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Preoperative observations and short-term outcome after partial external biliary diversion in 13 patients with progressive familial intrahepatic cholestasis

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Abstract

Background: Patients with progressive familial intrahepatic cholestasis (PFIC) often require liver transplantation to survive. An alternative approach is surgical diversion of bile, that is, partial external biliary diversion (PEBD). The aim of the study was to describe 13 patients with PFIC who have undergone PEBD.

Methods: Clinical and laboratory workups including growth data and histology specimens were analyzed to evaluate the short-term effects of PEBD. Follow-up, including liver biopsies, was performed 11 to 21 (median, 14) months post-PEBD.

Results: All patients showed typical features of PFIC. Eight out of 13 presented with variable signs of coagulopathy, and one patient presented with hypocalcemic seizures. The surgery was uneventful in all, but 4 patients were readmitted because of dehydration and electrolyte imbalance caused by excessive stomal losses. One month post-PEBD, 7 patients were apruritic. One patient had stomal dysfunction, showed no improvement on cholestasis after surgery, and had to undergo liver transplantation 2 months post-PEBD. At follow-up, significant biochemical improvement and gains in growth were seen in most of the patients.

Conclusions: Most of the patients with PFIC presented with signs of coagulopathy. Partial external biliary diversion had a dramatic effect on cholestasis and growth, although not all patients benefited from the surgery. Episodes of dehydration post-PEBD must be considered.

Progressive familial intrahepatic cholestasis (PFIC) constitutes a group of at least 3 different types (PFIC1-3) of autosomally inherited cholestatic diseases caused by a number of mutations in at least 3 different genes [1-3], presenting at early childhood. Apart from supplementation of fat-soluble vitamins [4,5], the only available treatment has been symptomatic, aiming at relieving the severe pruritus with antihistamines, cholestyramine, phenobarbital, or rifampicin [6,7]. In 1997, Jacquemin et al

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showed favorable clinical and biochemical response to ursodeoxycholic acid (UDCA; 20-30 mg/kg/day) in about 60% of patients with PFIC [8].

The first promising surgical treatment of pruritus in chronic cholestatic liver disease was described already in 1947 by Varco, using a T-tube to drain bile from 6 chronically cholestatic patients [9]. The first series of children with intrahepatic cholestasis (Alagille syndrome and PFIC) treated with external drainage of bile was published by Whitington and Whitington in 1988 [10]. This method, that is, partial external biliary diversion (PEBD), was quickly adopted by centers worldwide. Ileal exclusion is regarded as an alternative surgical option, but the results so far have been variable and somewhat discouraging [11,12]. The only other surgical alternative in patients with PFIC is orthotopic liver transplantation (OLT). There is still a high risk of complications in this procedure; and at least in the subgroup of children with PFIC1, the patients are not entirely cured post-OLT [13-15].

We have identified and treated patients with PFIC (formerly known as *Byler disease or syndrome*) at our center since the early 1980s. The first PEBD was performed in 1992; and until now, 13 patients with PFIC have undergone PEBD. Before the introduction of PEBD, our patients died sooner or later of liver failure or had to undergo OLT. The aim of this study was to characterize all patients with PFIC who underwent PEBD between 1992 and 2005 with regard to the preoperative findings and the postoperative outcome at 1-year follow-up.

1. Methods

Thirteen children (7 girls and 6 boys; A-M, Table 1) who fulfilled the diagnostic criteria for PFIC and underwent PEBD from 1992 to 2005 were included in the study. The diagnostic criteria as proposed by Riely [16] and Whitington et al [17] were as follows: jaundice with chronic unremitting cholestasis of early onset with pruritus; typical biochemical findings characteristic of the disease, including normal levels of γ-glutamyl transpeptidase; and the exclusion of other known causes of cholestasis including inborn errors of bile acid metabolism. At a time-point when the PEBD method was not yet available, 2 patients with PFIC2 underwent liver transplantation because of end-stage liver disease; and another previously stable patient suddenly deteriorated and died from a fulminant Epstein-Barr virus infection. A fourth patient with PFIC2, who was only sporadically followed at our center, did not undergo PEBD surgery because of serious psychosocial problems. Eight of the children included (patients B-I, born 1987-1998) were previously briefly presented as a part of an observational study on 85 children with neonatal cholestasis [18].

The 13 patients were followed from initial presentation, preoperatively, and postoperatively on a regular basis at our tertiary referral center for pediatric hepatology at the Department of Pediatrics, Karolinska University Hospital, Huddinge, Sweden. They underwent surgery at the

Table 1 Patient characteristics at presentation, at PEBD, and at 11 to 21 months of follow-up in 13 children with PFIC

Patients			Presenting feature		At PEBD	At follow-up	
ID	Sex	Genotype [a]	Age	Clinical picture	Age	Fibrosis stage [b]	Symptoms
A	M	+/+	6 mo	Pruritus, constipation	13 y	2 → 1	Pruritus [c]
B	M	+/+	3 mo	Lung hemorrhage	10 y	3 → 1	None
C	F	+/+	5 wk	Hyphema (eye bleeding)	3 y	3 → 3	None
D	F	+/+	4 wk	Epistaxis (nose bleeding)	3 y	3 → 3	None
E	F	+/+	3 mo	Epistaxis, easy bruising	18 mo	3 → 2	Pruritus [c]
F	M	+/+	3 wk	Biochemical cholestasis [d]	11 mo	3 → 4	Pruritus, FTT [e]
G	F	+/+	6 mo	Pruritus, normal PT	13 mo	3 → 0	None
H	F	+/+	4 wk	Biochemical cholestasis [d]	16 mo	2 → 1	None
I	F	+/x	6 mo	Easy bruising	19 mo	2 → 3	Pruritus
J	M	+/+	5 mo	Pruritus, seizures, prolonged PT	13 mo	3 → 3	None
K	M	−/−	6 mo	Pruritus, epistaxis, easy bruising	12 mo	1 → 1	None
L	M	−/−	1 mo	Easy bruising	6 mo	2 → 3	Pruritus
M	F	+/c	5 mo	Pruritus, jaundice	9 mo	4 → NA [f]	NA [f]

M indicates male; F, female; FTT, failure to thrive; NA, not applicable.

[a] +/+ = homozygous for the missense mutation 890A>G; −/− = no mutations found; +/x = compound heterozygous for 890A>G/3268C>T; +/c = compound heterozygous for 890A>G/3382C>T.

[b] 0 = no fibrosis, 1 = portal fibrosis, 2 = periportal fibrosis, 3 = bridging fibrosis, 4 = cirrhosis (determined according to Batts and Ludwig [22]).

[c] Had their first cholestatic episodes at follow-up and were apruritic 1.5 and 6 months later, respectively.

[d] Diagnosed early because of older sibling with the disease and had not developed any clinical signs of cholestasis.

[e] Was diagnosed with hepatocellular carcinoma 4 months after follow-up.

[f] Underwent living-related donor transplantation 2 months post-PEBD.