CME

Clinical Variability After Partial External Biliary Diversion in Familial Intrahepatic Cholestasis 1 Deficiency

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ABSTRACT

Objectives: Familial intrahepatic cholestasis 1 (FIC1) **deficiency is caused by a mutation in the *ATP8B1* gene. Partial external biliary diversion (PEBD) is pursued to improve pruritus and arrest disease progression. Our aim is to describe clinical variability after PEBD in FIC1 disease.

Methods: We performed a single-center, retrospective review of genetically confirmed FIC1 deficient patients who received PEBD. Clinical outcomes after PEBD were cholestasis, pruritus, fat-soluble vitamin supplementation, growth, and markers of disease progression that included splenomegaly and aspartate aminotransferase-to-platelet ratio index.

Results: Eight patients with FIC1 disease and PEBD were included. Mean follow-up was 32 months (range 15–65 months). After PEBD, total bilirubin was <2 mg/dL in all patients at 8 months after surgery, but 7 of 8 subsequently experienced a total of 15 recurrent cholestatic events. Subjective assessments of pruritus demonstrated improvement, but itching exacerbation occurred during cholestatic episodes. High-dose fat-soluble vitamin supplementation persisted, with increases needed during cholestatic episodes. Weight *z* scores improved (-3.4 to -1.65, $P < 0.01$). Splenomegaly did not worsen or develop and 1 patient developed an aminotransferase-to-platelet ratio index score of >0.7 suggesting development of fibrosis 24 months after PEBD.

Conclusions: Clinical variability is evident among genetically defined FIC1 deficient patients after PEBD, even among those with identical mutations. Recurrent, self-limited episodes of cholestasis and pruritus are reminiscent of the benign recurrent intrahepatic cholestasis phenotype. Despite diversion of bile from the intestinal lumen, weight gain improved while fat-soluble vitamin requirements persisted. Significant progression of liver disease was not evident during follow-up.

Key Words: Byler disease, fat-soluble vitamins, pediatric, progressive familial intrahepatic cholestasis, pruritus

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What Is Known

- Familial intrahepatic cholestasis 1 deficiency, caused by mutations in the *ATP8B1* gene, causes progressive hepatic disease and manifests with refractory pruritus, growth failure, and fat-soluble vitamin deficiency.
- Partial external biliary diversion improves pruritus, reverses growth failure, and arrests disease progression.

What Is New

- Partial external biliary diversion does not ameliorate the need for aggressive fat-soluble vitamin supplementation, particularly vitamins D and E.
- Recurrent episodes of cholestasis are common after partial external biliary diversion, often associated with both worsening pruritus and declining vitamin levels.

Progressive familial intrahepatic cholestasis type 1 (PFIC1) is caused by mutations in the *ATP8B1* gene. The encoded familial intrahepatic cholestasis 1 (FIC1) protein is a multiorgan aminophospholipid flippase with hepatic, enterocytic, pancreatic, and cochlear hair cell expression. In the liver, *ATP8B1* is involved in the maintenance of lipid composition at the canalicular membrane affording protection from the detergent activity of bile acids (1–3). Genotype-phenotype associations are complicated in patients with *ATP8B1* mutations. A number of genetic defects have been described that result in a continuum of FIC1 deficiency with varying clinical manifestations ranging from the more severe, progressive course characteristic of Byler's to the periodic episodes of benign recurrent intrahepatic cholestasis type 1 (4).

Byler's disease is a rare, progressive, fatal intrahepatic cholestatic condition originally described in Amish kindred (5,6). In-depth gene linkage analyses eventually identified the *ATP8B1* defect as the homozygous, missense mutation c.923G>T (p.G308V) (1,7). Subsequent advances have expanded our understanding of *ATP8B1* genetic variations and the phenotypic spectrum of the resulting cholestatic liver diseases. Consequently, a diagnosis of ''PFIC1'' is often assigned to children with low gamma-glutamyl transferase cholestasis and mutations in the *ATP8B1* gene. Although *ATP8B1* mutations are associated with a broad clinical spectrum, the more severe, progressive FIC1 deficient patients typically carry homozygous mutations (2,8).

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Pruritus is prominent in a number of pediatric cholestatic conditions, but is universal and severe among children with FIC1 disease. Children with FIC1 disease are burdened with an intense itch sensation resulting in behavior that ranges from mild rubbing limited to quiet moments during the evening to near constant self-destructive scratching. Symptomatic improvement in pruritus, optimization of nutritional status, and management of complications of chronic liver disease constitute the main medical avenues of treatment (9–13). FIC1 disease is, however, often refractory and progresses to cirrhosis (9). Liver transplantation may be complicated by the extrahepatic manifestations of FIC1 deficiency such as profound diarrhea leading to the development of liver steatosis in the graft (14–16). As a result, alternatives to transplantation have been pursued in hopes of improving symptoms and halting disease progression. Principal among these is the partial external biliary diversion (PEBD), which has been demonstrated to resolve cholestasis and pruritus, improve growth, and dampen disease progression both biochemically and histologically in children with a variety of cholestatic diseases (14,17–24). To date, no studies have, however, looked specifically at the response to PEBD in patients with FIC1 disease. Although a recent report highlighted the dissimilarities in the mode of presentation and early clinical course in a genetically homogeneous FIC1 deficient cohort (25), there is limited documentation of the long-term clinical responses after PEBD in FIC1 disease. Here, we aimed to describe the clinical variability after PEBD in FIC1 disease.

MATERIALS AND METHODS

Subjects

Patients with a genetic diagnoses of FIC1 disease who underwent PEBD between January 1, 2005 and December 31, 2015 and followed at the Children's Hospital of Pittsburgh of UPMC were identified by a retrospective medical record search. Records were analyzed to delineate demographics and pertinent clinical and biochemical information that included at least 1 year of assessment after PEBD. The study was approved by the institutional review board at the University of Pittsburgh.

Cholestasis was defined as a total bilirubin (TB) >2.0 mg/dL (34.2 μmol/L) (26). TB, rather than direct or conjugated bilirubin, was used to minimize the confounding effect of different laboratories reporting of the δ-bilirubin fraction, which is abnormally elevated in older children with cholestasis and not reflected in the conjugated bilirubin level (27–29). Pruritus activity was extrapolated using descriptive terms from the medical record. Genetic testing was obtained as part of routine clinical care. Specific testing for the *ATP8B1* c.923G>T mutation (p.G308V) was performed through the laboratory of the Clinic for Special Children (Strasburg, PA). Additional genetic testing was performed through the Medical Genetics Laboratory at the Baylor College of Medicine (Houston, TX).

Surgical Procedure

The technical approach for the placement of a surgical conduit in PEBD has been previously described (21,23,30). In short, a loop of jejunum roughly 15 to 30 cm from the ligament of Treitz is selected for use as the excluded bowel. The mesentery is dissected and the bowel is divided with a stapler. Similarly, a more distal portion is divided roughly 10 to 20 cm from the level of the first division. The proximal of end of the segment is anastomosed end-to-side to the gallbladder fundus and the distal end is brought out as a stoma thus constituting a properistaltic conduit between the gallbladder and the abdominal wall. An end-to-end jejunojejunostomy is then performed to place the intestine in continuity.

Statistical Analysis

t Tests were used for comparisons of continuous normally distributed variables. $P < 0.05$ was used as the threshold of significance.

RESULTS

Patient Characteristics

We identified 8 patients who met inclusion criteria (Table 1). The mutation associated with Old Order Amish (c.923G>T) was identified in 7 subjects and 1 had a heterozygous invariant splicing site mutation, c.2097+2T>C that has previously been reported in patients with FIC1 deficiency (1). Patients 2 and 7 were siblings, patients 3 and 4 were siblings, and patients 5 and 6 were cousins. In addition, patients 2, 5, 7, and 8 were included in a published manuscript describing the early clinical course of FIC1 disease before PEBD (25). At the time of biliary diversion, all patients demonstrated poor weight gain and medically resistant pruritus. All patients had cholestasis and all were receiving ursodeoxycholic acid therapy (Table 1). A liver biopsy was performed at the time of diversion in 2 patients (2 and 6) with an Ishak fibrosis stage of 1 in both. After the PEBD, patients were followed for a mean of 32 months (range 15–65 months).

Response to Diversion: Cholestasis

After PEBD, ursodeoxycholic acid was continued in 7 of 8 patients throughout the follow-up period. The TB level dropped <2 mg/dL in all patients by 8 months after PEBD (Fig. 1).

TABLE 1. Baseline characteristics in 8 patients with familial intrahepatic cholestasis 1 disease at time of partial external biliary diversion

ID	Sex	*ATP8B1* mutation	Age at PEBD, y	Total bilirubin*	GGT	ALT	AST	Weight *z* score	Itch present†
1	M	c.2097+2T>C	1.3	3.7	14	35	57	−3.12	Yes
2	F	c.923G>T	1.1	4.6	18	30	50	−3.5	Yes
3	F	c.923G>T	2.5	1.7‡	12	38	42	−3.95	Yes
4	F	c.923G>T	2.1	3.4	10	46	52	−3.84	Yes
5	F	c.923G>T	1.1	8.8	16	58	94	−3.17	Yes
6	F	c.923G>T	1.3	7.1	8	43	62	−4.1	Yes
7	F	c.923G>T	1.8	5	13	41	57	−2.7	Yes
8	F	c.923G>T	1.2	5.2	13	33	56	−2.78	Yes

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; PEBD = partial external biliary diversion.
*All patients receiving ursodeoxycholic acid (UDCA).
†All patients failed medical treatment hydroxyzine hydrochloride, rifampin, and diphenhydramine as single agent or in combination.
‡Of note, although the most recent total bilirubin value for patient 3 was 1.7 before PEBD, previous levels had been as high as 11.8.

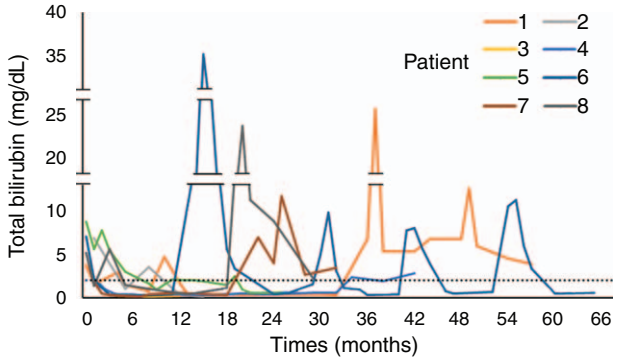

FIGURE 1. Total bilirubin (TB) levels after partial external biliary diversion (PEBD) in familial intrahepatic cholestasis 1 (FIC1) deficiency. Despite TB level normalization in all patients after PEBD, recurrent episodes were noted to occur in the majority of patients.

Recurrent transient episodes of cholestasis developed in 7 of 8 patients, with only patient 3 maintaining a TB <2 mg/dL for at least 15 months after PEBD (Fig. 1). During the period of observation, 15 cholestatic events occurred in 7 patients. No appreciable decrease in severity and/or duration was noted with each relapse within a given individual. Confounding clinical events associated with hospitalization for a cholestatic event included: bullous impetigo 4.5 years after PEBD (peak TB = 4.6 mg/dL); fever and liver biopsy suggestive of mild cholangitis 1.2 years after PEBD (peak TB = 29.2); and severe anemia (hemoglobin = 3.7 g/dL) due either to a viral syndrome or erythroblastopenia of childhood 1.6 years after PEBD (peak TB = 23.7 mg/dL). None of the additional cholestatic episodes were associated with hospitalizations.

Response to Diversion: Pruritus

After PEBD, itch is often better, not resolved, and can worsen periodically. Pruritus was subjectively improved after PEBD within 3 months in all patients. Pruritus recurred or did not completely resolve in all but 1 patient, although severity of itching rarely reached pre-PEBD levels. Episodes of pruritus were often associated with biochemical cholestasis, but itching did occur independent of a rise in TB.

Response to Diversion: Fat-Soluble Vitamins

Consistent with what we have previously reported (25), fat-soluble vitamin insufficiencies were near universal in this cohort before PEBD (Table 2). Importantly, we found that after PEBD, a similar or greater degree of vitamin supplementation was required to maintain adequate levels (Table 2). Although no clinical manifestations of vitamin deficiencies were noted, the indication for continued supplementation was due to biochemical evidence of deficiency after routine testing. Furthermore, we found that there appeared to be several trends as it relates to vitamin levels and recurrent cholestatic episodes. In divergent patterns, we noted that as TB levels increased, 25-hydroxy vitamin D and vitamin E levels decreased after PEBD (Fig. 2). This pattern was not evident as it relates to vitamin K (assessed by the international normalized ratio, data not shown). Interestingly, as has been commented on previously (25), supplementation with vitamin A after PEBD was not required with 4 patients demonstrating levels greater than recommended.

Response to Diversion: Growth

Weight *z* scores were recorded for all patients in the pre- and post-PEBD periods. Similar to other reports on FIC1 disease (5,25)

TABLE 2. Vitamin supplementation in familial intrahepatic cholestasis 1 disease

	MVI*		Vitamin A					Vitamin D				Vitamin E				
Patient	Pre	Post	Range of levels (pre)†	Range of doses (pre)‡	Avg level (pre)†	Range of levels (post)†	Range of doses (post)	Avg level (post)†	Range of levels (pre)§	Range of doses (pre)‖	Avg level (pre)§	Range of levels (post)§	Range of doses (post)‖	Avg level (post)§	Range of levels (pre)¶	Range of doses (pre)#	Avg level (pre)¶	Range of levels (post)¶	Range of doses (post)#	Avg level (post)¶
1	Y	N	61–53	0	57	34–60	0	48.2	5.0–12	2000–8000	8	6–133	0.25–0.4**	53.9	1.0–2.0	50–100	1.7	1.0–13	100–300	3.7
2	Y	N	8.0–56	2000–6000	32	–	0	–	5.0–40	8000–16,000	19.3	29–32	16,000	30.5	5–8.7	80–107	6.7	3.0–3.8	80–100	3.4
3	Y	N	36–79	0	57.5	72–77	0	74.5	5–49.7	–	23.7	47.3–90	16,000	68.7	2.7–7.5	–	5.8	8–9.8	200	9
4	Y	Y	–	–	–	39–115	0	85.4	4.3–11.5	4000–8000	7.9	19.3–50	8000–16,000	37.2	3.2	–	3.2	2.3–9.1	300–400	4.9
5	Y	Y	56	0	56	48–132	0	101.6	9.0–27	5000–16,000	19.8	19–165	12,000–40,000	66.7	1.9–5.0	25–133	3.5	1.0–11	60–200	4.2
6	Y	Y	30–65	0	47.5	48–79	0	63.5	15–33	2000–16,000	24	15–48	12,000–16,000	26.85	2.0–3.0	80–160	2.5	1.2–5	40–80	3.8
7	Y	Y	30	0	30	51–62	0	56.5	4.0–33	2000–16,000	18.5	32–75	8000–16,000	54	2.0–3.0	60–120	2.5	3.0–12	60–160	6.1
8	Y	Y	29–115	0	72	29–69	0	45.2	4.0–24	2000–20,000	17	4.0–46	8000–18,000	21	0.0–6.0	160–187	2.7	1 .0–11	160–200	4.3

MVI = multivitamin.
*Doses are supplementation in addition to 1–2 mL/day of ADEK or AquADEKs (Yasoo Health, Johnson City, TN), yes (Y) or no (N) at the end of each time period.
†Retinol-μg/dL (reference range 19–77).
‡IU/day of retinal.
§25-OH vitamin D (ng/mL; reference range 20–45).
‖IU/day of cholecalciferol.
¶IU/day of d-alpha tocopherol.
#Tocopherol (μg/mL; reference range 3.8–20.3).
**Dose in μg of calcitriol.

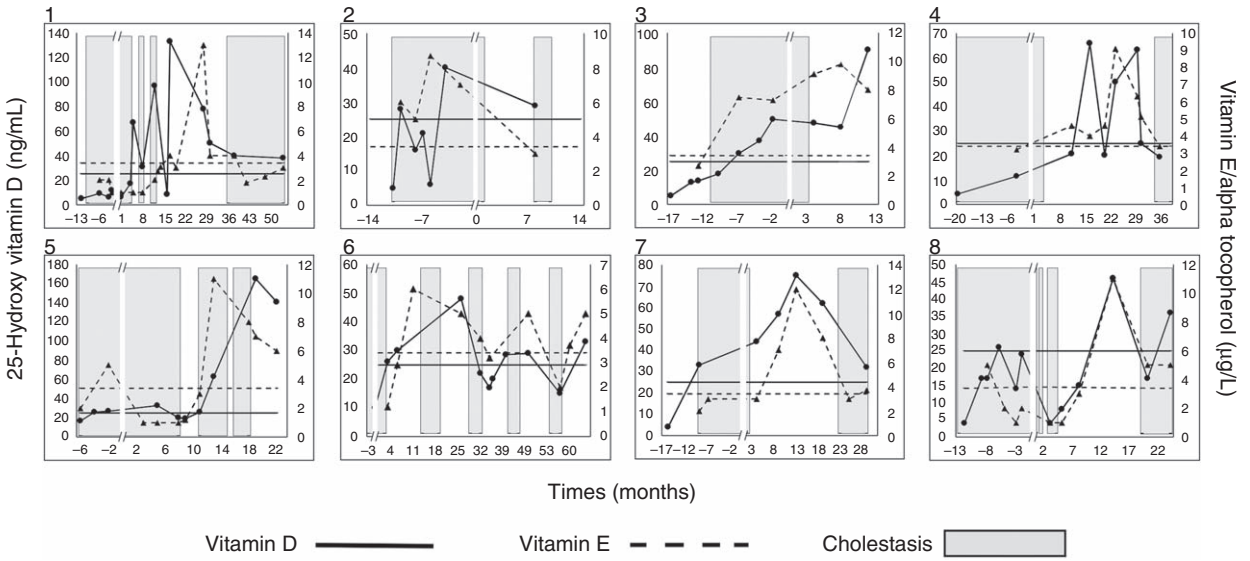

FIGURE 2. Variability in fat-soluble vitamin levels after partial external biliary diversion (PEBD). Fat-soluble vitamin levels (vitamin D and E) often fluctuated after PEBD despite continued aggressive supplementation (see Table 2). Horizontal lines represent lower limit of normal levels for both vitamin D and E on each graph. Levels were often noted to decrease when recurrent cholestatic events occurred. Shaded grey bars represent time periods of cholestasis with total bilirubin (TB) >2.0.

all 8 of the studied patients demonstrated poor weight gain despite aggressive nutritional and vitamin supplementation before PEBD (25). The mean weight *z* score at the time of PEBD was −3.4 (Table 1). After PEBD, weight *z* score demonstrated significant improvement with most recent assessments for each patient averaged to −1.65 ($P < 0.01$, Supplemental Digital Content 1, Fig. 1, *http://links.lww.com/MPG/A871*). Although all patients were counseled on the use of a calorically dense supplement following diversion, the degree of intake and length of supplement use after diversion is unknown.

Response to Diversion: Disease Progression

Surrogate markers of liver disease were assessed at the time of PEBD and at the most recent clinic visit and laboratory valuation to determine disease progression. Although 2 patients noted to have splenomegaly (without thrombocytopenia or other features of portal hypertension) on physical examination at the time of PEBD persisted with this findings, no patients progressed to develop splenomegaly (Supplemental Digital Content 2, Table 1, *http://links.lww.com/MPG/A872*). In addition, albumin, platelet, and the aspartate aminotransferase-to-platelet ratio index did not show significant differences over the follow-up period, which on average was 32 months to as long as 65 months. Patient 8 was noted to develop an aminotransferase-to-platelet ratio index score >0.7 suggestive of fibrosis (31) (Supplemental Digital Content 2, Table 1, *http://links.lww.com/MPG/A872*).

DISCUSSION

Severe pruritus to the point of self-destructive behaviors is a devastating manifestation of FIC1 disease. Initial reports of PEBD in children with cholestatic diseases including FIC1 deficiency highlighted complete and seemingly permanent resolution of pruritus, except for older patients with significant hepatic fibrosis or cirrhosis at the time of diversion (18,20,22,24). Institution of PEBD before development of severe liver injury in FIC1 disease is believed to interrupt the natural history, improve pruritus, and delay or prevent the need for liver transplantation. Our report represents the largest cohort of children with FIC1 disease, the majority having an identical mutation in the *ATP8B1* gene, who underwent PEBD. All patients received their diversion before 3 years of age with at least 15 months of follow-up. We observed that initial resolution of pruritus and cholestasis was interrupted by episodes of variably recurrent and self-limited symptoms of scratching and cholestasis. Despite these episodes, progressive liver disease did not appear to occur. Although weight gain improved in all patients after PEBD, serum levels of fat-soluble vitamins often fluctuated with cholestatic episodes and continued aggressive vitamin supplementation was needed.

Pruritus is a devastating complication of cholestatic liver disease, particularly among children with FIC1 disease. The mechanism that links cholestasis with such an intense itch sensation remains unknown but is postulated to involve pruritogenic substances metabolized by the liver that undergo enterohepatic circulation and accumulate in various tissues as a result of cholestasis (32,33). Itch-specific neural pathways, neurotransmitters, and receptors have been identified, but specific pruritogens in cholestatic diseases remain elusive. Bile acids have been proposed as a possible pruritogen. Bile acid kinetics in a small number of patients with FIC1 were similar between those with a successful PEBD and liver transplant suggesting that alteration of bile acid pool after PEBD is associated with improvement in symptoms (34). Studies in adults have, however, found no correlation between itch and serum or tissue bile salt concentration in patients with cholestasis (35), bile salt sequestrants perform no better than placebo in cholestatic pruritus (36), and symptomatic itch relief after nasobiliary drainage does not correlate with serum bile salt levels (37). Pruritus sensation has also been linked to the activity of autotaxin (ATX) and the phospholipid derivative product that it synthesizes, lyophasphatidic acid (LPA) (38,39). In patients with primary biliary cirrhosis and primary sclerosing cholangitis, the ATX-LPA axis appears to represent a key element in the pruritus of cholestasis (39). Although a recent report found that serum ATX activity did correlate with itch intensity in children with cholestasis, no patients with FIC1 disease were included in the study (40). Future investigations are needed to

explore the role of ATX-LPA in the signaling cascade of pruritus in FIC1 disease.

Prior studies that evaluated responses to PEBD in cholestatic diseases (17–22,24,41) have not looked specifically at patients with FIC1. Before this report, the largest published FIC1 cohort was from Halaweish and Chwals, which identified 5 genetically heterogeneous patients with PFIC1 with a follow-up period of 6 months; however, their analysis did not differentiate patients with FIC1 disease from other progressive cholestatic diseases (18). The overall consensus from these reports is that PEBD improves pruritus and growth, particularly in patients with minimal fibrosis at the time of PEBD (18,20,22,24).

Recurrent, self-limited episodes of cholestasis after PEBD is currently unexplained. Event variability occurred even in those with genetically identical *ATP8B1* disease causing mutations. The risk of cholangitis in patients after PEBD is unknown, but is likely low. In a cohort of patients who underwent biliary enteric reconstruction after excision of a choledochal cyst, postoperative cholangitis did not occur unless there was an anastomotic stricture (42). Although unpalliated FIC1 disease is often progressive with unremitting cholestasis and pruritus (5,6), we found that after PEBD, biochemical and patient-reported symptom improvement occurred without evidence of disease progression. We also, however, noted that interspersed within the overall improved clinical picture there were intermittent episodes of worsening jaundice and pruritus. Although confounding clinical disease may have contributed to several of the episodes of recurrent cholestasis, the majority of these attacks occurred independent of any identifiable disease causing event. The overall clinical course most mirrored what has been reported in patients with benign recurrent intrahepatic cholestasis type 1 (that is also associated with mutations in *ATP8B1*) (14). One possible explanation for our observations is the fact that biliary diversion is a difficult process to regulate, that is, the amount of bile diverted relative to what flows into the intestinal lumen. And although the exact mechanisms driving pathology in FIC1 disease is unknown, resultant variations in enterohepatic bile acid circulation due to PEBD may contribute to the periodic episodes seen after diversion.

Severe hepatic fibrosis or cirrhosis at the time of PEBD is associated with poor outcome (22,43). Only 2 of the 8 patients (patients 2 and 6) in the present study received a liver biopsy at the time of diversion, both with Ishak 1 fibrosis and each demonstrated variable post-PEBD courses.

Growth and nutritional deficiencies are important morbidities for patients with FIC1 disease and are additional indications to pursue PEBD (19,20,24). Growth response after PEBD in our cohort were in line with prior studies. Despite improvements in weight *z* scores, we found that PEBD did not ameliorate the need for aggressive vitamin supplementation, particularly vitamins D and E. Although vitamin deficiencies after total biliary diversion have been reported (44), this is the first description of the persistent supplementation needed after partial diversion. As above, variations in bile flow with diversion may account for our findings. With a high percentage of diverted bile, luminal bile acids can be low even though cholestasis is improved. Thus patients with marked improvement in cholestasis can still have insufficient luminal bile acids and accompanying complications such as major fat-soluble vitamin deficiencies. An interesting and important clinical clue is the pigment of the stool. Some children who are doing well post-PEBD have acholic stools and these are the children who have the highest vitamin requirements. In addition, we saw that during episodes of recurrent cholestasis, vitamin levels often fell precipitously to levels indicative of insufficiency despite their baseline supplementation. Our findings highlight the need to regularly monitor serum levels of fat-soluble vitamins after PEBD and adjust therapy to maintain suitable vitamin stores. These important and previously unreported findings will enable improved care provided to children with FIC1 deficiency post-PEBD.

The findings of our study should be interpreted within the context of some methodological limitations. This was a retrospective chart review and therefore contained many of the weaknesses that accompany such studies. Data analysis was limited by what had been collected and recorded in the medical chart. As such, despite a complete review for each patient, some data elements were not available for every episode of recurrent cholestasis. Linearity between data points is presumed and variations that may have existed are not represented. In addition, while standardized, validated itch assessment scores have been developed, the retrospective nature of the study did not enable their use.

In conclusion, our findings on the significant improvement in growth and pruritus after PEBD, in combination with an apparent decelerated disease progression, further validates its use in the management children with FIC1 disease. We, however, additionally report for the first time that considerable vitamin supplementation persists after PEBD. Furthermore, we report that recurrent episodes of cholestasis do occur, often in combination with both worsening pruritus and declining vitamin levels despite overall clinical improvement after PEBD. Genetic advances have enabled more specific disease assessments of PEBD—whereas most of the published literature clusters multiple intrahepatic cholestatic diseases into a single group, this is the first report to assess the clinical variability that can occur in a specific FIC1 deficient patient cohort. These findings may have broad implications for the post-PEBD clinical management of these patients.

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