blood pressure of 120/70 mmHg, pulse rate of 78 times per minute, respiration rate of 16 times per minute, temperature of 37°C, body weight 60 kg and height 158 cm with jaundice in skin, signs of excoriation due to scratching, and jaundice of the sclera. The patient's conjunctiva were not anemic, her pharynx was hyperemic, her tonsils were T1-T1, her lymph nodes were not palpable and her jugular venous pressure was not increased. Heart and lung examination were within normal limits. Abdominal examination proved to be soft, liver and spleen were not palpable, there was no tenderness or ascites, normal positive digestive sounds, and the extremities were warm, there was no edema or palmar erithema.

Laboratory findings in Koja Hospital of 2nd August 2000 revealed Hemoglobin level of 11.6 g/dl, leukocyte 10,500/ul, Hematocryte 32%, Platelet count 387,000/ul, LED 63 mm/hour, leukocyte differential count 0/2/0/78/17/3, billirubin urinalysis 3+, urine urobillinogen 1, other results were within normal limits. Laboratory findings on the 18th of August revealed total billirubin of 27.51 mg/dl, direct billirubin of 20.55 mg/dl, and indirect billirubin of 6.96 mg/dl, SGOT of 39 U/l, SGPT of 41 U/l, albumin of 3.87 g/dl, globulin of 3.06 g/dl, alkaline phosphatase of 583 U/l and GGT of 11 U, negative HbsAg, negative IgM anti-HAV, and negative Anti-Hbs. Laboratory tests over the past years demonstrated billirubin levels ranging from 6 to 17 mg/dl and normal or mildly alleviated SGOT/SGPT. ERCP at the Islamic Hospital of North Jakarta in the year 1998 demonstrated obstruction and stone in the billiary system. Her last ultrasound on the 2nd of August 2000 at the Koja Hospital demonstrated no obstruction or stone in the billiary system.

The problem in this patient was benign recurrent intrahepatic cholestasis and acute pharyngitis. The patient then underwent complete peripheral blood check, and hemostasis examination; total, direct and indirect billirubin measurement; measurement of other liver functions, ANA and liver biopsy. The patient also received ursodeoxycholic acid with a dose of 3 x 250 mg, ampicillin-sulbactam 2 x 375 mg and vitamin B complex 3 x 1 tablet and termination of oral contraception.

Repeat laboratory results are as follows: Hemoglobin level 10.1 g/dl, leukocyte 12,400/ul, Hematocryte 31%, Platelet count 410,000/ul, reticulocyte 11%, total billirubin 21.8 mg/dl, direct billirubin 16.7 mg/dl, SGOT 41 U/l, SGPT 34 U/l, BT 2 minutes and 30 seconds, CT 13 minutes, PT 11.1 (12.8), APTT 35.9 (35.3) and negative ANA. Biopsy findings demonstrated PA in the form of hard intra-cell and intra-canal cholestasis (see figure 1.), almost normal portal, and no significant abnormality between attacks, which are in accordance with the characteristics of benign recurrent intrahepatic cholestasis. The patient was then permitted to go home and was advised to return to the hospital immediately if the jaundice increased, there was fever or abdominal discomfort.

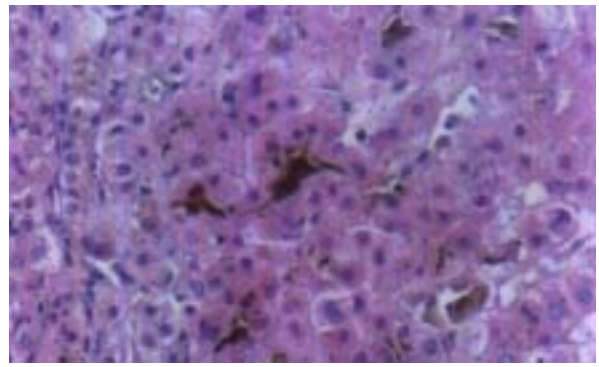


Figure 1. The picture of hispathology showed the form of hard intra-cell and intra-canal cholestasis.

The following week, the patient still suffered from jaundice, but her pharyngitis had resolved. The patient received ursodeoxycholic acid with a dose of 3 x 250 mg, cholestiramine 3 x 5 g (1 sachet) for only 2 days, ferrum supplements and 50 mg of prednisone (4-3-3 tablets) per day for 2 weeks which was tapered-off as the patient's clinical condition improved. Temporary billirubin level had reduced. Within 2 months the jaundice resolved together with other complaints, with a final total and direct billirubin level of 1.0 g/dl and 0.8 g/dl.

DISCUSSION

This is a rare case of cholestasis.[4] The intrahepatic cholestasis in this patient was established as a case of benign recurrent intrahepatic cholestasis based on an age of 35 years with recurrent jaundice 7 times in 7 years, that occured for 1 to 3 months with spontaneous resolution, accompanied by severe itching, white defecation, tea-colored urine, history of oral contraception for 7 and a half years, and family history of mother with jaundice. These symptoms are in accordance with BRIC, which inflicts young adults with recurrent jaundice for 1 to 4 months, spontaneous resolution, recurring within an interval of 1 month-20 years accompanied by severe itch-

ing, white defecation, tea-colored urine and family history.[1,3,4,5,6]

Oral contraception could initially induce attacks, but recurrent drug-induced cholestasis is not an appropriate diagnosis for this patient because in patients with drug-induced cholestasis, jaundice would resolve immediately after administration of the drug in question is terminated, while in this patient, jaundice could recur and resolve any time, independent of the use of oral contraception.[1,4]

The symptom of sore throat and cough could be a part of the BRIC syndrome, but a hyperemic pharynx and leukocytosis signifies a separate problem of acute bacterial pharingitis.

The diagnosis of BRIC is also supported by increased total and direct billirubin level, increased alkaline phosphatase, normal GGT and normal intra and extra hepatic findings based on ultrasound examination and cholangiography. Liver biopsy demonstrated hard intracellular and intra-canal cholestasis that most probably signifies the Summerskill-Tygstrup bile plug, characteristic of but not patognomonic for BRIC. Symptoms and signs of the patient's illness fulfill the criteria for benign recurrent intrahepatic cholestasis based on Summerskill-Tygstrup.[4]

Another examination to establish the diagnosis of BRIC is examination of the 18th chromosome,[1,8] which has not been performed due to impracticality and high-cost.

The patient received therapy to reduce itching, which was ursodeoxycholic acid and cholestiramine. The patient discontinued cholestiramine due to severely disturbing nausea.[1,3] The patient received antibiotics to deal with acute bacterial pharyngitis, also to anticipate signs of cholangitis, even though such cases are very rare. Such therapy does not require further hospitalization. The patient also received an immunosuppressive dose of corticosteroid, since BRIC is considered to be related to complex cellular responses of the bile system, even though this has not been established through research findings.[3,4]

The patient had been hospitalized 7 times prior to this one. This is definitely not cost-effective. If biopsy had been done earlier, the patient would not have spent as much on hospital care and examinations.

The patient should also receive adequate information on her disorder, which could recur any time. She should avoid any possible factors that could induce jaundice, and she should know the complications of her disorder, such as cholangitis, even though this rarely occurs. The patient is also advised to use other methods of contraception, such as IUD or sterilization.

REFERENCES

1. Erlinger S. Cholestasis. In: Schiff ER, Sorrell MF, Maddrey WC, eds. Schiff's diseases of the liver. 8thed. Philadelphia: Lippincott-Raven Publisher, 1999: 611-9.
2. Fallon MB, Anderson JM, Boyer JL. Intrahepatic cholestasis. In: Schiff L, Schiff ER, eds. Schiff's diseases of the liver. 7th ed. Philadelphia: JB Lippincott Company, 1997; I: 353-4.
3. Sherlock S. Cholestasis. In: Sherlock S, Dooley J eds. Diseases of the liver and billiary system 10th. Oxford: Blackwell Science Ltd, 1997: 230-2.
4. Desmet VJ. Cholestasis. In: Mac Sween RN, Anthony RP, Scheuer PJ, Burt AD, Portmann BC eds. Pathology of the liver. 3th ed. Edinburgh. Churchill Living Stone, 1994: 461.
5. Isselbacher KJ. Bilirubin metabolism and hyperbilirubinemia. In: Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL, eds. Harrison's principles of internal medicine. 13th. New York: Mc Graw-Hill, 1994; 2: 1453-4.
6. Sherlock S. Cholestasis. In: A colour atlas of liver disease. London: Wolfe Medical Publications Ltd, 1979: 104.
7. WebMD.http://www.icondata.com/health/pedbase/files/BENIGNRE.HTM. Benign Recurrent Intrahepatic Cholestasis. Full Paper. In: Pediatric database. 1994.
8. Klomp LW, Bull LN, Knisely AS, Doelen MA, Juijn JA, Berger R, Forget S, et al. A missence mutation in *FICI* is associated with Greenland Familial Cholestasis. HEPATOLOGI 2000; 32: 1337-41.
9. Arias IM. New Genetics of inheritable jaundice and cholestasis liver disease. Lancet. 1998.
10. Worman HJ. Current paper in liver disease. Abstract. Columbia University. hjw@columbia.edu.; 1999.