Two Neonatal Cases of Food Protein-Induced Enterocolitis Syndrome With Pale Stool and Transient Biliary Dilatation

Makita E[1], Kuroda S[1,2], Itabashi K[1], Taniguchi S[1], Maruyama A[1], Sato H[1], Ichihashi K[1]
[1]*Department of Pediatrics, Saitama Medical Center Jichi Medical University, Saitama, Japan*
[2]*Department of Pediatrics, Saitama Red Cross Hospital, Saitama, Japan*

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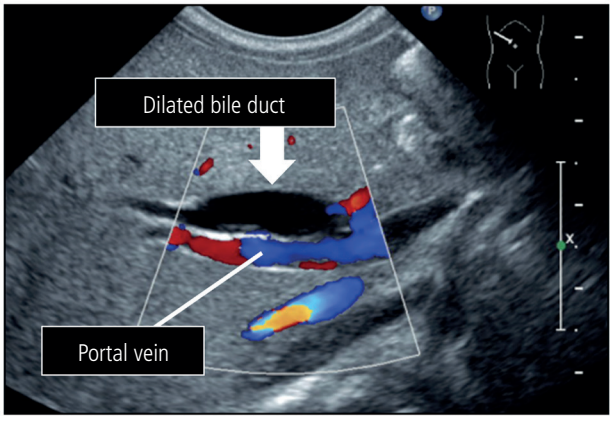
Food protein-induced enterocolitis syndrome (FPIES) is an IgE-independent allergic disease that manifests with gastrointestinal symptoms such as vomiting and diarrhea [1]. We report 2 neonatal cases of FPIES presenting with transient biliary dilatation and pale stool.

Patient 1 was a girl with a gestational age of 34 weeks and birth weight of 2206 g. Owing to the preterm birth, she was admitted to the neonatal intensive care unit. Enteral feeding with cow's milk was initiated on the day of birth, and the amount given was gradually increased. Pale stool (Supplementary Figure S1) was observed after 7 days; the patient had repeated vomiting episodes after taking cow's milk and exhibited general malaise, bloody stools, and diarrhea after 8 days (Supplementary Figure S2). Abdominal ultrasound revealed dilatation of the biliary tract (Supplementary Figure S3). A blood test revealed total bilirubin (T-Bil) of 14.10 mg/dL and direct bilirubin (D-Bil) of 1.51 mg/dL. The patient was suspected of having FPIES caused by cow's milk proteins. Consequently, she could no longer receive milk, and fluid supplementation and central venous nutritional therapy were initiated. Once vomiting and bloody stools had resolved with no recurrence after discontinuation of milk feeding, enteral feeding comprising breast milk or extensively hydrolyzed casein formula (New MA-1) was initiated from day 10, and no recurrence of symptoms was observed. A fecal test on day 8 revealed eosinophil accumulation; the blood test revealed cow's milk–specific IgE antibody titers of less than 0.10 UA/mL. In addition, an allergen lymphocyte stimulation test (ALST) with lactoferrin was positive, with a stimulation index (SI) of 4.06. Although transient elevation of D-Bil was also observed, D-Bil levels gradually normalized after peaking at 2.09 mg/dL on day 13. Ultrasound on day 9 revealed improvement in biliary dilatation. The patient continued to receive breast milk or extensively hydrolyzed casein formula and was discharged on day 22. She continued to receive either breast milk or extensively hydrolyzed casein formula orally after discharge, and no gastrointestinal symptoms were reported. An oral food challenge with cow's milk was performed at 5 months of age, after obtaining informed written consent from the patient's guardian. As a result, approximately 30 minutes after receiving 20 mL of milk, the patient developed swelling and redness on her face. After 1 month, cow's milk–specific IgE titers were 3.16 UA/mL.

Patient 2 was a girl with a gestational age of 39 weeks and birth weight of 3328 g. Oral feeding with cow's milk was introduced on the day of birth. The patient had repeated vomiting episodes after taking cow's milk from day 4. In addition, she experienced bloody stools, diarrhea (Supplementary Figure S4), and general malaise from day 7. She was subsequently referred to our hospital. FPIES caused by cow's milk proteins was suspected. In response, the patient no longer received milk, and fluid supplementation and central venous nutritional therapy were initiated. No vomiting was observed, and the patient's bloody stools improved, disappearing on day 12. Abdominal ultrasound on day 15 revealed biliary dilatation (Figure), as well as elevated D-Bil levels (>2 mg/dL). Enteral nutrition comprising breast milk or extensively hydrolyzed casein formula (New MA-1) was initiated on day 16, and no vomiting or bloody stools were observed. Although pale stools (Supplementary Figure S5) were identified on day 23, this symptom, as well as biliary dilatation, had disappeared by day 28. Cow's milk–specific IgE antibody titers were <0.10 UA/mL, and ALSTs with lactoferrin and κ-casein resulted in an SI of 10.75 and 31.97, respectively. Biliary dilatation and pale stools improved over time, and there were no organic disorders of the biliary tract. The patient continued to receive breast milk or extensively hydrolyzed casein formula and was released on day 37, with no recurrence of symptoms. However, 1 hour after accidental ingestion of processed products containing milk at age 1.3 years, she exhibited repeated vomiting and asthenia and was taken immediately to hospital, where she received intravenous corticosteroids.

To our knowledge, this is the first report of transient biliary dilatation and pale stool caused by FPIES.

FPIES is diagnosed based on a single major criterion and 3 or more other minor criteria [2-5]. FPIES is difficult to



Patient 2 (day 15)

Figure. Imaging findings. Abdominal ultrasound image showing the dilated bile duct (arrow). No color signal was observed.

diagnose because gastrointestinal symptoms are characteristic of various conditions. As the 2 cases we report exhibited the major criterion, as well as 3 minor criteria, both patients were diagnosed with FPIES. Patients' eosinophil-positive stools and positive ALST results also supported our diagnosis of FPIES [3,6]. There have been reports of patients whose condition transitioned from FPIES to an IgE-dependent immediate-type food allergy or was characterized by overlap of both conditions [7-9]. We believe that patient 1 developed an IgE-dependent milk allergy.

The symptoms of FPIES include vomiting, asthenia, pallor, and diarrhea (including bloody diarrhea). Hypotension and dehydration may also be observed in severe cases [1-5]. More cases complicated by bloody stools have been reported in Japan than in other countries [10], and the 2 cases we report also involved diarrhea accompanied by vomiting and bloody stools. Both patients had pale stools, high T-Bil levels in blood, and transient biliary dilatation that was confirmed via ultrasound. These symptoms were identified immediately before onset of vomiting and bloody stools in patient 1 and during the course of treatment administered to patient 2. We speculated that diminished function of the sphincter of Oddi and cholestasis were pathological states arising from FPIES-associated enteritis. After blood testing and ultrasound to distinguish the organic abnormalities of the biliary system, the patients' condition normalized only by eliminating the causative antigen. Therefore, we ruled out other diseases that cause biliary dilatation.

Biliary dilatation and pale stools may be observed in patients with FPIES. Hence, it is necessary to consider neonatal gastrointestinal allergies in the diagnosis of conditions exhibiting biliary dilatation and/or pale stools. Furthermore, more cases should be examined to elucidate the mechanism of transient biliary dilatation and pale stools related to FPIES.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Eishi Makita
Department of Pediatrics
Saitama Medical Center Jichi Medical University
1-847 Amanuma-cho, Omiya-ku, Saitama 330-8503, Japan
E-mail: r0947em@jichi.ac.jp

