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Hepatobiliary scintigraphy during cholestatic and noncholestatic periods in patients with progressive familial intrahepatic cholestasis after partial external biliary diversion

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Abstract

Background: The purpose of the study was to determine the distribution of excreted bile during cholestatic periods and in remission in patients with progressive familial intrahepatic cholestasis (PFIC) after surgery with partial external biliary diversion (PEBD), using hepatobiliary scintigraphy.

Methods: Using intravenously administered technetium Tc 99m–labeled mebrofenin, the distribution of bile during periods of biochemical cholestasis and in remission was investigated in patients with PFIC operated with PEBD. Stomal bile, urine, and feces from the patients were collected during 24 hours after administration of technetium Tc 99m–labeled mebrofenin; and the fractions of remaining radioactivity in the 3 compartments and the remaining isotopic activity in the body were quantified using scintigraphy.

Results: Nine patients (4 boys and 5 girls) were studied. The median age was 13 (range, 5-24) years, and they had been operated with PEBD at a median time of 10 (range, 4-14) years before entering the study. Thirteen scintigraphic examinations were analyzed: 8 during noncholestatic remission (n = 7 patients) and 5 during cholestasis (n = 3 patients). The patients studied during remission discharged a significantly larger fraction of isotopic activity through the stoma (median, 90% vs 22%; $P < .05$) and a significantly lower fraction through the urine (median, 2.5% vs 15%; $P < .05$) compared with the patients studied during cholestasis.

Conclusion: Hepatobiliary scintigraphy could detect substantial differences in the output of bile. Further studies are needed to determine whether these differences may explain the mechanism of the PEBD operation or merely are secondary to the degree of cholestasis.

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Progressive familial intrahepatic cholestasis (PFIC) is characterized by an early onset of chronic, unremitting cholestasis, including pruritus, failure to thrive, and life-threatening bleeding owing to malabsorption of fat and fat-soluble vitamins, and biochemically a conjugated hyperbilirubinemia with increased fasting serum levels of bile acids [1]. The serum levels of γ-glutamyl transpeptidase (GGT) may be normal or even paradoxically low as in low-GGT PFIC (types 1 and 2, caused by mutations in the genes *ATP8B1* and *ABCB11*, respectively) or increased as in PFIC type 3 (caused by mutations in *ABCB4*) [2]. All 3 genes are crucial for proper formation of bile; and mutations lead to abnormal retention of bile acids in the hepatocytes, resulting in a progressing fibrosis and eventually cirrhosis and death in most cases if left untreated [3].

Biliary drainage has been used for more than 75 years to treat patients with various intrahepatic cholestatic liver diseases [4]. In 1988, it was demonstrated that partial diversion of the bile flow through an external stoma (ie, partial external biliary diversion [PEBD]) relieved pruritus and decreased the biochemical cholestasis in a group of children with PFIC [5]. Since then, PEBD has been regarded a useful surgical treatment alternative to orthotopic liver transplantation in patients with PFIC [6]. We have recently described not only short-term relief of pruritus with decreasing biochemical cholestasis, but also catch-up in growth after PEBD in a majority of our patients with PFIC [7]. Further data suggest positive long-term effects including reversal of histologic cholestasis and fibrosis [8]. Still, the exact mechanisms explaining the positive effects of PEBD in most patients are still unknown.

Since the development of the first iminodiacetic compounds especially suitable for hepatobiliary imaging [9], different scintigraphic methods have been applied in differentiating biliary atresia from other causes of neonatal cholestasis, when evaluating biliary leaks, cholelithiasis, sclerosing cholangitis, and other intra- and extrahepatic causes of biliary obstruction [10], but also for the measurement of hepatic function [11]. The use of scintigraphy in PFIC has previously been described in 1 patient for the investigation of the patency of the biliary stoma [12].

Our aims with the study were to test the feasibility of the scintigraphic method in patients with existing simultaneous intestinal and diverted stomal bile flow and estimate the distribution of bile between the physiologic (intestinal) and artificial (diverted stomal) pathways. In addition, we wished to compare the distribution of bile during cholestatic and noncholestatic periods.

1. Patients and methods

1.1. Study population

Thirteen clinically, genetically, and histologically characterized children (7 girls and 6 boys) regularly followed at the Department of Pediatrics, Karolinska University Hospital, Huddinge, Sweden, fulfilled the diagnostic criteria for low-GGT PFIC [3,13] and underwent PEBD during the years 1989-2005. Nine (4 boys, 5 girls) of the 13 operated patients, with a median age of 13 (range, 5-24) years, were prospectively included in the study (Table 1). Eight of the 9 included patients with mutations in *ABCB11*, thus suffering from PFIC type 2, whereas 1 patient showed no mutations in *ATP8B1* or in *ABCB11*. They underwent PEBD at a median time of 10 (range, 4-13) years before inclusion in the study, and they all experienced shorter or longer periods (weeks to several months) of cholestasis after the surgical procedure as described elsewhere in

Table 1 Baseline characteristics of patients with PFIC operated with PEBD and examined with hepatobiliary scintigraphy

At presentation		At PEBD	At scintigraphy		
Sex [a]	*ABCB11* [b]	Age (y)	No. of examinations	Cholestatic status [c]	Age (y)
M	Pos	12	1	R; Fig. 1A; #1	24
M	Pos	10	1	R; Fig. 1A; #2	17
F	Pos	3	3	C; Fig. 1B; #1, #2, and #3	14-16 [d]
F	Pos	1.5	2	R; Fig. 1A; #4 and C; Fig. 1B; #4	14-15 [d]
F	Pos	1	1	R; Fig. 1A; #3	13
F	Pos	1.5	2	R; Fig. 1A; #5 and #6	12-13 [d]
F	Pos	1.5	1	C; Fig. 1B; #5	10
M	Neg	1	1	R; Fig. 1A; #7	5
M	Pos	1	1	R; Fig. 1A; #8	7

Cholestatic status, age, and reference to Fig. 1A, B.

[a] Sex: M indicates male; F, female.

[b] *ABCB11* disease genotype: Pos indicates homozygous mutations in the gene *ABCB11*; Neg, no mutation in *ABCB11* or *ATP8B1*.

[c] R indicates examination during remission; C, examination during a cholestatic period. "#" refers to Fig. 1A or 1B and number of chart.

[d] Examined at more than 1 occasion.