Fruit-Induced FPIES Masquerading as Hereditary Fructose Intolerance

abstract

Hereditary fructose intolerance (HFI) symptoms develop at first introduction of fruit during weaning. We report on an infant with suspected HFI who presented with repeated episodes of vomiting and hypotension after ingestion of fruit-containing meals. The first episode occurred at age 4 months. Despite negative genetic testing for HFI, strict avoidance of fruit ingestion resulted in lack of recurrence of symptoms. Oral-fructose-tolerance testing conducted with an apple mousse did not determine hypoglycemia or fructosuria but caused severe hypotension. Allergy evaluations were negative, and the history was diagnostic for fruit-induced food protein–induced enterocolitis syndrome. Because this non-immunoglobulin E–mediated gastrointestinal food hypersensitivity manifests as profuse, repetitive vomiting, often with diarrhea, leading to acute dehydration and lethargy, it may be misinterpreted as HFI. We advise pediatricians to consider food protein–induced enterocolitis syndrome in the differential diagnosis when there is a suspicion of HFI. Pediatrics 2014;134:e602–e605

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KEY WORDS
food protein–induced enterocolitis syndrome, hereditary fructose intolerance, food hypersensitivity, hypersensitivity, pediatrics

ABBREVIATIONS
ALDOB—aldolase B gene
FPIES—food protein–induced enterocolitis syndrome
HFI—hereditary fructose intolerance

Drs Fiocchi, Dionisi-Vici, Dahdah, Koch, and Cotugno collectively contributed to the conception, acquisition, analysis, and interpretation of data; contributed to the draft of the article; and revised it critically for important intellectual content; and all authors approved the final manuscript as submitted.

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Hereditary fructose intolerance (HFI) is a potentially fatal inherited metabolic disease caused by deficiency of aldolase B (ALDOB) activity. More than 40 disease-causing mutations are known. Typically, symptoms appear at weaning when fructose-containing foods are first introduced. The classic entry test to exclude HFI is a fructose-tolerance test that reveals hypoglycemia (maximal after 60 to 90 min), elevated blood fructose concentrations, aspartate aminotransferase and alanine aminotransferase elevations, and urinary fructose in affected children. HFI was hypothesized in the infant we report here, who developed vomiting and marked malaise within 60 minutes from his first fruit meal.

PATIENT PRESENTATION

Born to an unrelated parent couple, the infant boy was the product of a pregnancy with first-trimester spotting (treated with progesterone), regular fetal activity, and no maternal illness, smoking, or toxin exposure. His birth weight was 2920 kg, and he had a good spontaneous cry and respiration. The patient was a healthy, breastfed infant; however, in his fourth month he developed an acute episode of repetitive vomiting, irritability, pallor, and shock. Parents rushed to the closest emergency department where the clinical picture suggested the diagnosis of sepsis. Laboratory findings revealed incremented white blood cell count (49,000 per mm³) and mild transaminase elevation (alanine aminotransferase of 85, aspartate aminotransferase of 41 [normal: <40 UI/L]), whereas C-reactive protein was 2.7 mg/L (normal: <3.0 mg/L). Blood glucose was mildly elevated (113 mg/dL [normal: 50–90 mg/dL], 6.3 mmol/L [normal: 2.8–5.0]). The infant was hospitalized to be treated with a 10-day course of intravenous antibiotics. Two days after discharge, he again became suddenly pale and nervous, vomited 10 times, then became hypotonic. Brought to our emergency department, the infant appeared pale, lethargic, and floppy. On admission to our hospital, his consciousness level was diminished, but he responded to painful stimuli. Temperature was normal, and there were no focal signs of sepsis. Blood glucose was normal (106 mg/dL, 5.9 mmol/L), arterial acid-base indicated slight respiratory alkalosis (pH 7.51, Pco₂ of 24.9 mm Hg, Po₂ of 124.2 mm Hg, HCO₃⁻ of 19.3 mmol/L, arterial base excess (ABE) of 1.9 mmol/L). He was resuscitated with oxygen, intravenous dextrose, and stable plasma protein solution. His white blood cell count was 29,650 (neutrophils: 59%), whereas hepatic serology was normal. Because both episodes occurred after the first fruit (apple/banana) meals, HFI was suspected, and an allergist was consulted to exclude anaphylaxis to apple.

Skin-prick tests were negative for foods, including cow milk, apple, and banana. Specific immunoglobulin E (IgE) determinations (CAP Fluoro Enzyme Immuno Assay [CAP-FEIA]; Pharmacia, Upssala, Sweden) were negative for cow milk (0.12 kU/L), apple (0.10 kU/L), and banana (0.17 kU/L); total IgE levels were slightly elevated at 5 kU/L. Intravenous fructose-tolerance test was avoided for its intrinsic danger; and as an alternative, an oral-fructose challenge was performed with 4 doubling doses of apple mousse every 30 minutes, up to 110 mL. The challenge test was interrupted after the third dose because the infant developed severe hypotension, which was treated as an anaphylactic reaction with epinephrine, chlorpheniramine, and hydrocortisone sodium succinate administered via a percutaneous catheter. No hypoglycemia or hypertransaminasemia, hypophosphatemia, or hyperuricemia were recorded; urinary fructose was undetectable. Symptomatic control was achieved within 60 minutes. With suspicion of an atypical form of HFI, molecular tests for mutations in the ALDOB gene were scheduled, and strict avoidance of every fruit was advised. This diet proved effective and nothing untoward occurred in the intervening semester. Genetic tests were negative for the most common mutations of the ALDOB gene (ie, p.N120KfsX30, p.A150P, p.175D, p.Y204X, p.l257P, p.N335K), which account for >90% of HFI cases in the Italian population; before planning hepatic biopsy for enzymatic evaluations, the allergist was again consulted. On the basis of the history, he diagnosed a food protein–induced enterocolitis syndrome (FPIES). Prick-by-prick tests with native allergens and skin-prick tests carried out with commercial extracts of allergens associated in the literature with fruit allergy were confirmed negative. Currently, the child is aged 1 year and is free from food-related symptoms.

COMMENT

HFI presents from the first introduction of fruit with aversion for fructose-containing foods, vomiting, restlessness,

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Similarities and Differences in Laboratory Tests During Acute Phases of FPIES and HFI</th>
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<tr>
<td></td>
<td>FPIES</td>
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<tr>
<td>Glycemia after fructose and fruit ingestion</td>
<td>Normal</td>
</tr>
<tr>
<td>Increased blood leukocyte count</td>
<td>Extreme</td>
</tr>
<tr>
<td>AST, ALT</td>
<td>Possibly normal</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Absent</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>Absent</td>
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<tr>
<td>Metabolic acidosis</td>
<td>Absent; possible respiratory alkalosis from hyperventilation</td>
</tr>
<tr>
<td>Increased liver echogenicity</td>
<td>Absent</td>
</tr>
<tr>
<td>Fructosuria</td>
<td>Absent</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Pallor, sweating, lethargy, coma, jerks, and convulsions, albeit many equivocal symptoms have been reported. Although it may be disregarded for HFI, the reported case fits perfectly with the diagnostic criteria for FPIES, a non–IgE-mediated gastrointestinal food hypersensitivity presenting as acute dehydration and lethargy. The pathophysiology of FPIES remains poorly understood. It is generally thought that antigen-specific T cells, possible humoral antibody-specific responses, and proinflammatory cytokines that modify the permeability of the intestinal barrier are involved. This abnormal response to food antigen resulting in local inflammation is thought to lead to increased intestinal permeability and fluid shift. The presenting symptoms include repetitive emesis with onset 1 to 3 hours after the ingestion of the offending food, diarrhea with onset ~5 hours after ingestion, pallor, hypotension, hypothermia, and abdominal distension. Not all patients with acute reactions develop diarrhea.

Typically, affected children are mismanaged as being affected with acute viral gastrointestinal illness, anaphylaxis, necrotizing enterocolitis, methemoglobinemia, food poisoning, or sepsis, delaying diagnosis of FPIES for many months. Sometimes misdiagnoses lead to diagnostic/therapeutic interventions that are dramatically incorrect.

Foods responsible of FPIES include cow milk, soy, rice, oats, barley, chicken, turkey, egg white, green pea, peanut, sweet potato, white potato, fish, and mollusks. FPIES from fruit proteins has only been described in 2 Italian children. In 1 of these cases, HFI was suspected and a (presumably intravenous) fructose challenge was performed at 10 months of age with negative results.

Although HFI incidence in the pediatric population is ~1:20 000 live births, the incidence of FPIES is unknown. The only available study suggests that FPIES from milk may affect 1:500 children, but to date the number of published cases of FPIES from any cause do not exceed 400. Thus, it is not surprising that acute symptoms after fruit consumption are generally interpreted as being of metabolic origin. As often happens with rare diseases, there are no formally established criteria for the diagnosis of HFI. However, in most centers the diagnosis starts with a formal demonstration of the effects of fructose exposure and ends up with a direct sequencing of the ALDOB gene. Rarely, evaluation of the aldolase activity in liver tissue is needed. Because intravenous fructose challenge poses the risk of severe hypoglycemia, oral challenges are considered less dangerous and are often used to reduce the risk. However, oral challenges are not fully risk-free, and deaths have been documented in undiagnosed individuals with HFI who have been challenged unintentionally. The gold standard test for HFI has been for many years the direct assay of aldolase activity, performed in liver biopsy samples. Today, according to the US Government Genetic Tests Registry, these tests have been replaced by genetic tests, as sequence analysis of select exons, deletion/duplication analysis, and by sequence analysis of the entire coding region.

Our case adds HFI as a new form of potential misdiagnosis and mismanagement of FPIES. Given the similarity of the clinical presentation of the 2 conditions, a careful evaluation of laboratory data can provide hints as to the diagnosis even in the acute phase (Table 1). A collegial evaluation of these findings can avoid the risks and costs of a complex diagnostic itinerary. In conclusion, our report suggests that an allergist’s evaluation is needed for the differential diagnosis of atypical cases of HFI not fulfilling the “canonical” diagnostic criteria, to exclude FPIES from fruit proteins.

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