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Evaluation of vomiting and regurgitation in the infant

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At the conclusion of this activity, participants should be able to:

- Demonstrate knowledge of the diseases that are the major causes of food intolerance in infants
- Discuss the diagnostic tests that are best used to evaluate an infant with food intolerance

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Clinical Vignette

An 11-month-old, white boy presents for evaluation of vomiting and difficulty feeding. The patient was born full term after an uncomplicated pregnancy. He was initially breastfed but was noted to have difficulty feeding, often crying at the breast and spitting up.

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Despite his mother eliminating multiple foods from her diet, his symptoms persisted. By 3 weeks of age, he had been transitioned to a partially hydrolyzed formula, prescribed a histamine₂-blocker, and evaluated by a gastroenterologist for reflux. He was subsequently treated with a proton pump inhibitor for a period and weaned off the medication because he appeared to be doing well. At 7 months of age, cow's milk formula was reinstated. Shortly thereafter, the infant began gagging on both smooth and textured solids, with recurrence of frequent vomiting after feeding. Partially hydrolyzed formula and proton pump inhibitor therapy were restarted, but his symptoms failed to improve. He had no history of bloody stools, bilious emesis, failure to thrive, urticaria, dermatitis, or hypotension. The patient was otherwise developmentally appropriate for age. The family history was significant for an older sister with gastroesophageal reflux disease (GERD) and food allergies to milk and egg. Family history was negative for cystic fibrosis, celiac disease, or inflammatory bowel disease. The patient weight and height were greater than the 75th percentile at 5 months of age, but by 11 months his weight was just above the 25th percentile.

Introduction

Gastroesophageal reflux has been found in as many as 67% of infants at 4 months of age.¹ During infancy, the differential for persistent vomiting or regurgitation is broad and includes anatomical abnormalities of the gastrointestinal tract; infectious, metabolic, and neurologic disorders; and food allergy and intolerance. Gastrointestinal food hypersensitivities, which may present as vomiting or regurgitation, include a spectrum of disorders that result from adverse immune responses to dietary antigens, including IgE-mediated hypersensitivity (ie, true allergy), mixed syndromes (eg, eosinophilic esophagitis [EoE]), and non-IgE-mediated diseases, such as dietary protein-induced proctitis or enterocolitis.

Non-IgE-Mediated Gastrointestinal Food Reactions in Infants

In general, non-IgE-mediated dietary-induced enteropathies include proctitis or proctocolitis, enteropathy, and enterocolitis, which usually present early in life. Infants with dietary protein-induced proctitis generally seem healthy, with visible fresh blood that varies from specks or streaks to gross bleeding. A lack of other symptoms, such as vomiting or diarrhea, distinguishes this from IgE-mediated gastrointestinal food allergies. In contrast, more than 50% of patients with dietary protein-induced enteropathy present with vomiting, diarrhea, malabsorption, and failure to thrive.² They may also develop edema, abdominal distention, and anemia. The symptoms of food protein-induced enterocolitis syndrome (FPIES) are similar but more acute and severe than those observed in dietary protein enteropathy. FPIES is associated with bloody stools and the immediate development of profuse, repetitive vomiting that may lead to dehydration and shock. In contrast, the onset of symptoms in dietary protein-induced enteropathy may be delayed for days to weeks, requiring continual exposure to the offending food protein. Furthermore, it is not associated with bloody stools or the rapid symptoms seen in FPIES.

Disorders such as colic and GERD are sometimes attributed to food allergy. On the basis of studies using cow's milk elimination and subsequent challenge, a subset of patients with GERD appear to have cow's milk allergy (CMA) as the inciting agent.^{3–7} The actual percentage of patients with GERD that is attributable to CMA is unclear but has been estimated at 16% to 42%.^{5–7} These patients, however, often have diarrhea and/or other concomitant atopic manifestations, such as rhinitis or atopic dermatitis. Thus, CMA should be suspected when there are additional symptoms of CMA and/or poor response to standard medical therapy

for GERD. A trial elimination diet may be reasonable in those patients.

Colic is defined as unexplained paroxysmal bouts of fussing and crying that last 3 hours a day, for 3 days a week, for at least of 3 weeks' duration in an infant younger than 6 months.⁸ Despite these criteria, unexplained crying in an otherwise healthy infant is often labeled as colic. Although some evidence links colic to CMA, the strength of this relationship appears to be poor. It is clear that a large proportion of infants with symptoms of CMA have a high rate (44%) of colic and respond better to hypoallergenic formulas than antacids or low-lactose formula.⁹ However, because there is no evidence of an increased rate of atopy in infants with colic, the role of allergy in infants with colic without other symptoms of food allergy remains controversial.¹⁰

Food Allergies in Infants

Gastrointestinal immediate-type hypersensitivity is a form of IgE-mediated food allergy that can present at any age. Symptoms occur rapidly, generally within 2 hours of exposure, and can include nausea, abdominal pain, vomiting, and/or diarrhea. Although these symptoms may occur in isolation without other systemic symptoms, they are more commonly associated with reactions in other organ systems.

The eosinophilic gastroenteropathies (EoE, gastritis, gastroenteritis, and colitis) are collectively known as eosinophilic gastrointestinal diseases (EGIDs) and are a heterogeneous group of disorders defined by eosinophilic infiltration of at least one layer of the gastrointestinal tract. The symptoms of the EGIDs may overlap and include nausea, vomiting, abdominal pain, diarrhea, and obstruction, with the location, depth, and severity of eosinophilic infiltration defining the symptoms of the diseases.

The most common and best characterized of the EGIDs is EoE. Although the primary concern varies by age, the most common symptoms in children are pain, vomiting, and dysphagia. Infants and toddlers usually present with feeding disorders that are manifested as choking, gagging, or feeding refusal.¹¹ These symptoms can be mistaken for GERD, so a high index of suspicion for EoE must be maintained in patients with a history of atopy who are refractory to appropriate antireflux therapy. Diagnosis should be confirmed by characteristic endoscopic and biopsy findings.

Evaluation of Infants with Vomiting and Concern for Food Allergies

After excluding anatomical, metabolic, and infectious causes of vomiting, physicians often face a quandary in diagnosing gastrointestinal disease in infants. In general, diagnostic tests are not helpful in identifying food hypersensitivity in infants, and diagnosis, therefore, relies heavily on a detailed history and physical examination.

In the case of immediate IgE-mediated reactions, supportive tests, such as skin prick tests (SPTs) or specific IgE (sIgE) testing, are helpful in verifying suspicions obtained in the history. As mentioned in recent food allergy guidelines, it is important to stress that positive SPT or sIgE test results in the absence of clinical correlation do not equate to food allergies.¹² Confirmation of the cause-and-effect relationship usually requires appropriately designed challenge testing.^{13,14}

Unfortunately, most gastrointestinal food hypersensitivities are not IgE mediated and require reliance on elimination diets and food challenges. For example, no adjunctive tests are available to diagnose dietary protein-induced proctitis or CMA-associated GERD. A successful diagnosis can only be made through documentation of efficacious elimination of the causal food protein and recurrence of disease on rechallenge. Similarly, evaluation of FPIES involves excluding other causes of food intolerance, followed by monitoring for improvement on an elimination diet. In this setting, SPT is not

useful, and the results are negative in more than 90% of patients.¹⁵ Although patch testing showed promise in an early study by correctly predicting the outcome in 28 of 33 oral food challenges for FPIES,¹⁶ subsequent reports have been unable to document utility for these tests. Stool studies in FPIES may demonstrate fecal blood, leukocytes, eosinophils, and Charcot-Leyden crystals. In the short term, the peripheral blood neutrophil count is often greater than 3,500/mm³. Collectively, these studies may be helpful adjunctive tests to support a diagnosis and/or evaluate the response to an oral food challenge. The criterion standard for diagnosing FPIES is the oral food challenge. However, caution should be taken because up to 20% of food challenges for FPIES may lead to shock.¹⁵ Furthermore, confirmatory testing is often unnecessary if a classic history has been obtained.

Although endoscopic findings for FPIES are generally nonspecific, the diagnosis of dietary protein enteropathy often includes a combination of endoscopic biopsy and allergen elimination or challenge. Biopsy usually reveals variable degrees of small bowel villous injury, crypt hyperplasia, intraepithelial lymphocytes, and few eosinophils. Immunologic studies of affected infants have shown increased levels of milk IgA and IgG precipitins in 74% and 65%, respectively¹⁷; however, the diagnostic utility of these tests remains unknown.

Endoscopy is required for the diagnosis of the EGIDs. In the case of eosinophilic gastroenteritis, multiple sites may need to be biopsied because of the patchy nature of the eosinophilic infiltration, and biopsy specimens typically show at least 20 to 40 eosinophils per high-power field. Unlike the lower gastrointestinal tract, normal esophageal mucosa is devoid of eosinophils, whereas in GERD there often may be up to 10 eosinophils per high-power field. In contrast, EoE is defined by finding 15 or more eosinophils per high-power field in the maximally infiltrated areas of the esophageal epithelium in the absence of acid reflux disease. Other endoscopic findings common in EoE include fixed esophageal rings, feline folds, whitish exudates, longitudinal furrows, edema, and strictures, but none are considered pathognomonic because they can be found in other esophageal disorders. Barium contrast radiography can identify a number of the anatomical and mucosal abnormalities of EoE, but its sensitivity is low.¹⁸

Allergy evaluation in children with EoE is important but by itself does not provide any insight into the primary diagnosis. Once the diagnosis is confirmed, however, an allergy evaluation may be helpful in identifying food allergens and controlling concomitant atopic disease. Allergy testing often includes aeroallergen and food allergen testing. Several studies have shown the presence of aeroallergen sIgE in patients with EoE, but the role of these sensitivities in the pathogenesis of EoE is unclear. However, it may be helpful to consider atopic seasonality in determining when a subsequent biopsy should be performed.¹⁹

Food allergy testing is important because there is a high rate of concomitant food allergy in patients with EoE. Both serum sIgE tests and SPTs can help identify comorbid food-induced allergic disease in patients with EoE. The utility of food allergy testing to identify food allergies that are driving the EoE is less clear. Some studies suggest that SPTs, sIgE tests, and patch testing may have some benefit in identifying foods that might cause symptoms of EoE.¹⁹ However, these tests alone are insufficient to make the diagnosis of food allergy-driven EoE. Food triggers can only be definitively identified by documenting disease remission after specific elimination and/or recurrence on reintroduction.¹²

The Case Revisited

Because of his symptoms, the patient was advised to undergo an upper endoscopy and was referred to an allergy clinic for testing. Upper endoscopy revealed an esophageal mucosa with marked edema, white exudates, and a normal-appearing gastric body. Mi-

croscopic examination demonstrated more than 40 eosinophils per high-power field in both the proximal and distal esophagus, confirming the diagnosis of EoE. The SPTs revealed sensitivity to milk, egg, shellfish, peanut, cashew, almond, and sesame. The patient partially improved on an elimination diet. Addition of swallowed budesonide led to complete improvement of symptoms and, on subsequent endoscopy, disease.

Conclusion

Vomiting and regurgitation are common pediatric concerns, and physicians should be aware of when reassurance, further testing, or empiric avoidance is appropriate. The patient in this report was referred twice for an allergy evaluation. The first was for concern of GERD related to cow's milk protein hypersensitivity, and the second was for an allergy evaluation in relation to newly diagnosed EoE.

The evaluation and management of this patient highlight a few key points in the care of infants suspected of having gastrointestinal food hypersensitivities. First, the primary care physician recommended a partially hydrolyzed formula, which is not considered hypoallergenic.²⁰ Assuming CMA is a primary suspect, an extensively hydrolyzed formula or an amino acid formula should have been selected. Second, although the infant in our case is younger than the typical patient with EoE, the disease may occur at any age. In a series of 562 patients diagnosed as having EoE, 68% were younger than 6 years, and 36% were younger than 3 years.²¹ Finally, after the ultimate diagnosis of EoE, the patient's treatment included dietary avoidance; however, although some children do well on dietary elimination alone, many others (like our patient) require the use of topical corticosteroid therapy.^{22,23}

In 1998, the Workshop on Classification of Gastrointestinal Diseases of Infants and Children produced a list of 9 factors commonly leading to the diagnosis of immunologic reactions to dietary products in the gastrointestinal tract, which highlighted the difficulty in classifying these gastrointestinal hypersensitivities under a single unifying concept.²⁴ This case demonstrates the similarities of the many food-related gastrointestinal hypersensitivities, as well as the spectrum of disease processes and intricacies in diagnosing them. These are all issues that physicians need to be aware of when evaluating the infant with food intolerance.

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