

## GASTROENTEROLOGIC DISORDERS PRESENTING AS FOOD INTOLERANCE

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Adverse reactions to foods may be divided broadly as food allergy (an immune-mediated phenomena) or food intolerance.<sup>2</sup> With the possible exception of anaphylaxis, most adverse reactions to foods can be confused with primary gastrointestinal disorders and vice versa. Symptoms mimicking gastroenteritis, including nausea, vomiting, crampy abdominal pain, watery diarrhea, and flatulence, may be provoked by specific foods in patients with true allergy; they may also experience concomitant urticaria, flushing, rhinitis, asthma, and possibly anaphylaxis. Most food allergies are IgE-mediated immediate hypersensitivity reactions, but immune complex formation and cell-mediated immune reaction account for a minority of cases.<sup>9</sup> Although the pathophysiologic basis of celiac sprue is not fully understood, it is usually classified as a food allergy.<sup>2</sup>

Many patients who report food intolerance may in fact be suffering from gastrointestinal disorders. Individuals with lactase deficiency develop abdominal pain, bloating, and diarrhea after excessive intake of milk or dairy products; similarly, malabsorption of fructose and sorbitol may present as intolerance to fruits or "sugar-free" foods. Gastroesophageal reflux, pancreatitis, or delayed gastric emptying may be misdiagnosed as fatty food intolerance. Gastrointestinal toxicity from additives or chemical constituents of different foods may be confused with food intolerance. Finally, many patients (usually with functional bowel disease) seek medical care for a complex array of gastrointestinal and

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systemic symptoms erroneously attributed to food intolerance. In order that the reader may become familiar with the interactions between adverse food reaction and gastrointestinal diseases, we briefly discuss food allergy, gastrointestinal disorders presenting as food intolerance, and food intolerances commonly mistaken for gastrointestinal diseases.

## Food Allergy

Although a variety of gastrointestinal symptoms have been blamed on food allergy by the public and practitioners of clinical ecology, true hypersensitivity appears to be an uncommon disorder in adults.<sup>1, 30, 43</sup> Clinical ecologists believe that a wide variety of illnesses (particularly psychiatric) are caused by environmental allergies, but a recent, exhaustive review of the clinical ecology literature failed to find any scientific support for this theory.<sup>1</sup> Patients with reproducible responses to double-blind, placebo-controlled, food challenge (the gold standard for diagnosing food allergy), skin testing, and radioallergosorbent test represent less than 2% of all subjects with self-reported food allergies.<sup>43</sup> Food allergy should be considered in patients with history of atopy who develop abdominal pain, nausea, vomiting, diarrhea, urticaria, atopic dermatitis, angioedema, bronchospasm, rhinitis, or anaphylaxis shortly after eating. Although cow's milk, egg, seafood, nuts, and wheat are usually implicated in food allergy, a double-blind, placebo-controlled food challenge should be considered prior to initiating elimination diet in all but the most obvious cases.

In celiac sprue, ingestion of wheat gluten, specifically gliadin, is thought to trigger an immunologic response that destroys the small intestinal mucosa, resulting in malabsorption. Rye, barley, and oat also exacerbate celiac sprue because they contain prolamins, a substance similar to gliadin. Patients with celiac sprue may not appreciate the connection between their symptoms and grain, because the symptoms tend to be nonspecific, unrelated to eating and because gliadin and prolamins are found in a large variety of foods. Clinical manifestations of celiac sprue result from malabsorption of nutrients, including fat, carbohydrate, fat soluble vitamins, calcium, and iron; they consist of steatorrhea, weight loss, iron deficiency anemia, osteogenic bone disease, coagulopathy, and neuropathy. The diagnosis is established by a small bowel biopsy showing villous atrophy and crypt hyperplasia in a compatible clinical setting. A normal small bowel biopsy excludes untreated celiac sprue. An antigliadin antibody test is available, but its utility is unclear. Some patients as well as practitioners have "diagnosed" celiac sprue based solely on the history of food intolerance; it should be confirmed by a small bowel biopsy because historical diagnosis is frequently inaccurate. A gluten-free diet usually ameliorates the symptoms in a few days, followed by return of normal or near normal small intestinal mucosal morphology. Small number of patients refractory to dietary therapy respond to systemic corticosteroids.

## Gastrointestinal Toxicity Presenting as Food Intolerance

Ingestion of foods contaminated by bacteria, virus, chemical toxins, poisonous plants, or animals may cause acute gastroenteritis with abdominal pain, bloating, nausea, vomiting, and diarrhea. In most cases, the differential diagnosis of food poisoning is obvious from the acute presentation. Symptoms of histamine toxicity, including nausea, abdominal pain, diarrhea, vomiting, flushing, headache, and urticaria, may be mistaken for food intolerance.<sup>36</sup> Histamine is contained in improperly cooked fish (tuna, mackerel, bonito), wine, beer, and sausage. Ingestion of shellfish, strawberry, chocolate, and alcohol may release endogenous histamine stores and produce similar symptoms.<sup>36, 41</sup> Excessive intake of foods containing alcohol, caffeine, tyramine, tryptophan, serotonin, or alkaloids may all produce acute gastroenteritis-like syndromes that could be mistaken for food intolerance.<sup>36</sup>

## Gastrointestinal Disorders Presenting as Food Intolerance

### *Malabsorption*

The hallmark of malabsorption is painless diarrhea that can range from watery, small volume diarrhea of lactase deficiency to large volume steatorrhea of exocrine pancreatic insufficiency. Carbohydrate malabsorption usually presents with watery diarrhea, crampy abdominal pain, bloating, and flatulence because of the increased intestinal fluid reabsorption from the osmotic force of the unabsorbed carbohydrates and gas production from colonic bacterial fermentation. Fat malabsorption leads to steatorrhea, weight loss, and coagulopathy. Isolated, clinically significant protein malabsorption is unusual (Table 1).

Lactose intolerance due to nonpersistence of the intestinal brush border enzyme, lactase, affects between 50% and 100% of nonwhite

**Table 1. MALABSORPTION PRESENTING AS FOOD INTOLERANCE**

| Malabsorbed Nutrient | Foods Containing the Malabsorbed Nutrient           | Gastrointestinal Disorder       |
|----------------------|-----------------------------------------------------|---------------------------------|
| Carbohydrates        |                                                     |                                 |
| Lactose              | Milk, dairy products                                | Lactase deficiency, IBS         |
| Fructose             | Fruits, soft drinks, berries                        | Fructose malabsorption, IBS     |
| Sorbitol             | Peach, apple, pear, plum, sugarless gum, diet foods | Sorbitol malabsorption, IBS     |
| Fats                 | Fried foods, processed foods, meats                 | Chronic pancreatitis            |
| All nutrients        | Any foods                                           | Celiac sprue, Whipple's disease |

IBS = Irritable bowel syndrome

adults in the world. Any condition that damages the enterocytes may cause secondary lactase deficiency, which can persist after the resolution of the underlying illness. Congenital lactase deficiency is a rare autosomal disorder that presents at birth. The vast majority of patients with lactose intolerance have nonpersistence type of lactase deficiency. In these individuals, the lactase level declines with age to 5% to 10% of that present at birth. The diagnosis of lactase deficiency is usually made from history and the response to dietary manipulation; lactose H<sub>2</sub> breath test is available but rarely required. Most lactase-deficient individuals develop symptoms after ingestion of 12 to 18 g of lactose (equivalent to 1–1.5 glasses of milk); however, the presence of concomitant irritable bowel syndrome, altered gastric emptying, age, and the composition of the colonic microflora influence the absolute threshold for development of gastrointestinal symptoms. Because most individuals retain some lactase activity, total dietary elimination is rarely required. Whole milk is better tolerated than skim milk and larger amounts of dairy products can be absorbed if taken in smaller amounts throughout the day. Two to 4 lactase tablets (LactAid, LactAid Inc, Pleasantville, NJ) taken with lactose-containing foods are sufficient to prevent malabsorption and gastrointestinal symptoms in most subjects.

Deficiency of sucrase-isomaltase and congenital glucose-galactose malabsorption are rare disorders that present at infancy or childhood. Trehalase deficiency has been described but is of little clinical significance because it is found only in mushrooms.

Fructose or sorbitol malabsorption appears to be a common but underappreciated cause of intolerance to fruits, diet foods, and soft drinks. In one study, 38% of healthy normal volunteers malabsorbed 50 g of fructose, and 5 of the 6 patients developed abdominal cramps or diarrhea.<sup>33</sup> As with lactose intolerance, some patients with fructose malabsorption and functional bowel disease have a lowered threshold for development of abdominal pain.<sup>35</sup> Similarly, sorbitol malabsorption may be the underlying cause of intolerance to sugar-free gum, diet foods, apple juice, pears, peaches, and plums.<sup>18</sup> Rumessen and Gudmand-Hoyer found that 13 of 25 patients with functional bowel disease malabsorbed the combination of fructose and sorbitol, beyond that expected from the individual sugars; 8 developed moderate or severe abdominal pain and 3 had mild abdominal pain.<sup>35</sup> Both fructose and sorbitol intolerances are effectively treated by dietary manipulation.

Patients with fat malabsorption experience worsening steatorrhea after ingestion of fats and thus may complain of intolerance to fatty foods. Steatorrhea is suggested by bulky, foul smelling, floating, sticky stools; its diagnosis is confirmed by quantitative fecal fat measurement. Steatorrhea is usually a sign of serious gastrointestinal pathology and requires further investigation and treatment (Table 2). Enterokinase deficiency and defective amino acid transport leading to protein malabsorption do not commonly manifest with food-related symptoms.

**Table 2.** REPRESENTATIVE LIST OF CAUSES FOR FAT MALABSORPTION

|                                         |                                                                                                                                                                                                                                                                                          |
|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Defective Intraluminal Digestion</b> | Exocrine pancreatic insufficiency<br>Bacterial overgrowth<br>Chronic liver disease<br>Bile salt deficiency                                                                                                                                                                               |
| <b>Defective Mucosal Absorption</b>     | Drugs (cholestyramine, colchicine, neomycin)<br>Infectious (parasites, <i>Mycobacterium avium-intracellulare</i> )<br>Whipple's disease<br>Abetalipoproteinemia<br>Celiac and tropical sprue<br>Dermatitis herpetiformis<br>Immune (eosinophilic gastroenteritis, systemic mastocytosis) |
| <b>Postmucosal Obstruction</b>          | Intestinal lymphangiectasia<br>Lymphoma                                                                                                                                                                                                                                                  |

### *Reflux, Pancreatitis, Delayed Gastric Emptying, and Anorexia Nervosa*

Fats, mints, chocolate, coffee, tea, cola, alcohol, and citrus fruits frequently exacerbate gastroesophageal reflux symptoms. Although most individuals with gastroesophageal reflux have characteristic heartburn, their presentation may be surprisingly diverse and include chest pain (which may be indistinguishable from angina), nausea, regurgitation, dysphagia, odynophagia, or water brash. Still others are troubled predominantly by upper airway and pulmonary symptoms, including hoarseness, wheezing, aspiration pneumonia, or asthma. Given that gastroesophageal reflux is common and its presentation diverse, it is not surprising that patients can mistake gastroesophageal reflux for food intolerance.

Gastroesophageal reflux can be diagnosed on the basis of a typical history and by its response to acid suppression therapy. In equivocal cases, intraesophageal pH monitoring is used to assess the number of reflux episodes (total and those lasting >5 minutes) and the duration of esophageal pH less than 4 and correlate them to symptoms. Patients with dysphagia, odynophagia, systemic symptoms such as weight loss, or unresponsive to therapy should undergo endoscopy to exclude esophageal ulcer, stricture, or cancer. Endoscopy should also be considered in patients with long history of reflux symptoms to exclude Barrett's esophagus. Patients with occasional or mild symptoms are managed with life style modifications consisting of weight reduction, cessation of smoking, avoidance of aggravating foods, and elevation of the head of the bed. Patients with refractory symptoms, esophagitis, or ulcer are treated using H<sub>2</sub> receptor antagonists (e.g., ranitidine, cimetidine) or a proton pump inhibitor (e.g., omeprazole). Prokinetic agents such as metoclopramide and cisapride may be helpful in some cases as primary or adjunctive therapy. Because gastroesophageal reflux disease is a life-

long condition, younger patients with disabling symptoms should be considered for antireflux surgery.

Chronic pancreatitis and pancreatic cancer may present with fatty food intolerance either because it induces steatorrhea or exacerbates abdominal pain. Abdominal pain is dull, constant, located in the mid-epigastric area, radiates to the back, and worsens almost immediately after eating. The pain may be severe enough to induce anorexia and malnutrition. Fatty foods may further aggravate symptoms of delayed gastric emptying in patients with diabetes, prior gastric surgery, hypothyroidism, or neurologic diseases. Others with peritonitis, ileus, mechanical bowel obstruction, or functional gastric outlet obstruction could present as cases of food intolerance, although the acute constellation of symptoms and signs are usually distinct enough to easily separate these disorders from food intolerance. Finally, anorexia nervosa should be considered in young female patients who complain of nausea, vomiting, abdominal pain, and bloating after eating small amounts of food.

### *Irritable Bowel Disease*

Large surveys have shown that 20% to 33% of the population report possible food intolerance,<sup>3, 6, 43</sup> but these data were prone to bias and overestimated its true prevalence.<sup>28</sup> To date, only one published, population-based study has examined subjects with self-reported food intolerance using double-blind, placebo-controlled food challenge. Of the 20.4% of the population reporting food intolerance, only 1.4% had positive results.<sup>43</sup> Most individuals with self-reported adverse food reactions (including some with potentially life-threatening reactions<sup>44</sup>) do not seek medical care.<sup>3</sup> Patients presenting with possible food allergy only rarely have true hypersensitivity, but most are suffering from organic or biochemical diseases, or pseudo-food allergy.

Distorted reporting by the lay press, psychological susceptibility, and exposure to clinical ecology are thought to be important factors in the development of pseudo-food allergy.<sup>5, 30, 34, 37</sup> Patients with pseudo-food allergy who present with gastrointestinal complaints most likely have irritable bowel syndrome. These two disorders have many similarities. The patients are more likely to be female, younger, have vague and nonspecific symptoms, obvious signs of depression or other psychiatric illnesses, and poor insight into their disease process.<sup>30, 34, 42</sup> Rix et al found that patients with pseudo-food allergy had similar psychiatric profiles to those referred for psychiatric disorders; alternatively, patients with true food allergy did not have psychiatric abnormalities.<sup>34</sup> Many patients deny or refuse to consider the role of psychiatric disturbance in the pathogenesis of their symptoms, or they may believe "food allergy" to be the cause of the psychiatric symptoms.<sup>30</sup> Patients with continued delusions of food allergy have a worse prognosis compared with others.<sup>34</sup> The majority of patients with pseudo-food allergy have been previously "diagnosed," "treated," or exposed to clinical ecology.<sup>30, 34</sup> Because many physicians do not provide the needed, ongoing psychosocial support for patients with irritable bowel syndrome, they may em-

brace alternative medicine, such as clinical ecology, which blame their psychiatric symptoms on food allergy.<sup>19, 30</sup>

Irritable bowel syndrome consists of chronic or recurrent abdominal pain, altered bowel habits, and bloating for which no anatomic or biochemical abnormalities can be identified. Irritable bowel symptoms are reported by 20% to 44% of the population in developed Western nations.<sup>11, 19, 22</sup> Most persons with irritable bowel symptoms are well-adjusted individuals who do not seek medical care<sup>19</sup>; patients with irritable bowel syndrome have significantly more severe psychiatric abnormalities, independent of their symptoms.<sup>12, 43</sup> Irritable bowel syndrome constitute 10% to 25% of all office visits to gastroenterologists.<sup>15, 17</sup> Patients with irritable bowel syndrome also seek medical care more frequently for nongastrointestinal problems.<sup>11</sup> Alteration of intestinal motility, visceral hyperalgesia, psychiatric abnormality, and possible malabsorption are thought to be important factors in the pathogenesis of irritable bowel syndrome.<sup>7</sup> Food allergy or intolerance have been implicated also in the pathogenesis of irritable bowel syndrome based on uncontrolled, unblinded, studies<sup>20, 26, 32, 38</sup>; however, results of double-blind, placebo-controlled food challenges have been less impressive.<sup>4</sup> Based on the published data, a small number of patients with irritable bowel syndrome may have genuine food allergy or intolerance, usually in the setting of atopy or malabsorption syndromes such as lactase deficiency.<sup>4, 25, 27</sup> Because irritable bowel syndrome is very common, it is not surprising that some patients will have food intolerance, but in general, there is no association between irritable bowel syndrome and food intolerance.<sup>38, 44</sup>

Although there are no specific diagnostic tests for irritable bowel syndrome, it can be diagnosed accurately based on exclusion of organic and biochemical diseases and fulfillment of specific criteria.<sup>29</sup> A thorough history and physical examination; stool examination for ova, parasites, and occult blood; and sigmoidoscopy are sufficient to rule out organic diseases. Complete blood count and chemistries are usually obtained but are probably not helpful. Barium enema, colonoscopy, upper endoscopy, or rectal biopsy should be performed as indicated on an individual basis. Further testing or repeated testing should be avoided because it reinforces the abnormal illness behavior, i.e., more testing is needed to uncover the "real" disease. A diagnosis of irritable bowel syndrome is established if no organic or biochemical abnormalities are detected and if the patient meets the following criteria as suggested by Drossman et al: at least 3 months of continuous or recurrent abdominal pain relieved with defecation and associated with altered pattern of defecation (stool frequency, form, passage, presence of mucus, or bloating) at least 25% of the time.<sup>13</sup>

Irritable bowel syndrome patients with mild symptoms and without significant psychiatric illness usually respond to education, reassurance, and dietary manipulation such as avoidance of lactose. An adequate fiber intake should be encouraged. Medical therapy including antispasmodics or antidiarrheals may be helpful. Patients with severe unremitting symptoms or overt psychiatric illness respond poorly to most thera-

pies.<sup>7</sup> In one study, such patients had significantly higher rates of nongastrointestinal symptoms, past history of sexual abuse, alcohol, sedative, or narcotic use, and had worse symptoms induced by stress.<sup>22</sup> Regardless of symptoms, narcotics should be avoided; antidepressant therapy may be helpful in a limited number of patients. A stable patient-physician relationship is important and may reduce hospitalization.<sup>29</sup> Despite the bleak outlook, the overall survival is not significantly different from the normal population.<sup>29</sup>

### **Food Intolerance Erroneously Attributed to Gastrointestinal Disease**

Individuals with real or perceived food intolerance may erroneously attribute their symptoms to gastrointestinal diseases. Although intolerance to fatty foods has been long said to be a symptom of gallstone disease, little scientific data support this observation.<sup>10, 14</sup> Diehl et al showed that although postprandial pain was associated with gallstone disease, types of food eaten were not; in fact, fatty food intolerance was significantly more common in patients without gallstone disease.<sup>10</sup> Fatty food ingesting also does not significantly alter gallbladder function.<sup>24</sup> Most patients with fatty food intolerance probably suffer from gastroesophageal reflux disease or irritable bowel syndrome. Similarly, intolerance to spicy or acidic foods is often erroneously associated with peptic ulcer disease.

Although food intolerance may be seen in patients with Crohn's disease, it does not appear to be an important factor in the pathogenesis or the treatment of Crohn's disease.<sup>31</sup> Finally, food allergy has been evoked as a possible cause of eosinophilic gastroenteritis.<sup>40</sup> Talley et al reported that 52% of patients with eosinophilic gastroenteritis had history of food intolerance or allergy.<sup>39</sup> Unfortunately, it is impossible to determine the relevance of food intolerance in eosinophilic gastroenteritis, because it is too rare to be studied in a scientific fashion. Eosinophilic gastroenteritis (more correctly enteritis, because it can involve any part of the gastrointestinal tract) is a rare disease characterized by patchy infiltration of the gastrointestinal tract with eosinophils, in the absence of extraintestinal or parasitic diseases.<sup>21, 39</sup> Hypereosinophilia is found in approximately 75% of patients but is not a prerequisite for diagnosis. Traditionally, the disease has been divided into mucosal, muscularis, and subserosal types depending on the distribution of the eosinophils. Signs and symptoms include diarrhea, nausea, vomiting, malabsorption, abdominal pain, and intestinal obstruction; ascites may be found in patients with subserosal disease. Diagnosis is suggested by thickened folds on radiographic studies and confirmed by histopathology showing eosinophilic infiltration of the gut. Endoscopic biopsies of the effected area are usually diagnostic, but some may require full thickness biopsy. The majority of patients respond favorably to systemic corticosteroids with remission of disease activity.

## CONCLUSION

The majority of patients with adverse food reactions do not have true food allergy, but gastrointestinal disorders including malabsorption, gastroesophageal reflux disease, and irritable bowel syndrome. In most cases, the diagnosis can be made based on history and response to dietary manipulation or symptomatic therapy. Irritable bowel syndrome should be considered in patients without objective evidence of gastrointestinal abnormality who complain of chronic or recurrent abdominal pain associated with altered bowel habits.

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