

FOOD PROTEIN INDUCED ENTEROCOLITIS SYNDROME IN INFANCY

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Abstract

Food protein induced enterocolitis syndrome is a non IgE-mediated food allergy that typically presents in infancy, with repetitive vomiting that begins approximately 1 to 4 hours after food ingestion often accompanied by lethargy and pallor and can be followed by diarrhea. Two months old male infant presented with severe vomiting and diarrhea few hours after introduction of milk formula. On examination subicteric, severe dehydrated, with abdominal distention, systolic heart murmur 2/6, and minor facial dysmorphism. Initial laboratory tests showed hyponatremia, metabolic acidosis, liver damage and direct hyperbilirubinemia. Infant was rehydrated, electrolyte and acid-base disturbances were corrected, ursodesoxycholic acid was introduced and extensive hydrolysed nutrition was started. Causes for cholestasis were excluded. After stabilization, follow up formula was introduced with the appearance of the same clinical presentation as 6 months ago. One month later 2 hours after unintentional intake of milk with the recurrence of vomiting and diarrhea, which confirmed the suspicion of food protein induced enterocolitis syndrome. Development of tolerance in patients with cow's milk-induced food protein induced enterocolitis syndrome occurs by the age around 3 years. There is need for identification of noninvasive biomarkers, understanding the pathophysiology, and having uniform approaches to diagnosis and management.

Key words: infant; food protein; enterocolitis syndrome; cow milk

Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE mediated food allergy that typically presents in infancy. It is characterized by recurrent vomiting 1-4 hours after food ingestion, often with lethargy and pallor, and in some patients, diarrhea. The lack of skin and respiratory symptoms and delayed onset distinguish it from anaphylaxis (Jarvinen, K., & Nowak-Wegrzyn, A., 2013). In more severe cases, symptoms may include hypothermia, acidemia, methemoglobinemia, and hypotension, which can mimic sepsis (Jarvinen, K., & Nowak-Wegrzyn, A., 2013 & Caubet et al., 2014 & Ruffner et al., 2013). The clinical severity depends on the amount and frequency of the trigger food, the patient's phenotype, and age (Mehr et al., 2009).

FPIES is most commonly triggered by cow's milk (CM) and soy proteins but can also be caused by rice, oats, and other solids. Recent studies show that nearly any food can trigger FPIES (Nowak-Wegrzyn et al., 2017 & Groetch et al., 2021 & Nowak-Wegrzyn et al., 2003). The clinical picture of FPIES caused by CM and soy proteins manifests at an earlier age (less than 6 months), while FPIES caused by solid food proteins usually manifests between 6 and 12 months (Nowak-Wegrzyn et al., 2017). Acute FPIES begins with vomiting within 1-4 hours of food ingestion, when food is ingested intermittently or after a long period of avoidance. Diarrhea, sometimes with mucus or blood, occurs between 5-10 hours after ingestion and may last up to 24 hours (Caubet et al., 2014 & Mehr et al., 2009). Chronic FPIES, reported in infants on milk or soy-based formula, presents with persistent vomiting, diarrhea, and failure to thrive, usually before 4 months of age (Groetch et al., 2021).

The pathophysiology mechanism of FPIES is still not sufficiently studied, but it is known to involve antigen-specific T lymphocytes, antibodies, and cytokines that cause inflammation with a consequent increase in intestinal permeability and increased secretion of water and electrolytes into the intestinal lumen (Powell et al., 1989).

Case presentation

A 2-month-old male infant presented with severe vomiting and over 10 watery stools a few hours after introduction of a milk formula. On examination infant was afebrile, subicteric, with signs of hypotrophy and severe dehydration, abdominal distension, systolic heart murmur 2/6 in the middle precordium and minor facial dysmorphism. Initial laboratory tests with hyponatremic dehydration ($\text{Na} = 130 \text{ mmol/L}$, $\text{K} = 3.2 \text{ mmol/L}$), metabolic acidosis ($\text{pH} = 7.32$, $\text{pCO}_2 = 32.8 \text{ mmHg}$, $\text{HCO}_3 = 17.5 \text{ Eq/L}$, $\text{BE} = -9.3$), elevated liver enzymes ($\text{AST} = 185 \text{ U/L}$, $\text{ALT} = 85 \text{ U/L}$, $\text{GGT} = 72 \text{ U/L}$) and direct hyperbilirubinemia ($\text{Bill T} = 144.6 \text{ umol/L}$, $\text{Bill D} = 70.1 \text{ umol/L}$). Abdominal ultrasound was normal. Rehydration therapy and ursodeoxycholic acid were initiated, metabolic acidosis was corrected, and feeding with extensively hydrolyzed formula (eHF) was started. Given cholestasis with dysmorphic features, Alagille syndrome was suspected. A multidisciplinary team—gastroenterologist, dysmorphologist, cardiologist, neurologist, and ophthalmologist—was involved. Abdominal CT, spinal X-ray, and cranial ultrasound were normal. Echocardiography showed a systolic pressure gradient (SPG) of 20 mmHg over the pulmonary artery. Extensive infection screening (HSV I/II, EBV, CMV, Rubella, Toxoplasmosis, Hepatitis A/B/C, Rotavirus, Adenovirus, blood culture, urine culture, stool culture) was negative. Metabolic screening, sweat test, ceruloplasmin, and alpha-1 antitrypsin were normal. Genetic testing for coeliac disease and Alagille syndrome was negative. During the hospital stay, the infant's general condition improved with a gradual decrease and normalization of total and direct bilirubin values and an increase in body weight. After discharge from the hospital, the infant was followed up once a month in the pediatric gastroenterology outpatient clinic with normal biochemical analyses and weight gain. Second echocardiography with SPG up to 15 mmHg over arteria pulmonalis and over arcus aortae. At 8 months, after introduction of a follow-up formula, the infant experienced repeated vomiting (>10 episodes) and 24-hour diarrhea with moderate dehydration requiring IV fluids. eHF was reintroduced due to suspected acute FPIES. Total IgE and specific IgE for food allergens were negative. One month later after 2 hours of unintentional intake of solid food containing milk with the recurrence of vomiting and diarrhea with consequent moderate-severe dehydration, metabolic acidosis, which confirmed diagnosis of acute FPIES.

Discussion

For the diagnosis of acute FPIES, the patient must meet the major criterion and that is vomiting 1 to 4 hours after food ingestion without classic IgE-mediated symptoms from skin and respiratory system, and at least three minor criteria (Nowak-Węgrzyn et al., 2017). Minor criteria include a repeated reaction to the same or different food, lethargy, pallor, need for emergency care, parenteral rehydration, diarrhea within 24 hours, hypotension, and hypothermia (Nowak-Węgrzyn et al., 2017). Our case fulfilled the criteria for acute FPIES, although the initial cholestasis and elevated liver enzymes required further investigation. Treatment of FPIES depends on the severity of the clinical presentation. Mild forms of acute FPIES (1-2 episodes of vomiting, without lethargy) can be treated at home with oral rehydration solutions, while persistent nausea and vomiting with moderate dehydration (> 3 episodes of vomiting) with oral ondansetron. In severe clinical presentation (severe lethargy, hypotonia, hypothermia), patients should be hospitalized and treated urgently because 15-20% of these patients may develop hypovolemic shock. The most important part of treatment is to restore hemodynamics with aggressive rehydration with isotonic solutions and after initial stabilization, to continue with maintenance parenteral rehydration. In these patients with severe clinical presentation, intravenous ondansetron has a faster onset of action (Ford, L.S., & Konstantinou, G.N., & Caubet, J.C., 2021). In our case, symptoms resolved after rehydration, so ondansetron was not required. In the most severe cases, patients may require oxygen, mechanical ventilation, vasopressors, bicarbonates for acidosis, or methylene blue for methemoglobinemia.

An oral food challenge (OFC) is recommended when the diagnosis is uncertain, no trigger food has been identified, or symptoms persist despite dietary changes. It is also used to confirm the resolution of FPIES. The OFC must be performed under hospital supervision due to the risk of severe reactions (Sicherer, S.H., 2005). Intravenous access should be secured, and observation for at least 4–6 hours is required. In CM-induced FPIES, specific IgE should be measured before OFC to assess for progression to IgE-mediated

allergy. In our case six months after initial stabilization, mother reintroduced only one meal of follow up formula with the appearance of repetitive vomiting more than 10 times and diarrhea lasting 24 hours with moderate dehydration treated with intravenous fluids. Due to suspicion of acute FPIES, eHF nutrition was reintroduced into the diet. Total IgE and specific IgE for nutritive allergens were negative. One month later after 2 hours of unintentional intake of solid food containing milk with the recurrence of vomiting and diarrhea with consequent moderate-severe dehydration and metabolic acidosis, which confirmed diagnosis of acute FPIES.

Long-term management of FPIES requires elimination of trigger foods, an appropriate dietary plan, treatment of symptoms after re-exposure, and monitoring for their resolution (Groetch et al., 2021). Infants with CM/soy-induced FPIES should avoid foods containing these allergens (Jarvinen, K., & Nowak-Węgrzyn, A., 2013, & Miceli Sopo et al., 2014). Infants with CM/soy-induced FPIES can be breast-fed or use a hypoallergenic formula, such as casein-based extensively hydrolyzed formula, although 10–20% of these infants will require an amino acid formula (Caubet et al., 2014 & Nowak-Węgrzyn et al., 2003). If a breastfed infant develops symptoms of FPIES shortly after breastfeeding, the mother should eliminate the suspect food from her diet and seek consultation with a food allergy specialist and a nutritionist for further dietary management. If symptoms do not resolve despite the mother's elimination diet, breastfeeding should be discontinued and the infant should be fed with hypoallergenic formula (Monti et al., 2011). About 20% of patients with FPIES caused by CM proteins may show cross-reactivity with soy proteins and therefore soy-based formulas are not recommended in the diet (Nowak-Węgrzyn et al., 2017). Due to the high homology of protein sequences, sheep and goat milk are not recommended in the diet (Miceli Sopo et al., 2014). Infants with FPIES caused by CM or soy proteins are more likely to develop a reaction to solid foods, especially rice and oats. Recent recommendations are not to delay the introduction of complementary foods beyond the sixth month to avoid the possible occurrence of FPIES (Fleischer et al., 2013). It is recommended to introduce only one food into the diet with a break of at least 4 days before introducing another food to note the development of any reaction (Groetch et al., 2013). The development of tolerance in patients with FPIES induced by CM or soy proteins occurs at a younger age compared with patients with FPIES induced by cereals or other foods. Katz et al., 2011 found that 60% of patients with FPIES induced by CM proteins develop tolerance by the age of 1 year, 75% by the second year, and 85% by the third year of life.

Conclusion

FPIES remains a challenging diagnosis due to its delayed, nonspecific presentation and lack of confirmatory biomarkers. Early recognition, proper dietary management, and structured follow-up are critical for preventing complications and achieving favorable outcomes. Further research is needed to elucidate the underlying mechanisms, identify biomarkers, and develop standardized protocols for diagnosis and treatment.

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