

A Rare Case of Fetal Onset, Food Protein-Induced Enterocolitis Syndrome

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Established Facts

- The detection of allergens in the amniotic fluid and fetal blood has provided evidence of intrauterine allergen exposure through transamniotic and transplacental transfer.
- The fetus is sensitive to environmental exposure.

Novel Insights

- Food protein-induced enterocolitis syndrome, not only sensitization, can develop in utero.
- Many food protein-induced enterocolitis syndrome cases that occurred in the early neonatal period could show some signs in utero. Most of these cases might not be noticed.

Keywords

Food protein-induced enterocolitis syndrome · Fetal onset · Oral food challenge · Allergen-specific lymphocyte stimulation test · Cow's milk allergy

Abstract

Background: Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy. The pathological mechanism of FPIES is intestinal inflammation, and cell-mediated hypersensitivity is presumed to play an important role in its development. **Case Report:** The first case in which significant fetal intestinal distension suggested fetal onset of

FPIES is reported. A 2,334-g male was born at 34 weeks by vaginal delivery. **Results:** In utero, he had significant intestinal distension on ultrasonography and MRI. A few hours after the first feeding, he produced bloody stool and showed abdominal distension. In this case, FPIES was not only caused by cow's milk protein diagnosed clinically and by an allergen-specific lymphocyte stimulation test, but also by breast milk diagnosed by oral food challenge. The clinical course and laboratory results strongly suggested not only fetal sensitization but also fetal onset. **Conclusion:** This report might be helpful for prompt diagnosis and treatment and, furthermore, lead to elucidation of the pathogenesis and pathophysiology of FPIES.

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Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy with an incidence of about 15/100,000/year [1]. It presents with vomiting, diarrhea, bloody stools, lethargy, and/or weight loss. FPIES is its own entity that may be difficult to distinguish from necrotizing enterocolitis. In severe cases, it leads to complications such as severe metabolic acidosis and shock because of copious intestinal bleeding, intestinal rupture, and/or disseminated intravascular coagulation [2]. The pathological mechanism of FPIES is intestinal inflammation [3], and cell-mediated hypersensitivity is presumed to play an important role in the development of the disease [4, 5]. However, the detailed pathogenesis and pathophysiology of FPIES remain to be elucidated.

FPIES can develop during the first year of life [3]. There are rare cases that develop in the early neonatal period, from the first hours of life to a few days after birth [6]. These cases suggest the presence of intrauterine sensitization, because sensitization requires several days. There are several reports that some allergens (lactoferrin, inhalant allergen, nicotine, and insulin) are transferred to the amniotic fluid. Fetal exposure to these antigens must occur from at least midway through gestation [7, 8]. It is possible that FPIES, not only sensitization, develops in utero. However, there have been no reports of fetal onset of FPIES. The first case in which significant fetal intestinal distension suggested fetal onset of FPIES is reported.

Case Report

A 2,334-g male infant was born at 34 weeks' gestation by vaginal delivery following complete rupture of the membranes. His Apgar scores were 8 and 9 at 1 and 5 min, respectively. His 39-year-old mother consumed yoghurt made from cow's milk daily. His mother had allergic rhinitis, his father had atopic dermatitis, and his brother had food allergy to sesame and walnut. There were no signs of polyhydramnios. At 32 weeks' gestation, he had significant intestinal distension on ultrasonography (Fig. 1) and MRI (Fig. 2). After birth, he did not need any respiratory support. Physical findings showed no features of malformations but slight abdominal distension; however, abdominal X-ray did not show abnormal intestinal distension. Laboratory results showed a total white blood cell count of $31.0 \times 10^3/\mu\text{L}$ with 26.0% eosinophils, hematocrit was 41.1%, platelets were $333,000/\text{mm}^3$, C-reactive protein was 0.08 mg/dL, and serum albumin 2.8 mg/dL; liver function, other blood chemistries, and the coagulation profile were normal before initial feeding. The examination of blood, urine, and stool culture was negative.

The infant was initially fed 5 mL of cow's milk-based formula (CM) at 4 h of life. Within a few hours after the first feeding, the first meconium passed, and there was bloody stool. In addition, abdominal distension, with significant intestinal distension on ab-

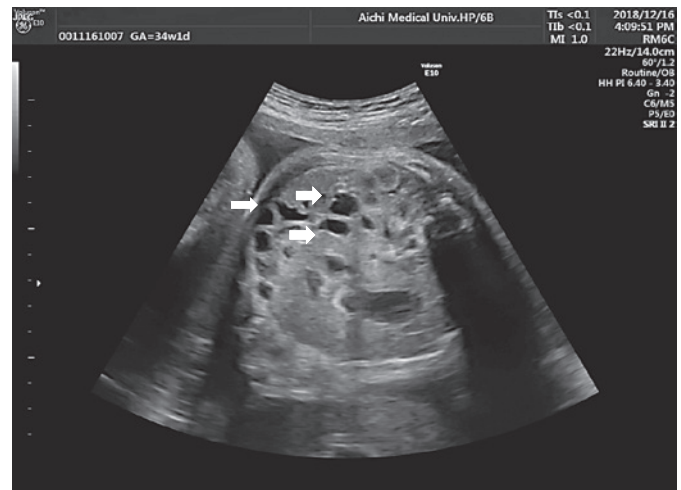


Fig. 1. Abdominal ultrasound of the mother at 34 weeks' gestation. The arrows show intestinal distension.

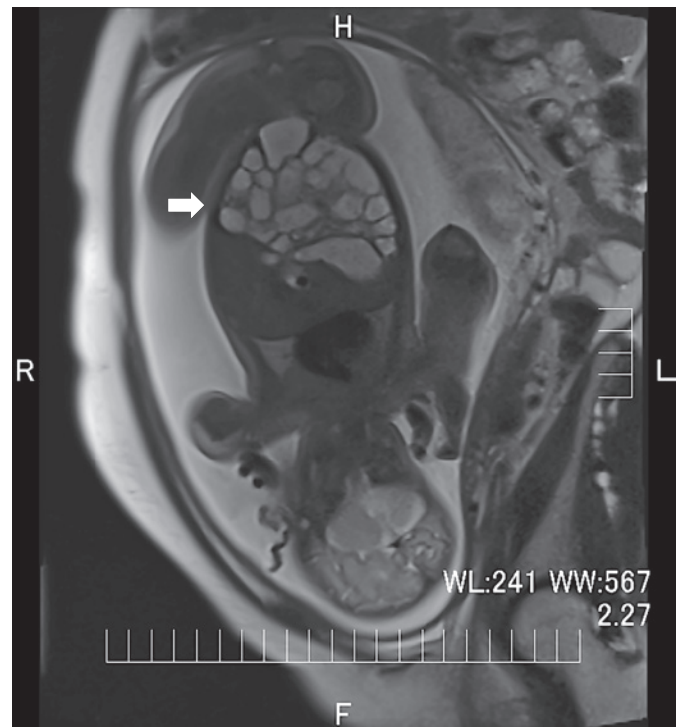


Fig. 2. T2-weighted magnetic resonance imaging of the mother at 33 weeks' gestation. The arrow shows intestinal distension with high intensity that is the same level as amniotic fluid.

dominal X-ray, was noticed. The abdominal distension disappeared after enteral feeding had been suspended. On day of life (DOL) 1, CM was re-introduced, and abdominal distension and bloody stool reappeared. Then, suspecting FPIES to cow's milk proteins, the feeding was changed to hydrolyzed formula and/or breast milk.

On DOL 6, he had again abdominal distension and lethargy with 45 mL of hydrolyzed formula and/or breast milk every 3 h. The amount of breast milk was almost half of the total feeding. Laboratory results showed a total white blood cell count of $25.9 \times 10^3/\mu\text{L}$ with 22.0% eosinophils, hematocrit was 37.3%, platelets were $514,000/\text{mm}^3$, C-reactive protein was 0.13 mg/dL, and serum albumin 3.2 mg/dL; liver function and other blood chemistries were normal. Blood gas analysis showed pH 7.217, bicarbonate ion 17.6 mmol/L, base excess -9.8 mmol/L, anion gap 13.8, and lactate 11.8 mg/dL. The examination of blood, urine, and stool culture was negative. The abdominal distension disappeared after enteral feeding was suspended.

On DOL 8, feeding exclusively by amino acid-based formula was started. Allergen-specific IgE antibodies in CM, β -lactoglobulin, casein, and α -lactalbumin were all negative. The infant was positive for cow's κ -casein and lactoferrin but not for human α -lactalbumin on the allergen-specific lymphocyte stimulation test (ALST) (stimulating indices 2.55, 16.62, and 1.04, respectively). Urinary organic acid and amino acid analyses were within normal limits.

On DOL 10, he started to take lactose-containing multiple vitamin supplement to prevent avitaminosis. On DOL 19, he had an oral food challenge (OFC) with breast milk. The OFC was considered positive because of watery diarrhea, abdominal distension, and metabolic acidosis with pH 7.288, bicarbonate ion 16.6 mmol/L, and base excess -9.2. According to his clinical course, laboratory data, and OFC, FPIES to CM was diagnosed. An OFC using CM and hydrolyzed formula was not performed because it was judged to be too dangerous. He was discharged on DOL 32. At the 7-month follow-up, his symptoms had not recurred. He received only amino acid-based formula until 5 months of age. At 6 months of age, he started a baby food without CM protein. His weight gain and linear growth were adequate for his age.

Discussion and Conclusion

Food allergy is an adverse reaction following exposure to food due to an abnormal immunologic response to the food itself [4]. Food allergies are IgE mediated or non-IgE mediated. Among them, FPIES is a non-IgE cell-mediated gastrointestinal food allergy that presents in infancy [4]. FPIES is characterized by gastrointestinal symptoms such as vomiting, diarrhea, and bloody stool, progressing to hypotension and acidemia in the most severe cases [2].

FPIES is a rare disorder [1] and difficult to diagnose because the symptoms, laboratory data, and radiographic findings are nonspecific. There have been several reports that FPIES could mimic necrotizing enterocolitis, other surgical diseases, and congenital metabolic disease, such as lactase deficiency and enterokinase deficiency [2]. These reports suggested that many FPIES infants might be misdiagnosed. The gold standard for FPIES diagnosis is an OFC. Although laboratory findings alone cannot confirm the diagnosis of FPIES, some general trends are

common in these infants, including leukocytosis with an eosinophil predominance, thrombocytosis, hemocult-positive stools, anemia, hypoalbuminemia, positive ALST, and radiographic findings [1, 5]. ALST is more specific than other laboratory findings. Kimura et al. [5] indicated that ALST was a very useful laboratory test for the diagnosis of FPIES caused by CM. This method is highly specific for the diagnosis of FPIES caused by CM, and the positivity rate is 88%. In the present case, abdominal distension and bloody stool were caused by CM, with eosinophilia and the ALST positive for CM protein. In addition, lactose-containing vitamin supplement did not induce any symptoms, and follow-up until 7 months of age leads to exclude rare congenital metabolic diseases such as congenital lactase deficiency and enterokinase deficiency. These results led to the diagnosis of FPIES caused by CM protein.

In exclusively breastfed infants, FPIES is rare. Nevertheless, the presence of antigenically intact cow's milk protein in the breast milk of mothers who consume cow's milk has already been proven [9]. The mother of this infant consumed yoghurt made from cow's milk daily. In this case, the positive OFC for breast milk might have been due to cow's milk protein in breast milk, because the ALST for human α -lactalbumin was negative.

Cell-mediated hypersensitivity is assumed to be the major mechanism of FPIES [4, 5]. However, much remains to be elucidated about its pathogenesis. Immune system reprogramming occurring in utero and prenatal sensitization could be responsible for FPIES occurring in the early newborn. There are several lines of evidence that suggest that the fetus is sensitive to environmental exposure [6]. Furthermore, the detection of allergen in the amniotic fluid and fetal blood has provided evidence of intrauterine allergen exposure through transamniotic and transplacental transfer [7, 8]. The presence of allergen and initiation of antigen-specific responses may occur via the gut in utero [7]. We assume the possibility that FPIES, not only sensitization, develops in utero. However, there have been no reports of fetal onset of FPIES. The present case showed significant intestinal expansion in the fetal period (at 32 weeks' gestation) and bloody stool after initial feeding. In addition, the clinical course did not show any other causes, such as necrotizing enterocolitis, other surgical diseases, or a metabolic disorder. The quantity of amniotic fluid swallowed by the fetus increases rapidly after the second trimester [10]. These results strongly suggest not only fetal sensitization but also fetal onset. We assume that many FPIES cases that occur in the early neonatal period may show some symptoms in utero, which may.

Two limitations of this report must be considered. The first is that CM protein could not be detected in amniotic fluid. Second, sensitization and onset in utero were not shown directly. In the future, we need CM protein detection in the amniotic fluid, ALST results, and evaluation of leukocytosis with eosinophilia in umbilical cord blood (instead of the OFC) since the OFC is not an option in the fetus.

In conclusion, the first case of fetal onset FPIES was described. FPIES is difficult to diagnose but easily misdiagnosed. Severe FPIES can lead to various complications and can affect growth and development. Prompt diagnosis and treatment of FPIES are very important. This report might be helpful for a prompt diagnosis and treatment and help to elucidate the pathogenesis and pathophysiology of FPIES.

Acknowledgment

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Statement of Ethics

The parents provided written, informed consent to publish this case, including the publication of images.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.I. and H.K. wrote the manuscript. S.A., M.M., S.T., H.U., T.K., T.M., and Y.Y. collected and analyzed the data. All the authors read and approved the final manuscript.