Annals of Tropical Paediatrics (1999) 19, 215–217

Benign recurrent intrahepatic cholestasis in a Saudi child

KHALID AL DREES, ABDULLAH AL ZABEN, ABDULRAHMAN AL AMIR & ABDULKADIR ABDULLA*

*Gastroenterology Division, Department of Paediatrics, and *Department of Pathology, King Fahad National Guard Hospital, Riyadh, Saudi Arabia*

(Accepted 16 November 1998)

Summary We report a case of benign recurrent intrahepatic cholestasis (BRIC) in an 11-year-old Saudi girl who developed three episodes of pruritus and jaundice at the ages of 4, 8 and 9 years. These episodes were almost stereotypic and lasted 5–8 weeks. Although she had elevated liver enzymes and serum bile acids in her blood during the attacks, they returned to normal between attacks. Thorough investigation excluded other causes of liver disease and her recurrent attacks were shortened by cholestyramine therapy. A diagnosis of BRIC should be kept in mind in patients with cholestasis.

Introduction

In children and adults, many liver diseases present with cholestatic features. The prognosis varies with the natural history of each disease and many, but not all, will progress to cirrhosis. Benign recurrent intrahepatic cholestasis (BRIC) is uncommon but well described in the literature and is associated with normal life expectancy.[1] It is important to counsel affected families appropriately and to avoid unnecessary and expensive investigations.[2] To the best of our knowledge, BRIC has not been reported previously from Saudi Arabia.

Case report

An 11-year-old Saudi girl is the eldest child of healthy, first-degree, consanguineous parents. At the ages of 4, 8 and 9 years she developed recurrent clinical attacks of obvious jaundice and pruritus, precipitated by febrile illnesses with no history of ingesting any pharmaceutical or herbal medicine. These attacks resolved after 5–8 weeks and were curtailed by cholestyramine. Despite this, she maintained normal health and normal growth. She presented each time with jaundice and pruritus but no other associated clinical symptoms and no change of stool colour. Pruritus preceded jaundice by 2 weeks. There was no history of chronic liver disease in the family. Between the attacks, the girl was perfectly normal. Physical examination at her last follow-up visit found her weight and height to be normal; there was no jaundice, peripheral oedema, clubbing, hepatomegaly or splenomegaly. Results of the rest of the examination were likewise unremarkable.

Results of liver function tests for the three attacks are shown in Table I. Results of other laboratory investigations during the attacks

Reprint requests to: Dr Abdullah Al Zaben, Department of Paediatrics (Gastroenterology Division), King Fahad National Guard Hospital, PO Box 22490, Riyadh 11426, Saudi Arabia. Fax: + 1 252 0088; e-mail: zaben81@hotmail.com

0272-4936/99/020215-03 $9.00
Carfax Publishing

TABLE I. Liver function tests and serum bile acid in the three episodes (μmol/l)

	1st episode	2nd episode	3rd episode	Normal
Total bilirubin	107	219	134	0–17
Direct	50	198	95	0–5
ALKP*	1477	1222	1108	135–560
AST	44	95	39	15–37
ALT	39	55	54	30–55
GGTP**	NA	13	22	5–32
Bile acid	NA	25.8	406	<8.8

*Alkaline phosphatase; **gamma glutamyl transpeptidase; NA: not available.

(complete blood counts, erythrocyte sedimentation rate, serum electrolytes, calcium, phosphorus, total protein, albumin, cholesterol and coagulation markers) were normal. Screening for hepatitis A, B and C, cytomegalovirus and Epstein Barr virus yielded negative results. Serum immunoglobulins and serology for antinuclear antibodies, anti-smooth muscle antibodies and anti-liver-kidney-mirosomal antibodies were negative. Serum copper, ceruloplasmin, 24-h urine copper and sweat chloride test results were normal. Laboratory findings were normal after the second and third attacks also. Ultrasonography for the liver, biliary tree and the kidneys yielded normal results. CAT scan of the abdomen and endoscopic retrograde cholangiopancreatography (ERCP) were normal.

Percutaneous liver biopsy was performed after the third episode and the histopathology showed normal tissue and excluded abnormal acute, chronic or cholestatic changes. The girl has attended the clinic regularly for the past 2 years and there has been no recurrence of jaundice.

Discussion

BRIC was first described in two patients who had repeated attacks of cholestatic jaundice by Summerskill & Walshe in 1959.[2]

Diagnosis has been based on the following criteria: (i) several attacks of jaundice, pruritus and biochemical disorders indicating cholestasis; (ii) bile plugs in the liver specimen; (iii) normal intrahepatic and extra-hepatic bile ducts at cholaniography; (iv) absence of factors known to produce intrahepatic cholestasis; and (v) symptom-free intervals of several months or years.[3] These criteria were fulfilled by our child.

The cause and pathogenesis involved in the onset and recurrence of cholestasis are unknown, but high serum bile acid concentration at onset of episodes, similar to what was seen in our child, suggests that the primary cause of cholestasis might be either hepatocellular bile acid transport defect or an intrinsic abnormality in hepatocyte bile acid secretion.[3] In fact, altered bile acid metabolism was proposed, based on demonstration of an increased influx of sulphated lithocholoic acid conjugates from the intestine in patients with BRIC.[4] The episodes are associated with upper respiratory tract infections, influenza, otitis media, acute gastro-enteritis or abdominal pain. In the study of two patients followed for years by Bijleveld *et al.*, nine of 11 episodes of cholestasis began in the winter months.[5] In our patient, the episodes followed non-specific febrile viral infections but were not related to the weather. The episodes in some patients occurred during pregnancy or oral contraceptive use.[3] This is important information for our female patient and her family. The number of episodes has ranged from one to 27 and the duration from 2 weeks to more than 2 years.[2,5] Three episodes were documented in our patient over 7 years.

Although the clinical features include jaundice, pruritus, abdominal pain, nausea, vomiting, fatigue, anorexia and weight loss,[3] our child presented with only jaundice and pruritus.

Laboratory findings are non-specific. Serum conjugated bilirubin is elevated three- to ten-fold. Serum transaminases are normal or only slightly increased. Normal serum gamma-glutamyl transpeptidase (GGTP) has been considered suggestive of BRIC in patients with cholestasis.[3] Maggiore *et al.* studied serum levels of GGTP from 398 children with cholestatic liver disease and concluded that there are two groups based on elevated or normal GGTP. A persistently normal serum level of GGTP would suggest that cholestasis is not associated with bile duct inflammation but rather is due to a cellular or canalicular disorder.[6] Serum bile acids may be markedly elevated, sometimes before the rise in serum bilirubin and alkaline phosphatase.[7] All these laboratory findings were noticed in our patient. CT scan of the abdomen and ERCP done in our patient showed no evidence of biliary tract extrinsic or intrinsic obstructive causes such as gall-stones or choledochal cyst.

Results of light microscopic examination of liver biopsy in the icteric period are normal or show minimal reactive changes similar to that observed in our patient.[3,5] During the attack, histology of the liver shows centrilobular cholestasis with mild inflammatory infiltration of portal spaces with mononuclear cells.[3]

It has been suggested that BRIC inheritance is either recessive or dominant with incomplete penetrance.[3] Houwen *et al.* were able to map the gene to chromosome 18 using a genome search for shared segment in three patients from an isolated community. The availability of a set of mapped markers now permits genetic association studies to be undertaken across the entire genome, based on linkage disequilibrium between a disease locus and particular marker alleles or haplotypes.[8] Subsequently, the same region was reported to be the locus for the progressive familial intrahepatic cholestasis type 1 (Byler disease) gene.[9] Recently, both diseases were reported to be caused by mutations in a single gene which was called familial intrahepatic cholestasis 1 (FIC1).[10]

Our patient's clinical, biochemical and histopathological data are consistent with BRIC diagnostic criteria. This disease must now be recognized as a cause of recurrent cholestasis in children and adults from Saudi Arabia and should be included in the differential diagnosis of such problems.

References

1 Balsells F, Wyllie R, Steffen R, Kay M. Benign recurrent intrahepatic cholestasis: improvement of pruritus and shortening of the symptomatic phase with rifampicin therapy: a case report. Clin Pediatr Phila 1997; 36:483–5.

2 Wareham NJ, Dickson CJ, Baskerville PA. Benign recurrent intrahepatic cholestasis. J R Soc Med 1985; 78:955–6.

3 Brenard R, Geubel AP, Benhamou JP. Benign recurrent intrahepatic cholestasis. A report of 26 cases. J Clin Gastroenterol 1989; 5:546–51.

4 Bijleveld CM, Vonk RJ, Kuipers F, *et al.* Benign recurrent cholestasis: altered bile acid metabolism. Gastroenterology 1989; 97:427–32.

5 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; 4:532–7.

6 Maggiore G, Bernard O, Hadchouel M, Lemonnier A, Alagille D. Diagnostic value of serum gamma glutamyl transpeptidase activity in liver diseases in children. J Pediatr Gastroenterol Nutr 1991; 1:21–6.

7 Riely CA. Familial intrahepatic cholestasis. Semin Liver Dis 1987; 7:119–33.

8 Houwen RH, Baharloo S, Blankenship K, *et al.* Genome screening by searching for shared segments: mapping a gene for benign recurrent intrahepatic cholestasis. Nature Genet 1994; 8:380–6.

9 Carlton V, Knisely A, Freimer N. Mapping of a locus for progressive familial intrahepatic cholestasis (Byler disease) to 18q21–q22, the benign recurrent intrahepatic cholestasis region. Hum Mol Genet 1995; 6:1049–53.

10 Bull L, Van Eijk M, Palwlikowaska L, *et al.* A gene encoding a P-type ATPase mutated in two forms of hereditary cholestasis. Nature Genet 1998; 18:219–24.