CASE REPORT

Friend or foe? Figuring out the difference between FPIES, IgE-mediated allergy and food intolerance

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SUMMARY

Most physicians recognise the severe nature of the anaphylactic reactions associated with IgE-mediated food allergy. Adverse reactions to food involving non-IgE mechanisms are often less well understood and are often not diagnosed. Food protein-induced enterocolitis syndrome (FPIES) is an example of a severe non-IgE immune-mediated food reaction that is part of a spectrum of what is believed to be T-cell-mediated reactions. FPIES results in excessive emesis and diarrhoea hours after ingestion of the offending food. While common triggers include milk, soy, wheat and oat, some children may have multiple triggers, leading to malnutrition from lack of food options and unusual developmental concerns related to food aversion.

BACKGROUND

Adverse reactions to foods include immune-mediated and non-immune-mediated reactions. Non-immune-mediated food reactions include food intolerance (eg, lactose intolerance due to lactase deficiency or reactions due to the pharmacological effects of foods¹ (eg, jitteriness due to caffeine), presence of toxins or neurological effects (eg, runny nose due to spicy foods)). Often food intolerance is mislabelled as food allergy. It is critical for physicians to be able to distinguish between the intolerances and immune-mediated reactions, as the latter may be life-threatening and requires a different management strategy. The impact that the label 'food allergy' has on quality of life is not inconsequential—diligently reading all food labels, avoiding restaurants, inability to participate in birthday parties or school activities for fear of death can have familial and social repercussions. IgE-mediated reactions require carrying an epinephrine autoinjector. IgE-mediated food reactions and FPIES are potentially fatal immune-mediated reactions. However, although lay literature and professional studies extensively report on IgE-mediated immune reactions to foods, relatively little is known on non-IgE-mediated immune reactions to foods.

CASE PRESENTATION

A 2-month-old male infant presented to the emergency room (ER) with failure to thrive. Pregnancy history was unremarkable apart from maternal hypertension. He was born at term, with a birth weight of 3.26 kg. He was fed cow's milk-based formula from birth to 1 month of age, and gained weight appropriately. Owing to spitting up and gasping, his mother changed his formula to a different cow's milk-based formula at 1.5 months of

age. The mother indicated that feeding was especially prolonged, sometimes lasting up to 2 h. His mother felt that he seemed hungry (by his crying), so she added fortified infant cereal to his formula 1 week later (10 days prior to admission). His weight on admission was 2.778 kg.

The patient was on no medications, and had no known allergies. There was a family history of atopy in the form of asthma, eczema, food allergy, penicillin allergy, allergic rhinitis and latex allergy in a number of family members.

In the ER, the patient was noted to be emaciated, with visible ribs, wasted neck and little adipose tissue visible on the legs. He was non-dysmorphic, and dehydrated. Vital signs included a temperature of 35.7°C, heart rate 139/minute, respiratory rate 42/minute, O₂ saturation 98% on room air.

Investigations included a complete blood count with 20% eosinophils. Electrolytes and renal function were normal. His glucose was 2.8 mmol/L, albumin 21 g/L, C reactive protein 52 mg/L, lactate 2 mmol/L. Urinalysis showed 6–10 white cell count and 3–5 red blood cells per high powered field (his urine was found to contain *Escherichia coli* on further workup, which was treated with appropriate antibiotics).

During his 2-week course in hospital, the patient continued to have difficulty gaining weight, despite adequate calories on cow's milk-based formula. The formula was switched to an extensively hydrolysed formula, and he quickly gained an average of 60 g/day (figure 1). Early evidence of malnutrition and hypoalbuminaemia (pitting peripheral oedema) improved with improved nutrition. Glucose levels were within normal range during his feeding with the extensively hydrolysed formula.

Workup for poor weight gain, including complete blood count, liver and renal function, thyroid, metabolic screen, sweat chloride and infectious screening did not reveal any pathological findings. He was discharged on extensively hydrolysed formula, gaining weight steadily, with a diagnosis by the hospital medical team of cow's milk protein allergy. His mother was instructed to avoid solid foods until 6 months of age, and maintain a dairy-free, soy-free diet. Weight at discharge was 3.48 kg, below the third centile.

Owing to difficult social circumstances, the patient was transferred into foster care, where he continued feeding with extensively hydrolysed formula. During the following year this patient was evaluated numerous times in the ER and allergy clinic due to severe vomiting and diarrhoea leading to dehydration after exposure to rice, oat, barley and milk (table 1).

CrossMark

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WHO GROWTH CHARTS FOR CANADA

BOYS

BIRTH TO 24 MONTHS: BOYS

Length-for-age and Weight-for-age percentiles

NAME: _____

DOB: _____ RECORD # _____

SOURCE: Based on the World Health Organization (WHO) Child Growth Standards (2006) and adapted for Canada by Dietitians of Canada, Canadian Paediatric Society, the College of Family Physicians of Canada and Community Health Nurses of Canada.

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Figure 1 Patient's growth parameters prior to diagnosis and after intervention.

At 11 months of age, he was electively admitted to the hospital for 6 days for a number of food challenges. His diet was limited, and his development with respect to feeding skills (feeding himself, holding a cup) was delayed. In hospital, he successfully passed four food challenges (beef, chicken, quinoa and chickpeas), and failed four food challenges (wheat, corn, potato and egg). The failed challenges occurred within 1–2 h

post-ingestion of 1 oz challenge dose. He developed lethargy, recurrent vomiting and diarrhoea, which was sometimes bloody. These events were easily managed, since he had a stable intravenous access already in place. He would be back to his usual self by the next morning. With this information, his diet was expanded, and a referral to the feeding team was made to learn feeding skills.

Table 1 Summary of patient's clinical complaints, investigations and management

Age	Suspected culprit food	Clinical presentation	Investigations in healthcare facility	Outcome
6 months	Rice	Tried a teaspoon of an organic brown rice cereal (milk and soy free), and within 45 min, he began to vomit profusely. He continued vomiting for most of the evening, with severe diarrhoea. He was well by the next day	Evaluated by the allergy clinic. He had a weight of 9.07 kg (over 50th centile), an otherwise unremarkable examination. Skin prick testing to cow's milk, rice, soybean and soymilk were negative	He was diagnosed with food protein-induced enterocolitis syndrome (due to rice, milk and possibly soy hypersensitivity) Carrot, sweet potato, squash, peas, and green beans were consumed without difficulty
6 months	Oat	He tried oats, and 2 h later he experienced severe emesis and diarrhoea	He was assessed in the ER, and was found to be dehydrated. He was treated with oral rehydration (intravenous access was difficult) A small amount of oat was introduced again into the diet a few days later. After an hour, he began vomiting with bloody, profuse diarrhoea He was evaluated in the ER and treated with intravenous fluids	Gradual improvement over the following 24 h Avoidance of oat recommended
6 months	Barley	He tried barley, and a couple hours later he began to vomit profusely with copious diarrhoea	He was seen in the ER, and hydrated with intravenous fluids. He returned to baseline by the next morning. His foster mother was concerned about trying new foods	Avoidance of barley recommended
12 months	Milk	He ate a chocolate chip that contained milk, and after 1 h vomited 12 times	He was assessed in the ER, but no treatment was necessary	Continuous avoidance of cow's milk recommended

ER, emergency room.

He is planned to return in 6 months for a number of hospital-supervised challenges to assess the development of tolerance and expand his limited diet.

DIFFERENTIAL DIAGNOSIS

Food poisoning, viral gastroenteritis, sepsis, necrotising enterocolitis, ileus, Hirschsprung disease, intussusception, metabolic disorders, methemoglobinemia food protein-induced proctocolitis, food protein-induced enteropathy, eosinophilic gastroenteropathies, gastroesophageal reflux disease, IgE-mediated anaphylaxis, pyloric stenosis, volvulus, bacterial enteritis and parasites may be suspected and investigated.^{2 3}

DISCUSSION

Food protein-induced enterocolitis syndrome (FPIES) is on the severe end of a spectrum of non-IgE immune-mediated hypersensitivities, resulting in gastrointestinal and systemic inflammation in infants,⁴ with the most mild being cow's milk proctocolitis, which is characterised by the presence of blood in the stool but usually no other systemic signs.⁵ The clinical presentation is significantly different than an IgE-mediated reaction. IgE-mediated reactions are characterised by rapid (within 2 h of exposure) development of symptoms including urticaria, angioedema, respiratory symptoms, gastrointestinal symptoms (eg, diarrhoea and vomiting), neurological symptoms, cardiovascular collapse and death.^{2 6} In contrast, FPIES typically occurs more than 2 h after consuming the offending food (although can occur earlier⁶) and results in severe gastrointestinal symptoms, including emesis and diarrhoea, potentially leading to dehydration and shock. On presentation to the ER, infants may appear septic and common investigations and management include sepsis workups, abdominal imaging and surgical consults.⁴ Symptoms usually rapidly resolve with rehydration.²

Typical offending foods include cow's milk protein, soy and rice, but many foods have been reported, including meats, grains (oat, barley, wheat), poultry (chicken, turkey), legumes (green peas, lentils, string beans, peanut), sweet potato, squash, egg,

fruits (orange, banana), white potato, corn, lamb and fish.^{4 7-12} Criteria to diagnose FPIES include age less than 9 months, exposure to causative food causing repetitive emesis and diarrhoea within 24 h, removal of causative food resulting in resolution of symptoms, absence of IgE-mediated symptoms and re-exposure causing typical symptoms within 24 h.^{4 7 3} Typical symptoms include emesis (100%), lethargy (77–85%), pallor (14–67%), diarrhoea (25%), bloody stool (0–4.5%). As in our case, many children react to more than one food, however, this varies among studies.^{4 6 7} Older children and adults may develop FPIES to fish and shellfish.²

The aetiology of FPIES is unclear. Antigen-specific T cells, antibodies and cytokines are thought to cause inflammation, resulting in permeability of the gastrointestinal barrier. This increased permeability may lead to a fluid shift into the gastrointestinal lumen, resulting in emesis, diarrhoea, dehydration and lethargy.⁴ Evidence of inflammation and infiltration of various cells can be seen on endoscopy, colonoscopy and biopsy.⁴

Workup in the acute setting is related to the severe emesis, diarrhoea, and dehydration that infants present with. While emesis may be a feature of anaphylaxis, skin prick testing to detect food-specific IgE is not helpful.⁴ The predictive value of atopy patch testing has not been established for FPIES.^{13 14} Patients with FPIES may also have peripheral eosinophilia, but this is not specific for FPIES.^{15 16} Oral food challenges are considered positive for FPIES if there is repetitive emesis, without other symptoms of an IgE-mediated reaction, within 30–240 min of ingestion of the suspected food.¹⁶

Acute management involves rehydration (fluid replacement), and correction of any accompanying metabolic disturbances. In contrast to IgE-mediated food allergy, prompt treatment with epinephrine is usually not required unless hypotension not responsive to fluids develops. In cases in which food-specific IgE is detectable and a history consistent with an IgE-mediated food allergy is present as well, an epinephrine autoinjector should be prescribed.⁴

Long-term management is to avoid the offending food.² While it is generally felt that exclusive breastfeeding is

protective, there have been two case reports of infants who experienced FPIES to foods in the mother's diet.^{17 18}

FPIES prognosis is good. Although very severe reactions can occur, to date, there are no published reports of death or residual disease attributable to FPIES.⁶ Many infants outgrow FPIES—studies have reported that by the age of 3 years, 60% had outgrown cow's milk FPIES, 27–83% had outgrown soy FPIES, 40–80% had outgrown rice FPIES, 67% had outgrown vegetable FPIES.⁴ Another study showed that for cow's milk FPIES, there was a resolution of 50% by 1 year, 75% by 18 months, 89% by 2 years and 94% by 30 months.⁶ Challenges should be performed on a regular basis, every 12–18 months,⁴ until resolution of FPIES. The choice of whether to do the challenge in the hospital with intravenous access or the outpatient setting is a matter of debate, and likely depends on the degree of symptoms experienced by the particular patient.²

Learning points

- ▶ Non-IgE-mediated reactions to food can be severe.
- ▶ IgE-mediated food reactions consist of life-threatening symptoms that include the respiratory, gastrointestinal, dermatological, cardiovascular and neurological systems. Patients with IgE-mediated allergy need to strictly avoid the offending food and carry an epinephrine autoinjector.
- ▶ Food protein-induced enterocolitis syndrome (FPIES) is a T-cell-mediated response whose exact aetiology is unclear; ingestion of offending foods is typically followed several hours later by diffuse emesis and diarrhoea.
- ▶ Most infants with FPIES grow out of it by school-age; dehydration and shock on re-exposure is the main concern, and hence challenges should be performed under the supervision of a physician at a healthcare facility.
- ▶ Patients with FPIES do not require an epinephrine autoinjector.

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