The Role of Hidden Food Allergy/Intolerance in Chronic Disease

by Alan R. Gaby, M.D.

Abstract

A large body of medical literature has indicated that hidden food allergy is a frequent cause of a wide range of physical and mental conditions. Hidden allergies can be "unmasked" by means of an elimination diet, followed by individual food challenges. Although the concept of hidden food allergy remains controversial, the evidence strongly suggests that identification and avoidance of allergenic foods can relieve a number of common and difficult-to-treat medical problems.
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Introduction

Food allergy is well recognized in clinical medicine as a cause of acute attacks of asthma, angioedema and urticaria, and as a contributing factor in some cases of eczema and rhinitis. These types of allergic reactions are considered to be mediated by IgE antibodies, and usually can be diagnosed by medical history and skin-prick or IgE-radioallergosorbent (RAST) tests.

Another type of food reaction, often referred to as "hidden" or "masked" food allergy, has been the subject of controversy for many years. Some practitioners have observed that hidden food allergies are a common cause of (or triggering factor for) a wide range of physical and emotional disorders. According to one estimate, as many as 60 percent of the population suffers from undetected food allergies.[1] A wide range of symptoms and disorders are reported to have a significant allergy component. See Table 1. On the other hand, many conventional physicians doubt hidden food allergy is a common problem, and some even deny altogether its existence as a clinical entity.

Skeptics emphasize the fact that many of the conditions said to be related to allergy fluctuate in severity and have a significant psychological component. Consequently, it may be difficult to distinguish between a true food reaction and a conditioned (psychogenic) response or a spontaneous exacerbation of symptoms. It also has been pointed out that food-induced symptoms should not be called allergies unless an immune-mediated mechanism can be demonstrated. While it is true many food reactions would be more appropriately labeled food intolerance, the term "allergy" will be used in this article in reference to adverse reactions to foods.

Proponents of the food allergy-disease connection argue that hidden food allergies are often overlooked because they are difficult to identify. Unlike the more obvious immediate-hypersensitivity reaction that can trigger acute asthma or anaphylaxis, a hidden food reaction frequently can be delayed by many hours or even several days.

Alan R. Gaby, M.D. - Professor, Bastyr University; Past-president, American Holistic Medical Association; Contributing Medical Editor, Townsend Letter for Doctors and Patients; Contributing Editor, Alternative Medicine Review.
Correspondence address: 125 NE 61st Street, Seattle, WA 98115

Identifying a cause-effect relationship between ingestion of specific foods and development of symptoms is said to be further complicated by the tendency of people to become addicted to the foods to which they are allergic. This so-called "allergy-addiction syndrome" has been observed by numerous clinicians[2] and appears to be consistent with Selye's description of the "general adaptation" response to stress.[3,4] Thus, patients often experience short-term relief after ingesting foods which are later demonstrated to be the cause of their chronic symptoms. This paradoxical response can render medical histories and diet diaries virtually useless for detecting hidden allergies.

Hidden food allergies can usually be "unmasked" by means of an elimination diet.[5] After a patient has been on a hypoallergenic diet for a period of time (typically one to three weeks), chronic symptoms disappear or improve and the body reverts from a state of allergy-addiction (corresponding to Selye's adaptation stage) to one of increased alertness and sensitivity (corresponding to Selye's alarm stage). In this hypersensitive state, ingestion of an offending food results in a rapid and exaggerated reaction, allowing the patient to identify previously unsuspected allergens. See Table 2 for a list of foods most commonly associated with food allergies or intolerances.

Ideally, studies of hidden food allergy should be conducted using double-blind, placebo-controlled food challenges, in order to rule out placebo responses and spontaneous fluctuations in symptom severity. Some of the research reviewed in this article has used a double-blind design; and most of these studies have confirmed the importance of food allergy in the etiology of certain chronic conditions. Most of the other studies on food allergy have lacked placebo controls. Nevertheless, the results of these studies have frequently been impressive, especially when compared with results of conventional therapy. Following is a review of selected studies on the relationship between food allergy and certain common medical conditions.

Table 1. Conditions which frequently have allergic components

fatigue	enuresis
migraines	epilepsy
irritable bowel syndrome	eczema
inflammatory bowel disease	psoriasis
gallbladder disease	aphthous ulcers
arthritis	otitis media
asthma	other recurrent infections
rhinitis	
attention deficit-hyperactivity disorder (ADHD)	

Migraine

Food allergy has been mentioned as a cause of migraine as early as 1930. In a study of 55 migraine patients, avoidance of allergenic foods, combined with general supportive care, resulted in complete or near-complete freedom from symptoms in 29 patients (52.7%) and partial improvement in an additional 21 (38.2%).[6] In a 1935 study, 66.3 percent of 127 migraine patients experienced partial or complete relief of symptoms after following an elimination diet.[7] Heymann reported in 1952 that food reactions were the cause of migraine in 15 of 20 patients.[8] Speer also found that foods (mainly milk, chocolate, cola, and corn) were common triggers for migraine.[9]

Egger et al placed 88 children suffering severe, frequent migraines on an oligoantigenic diet consisting typically of one meat (lamb or chicken), one carbohydrate (rice or potato), one fruit (banana or apple), one

Table 2. Foods most commonly associated with allergies

dairy products	citrus fruits
wheat	pork
eggs	rye
corn	beef
chocolate	tomato
tea	peanuts
coffee	barley
sugar	nuts
yeast	seafood
soy	

vegetable (Brassica), water, and vitamin and calcium supplements for 3-4 weeks.[10] Patients who did not improve were offered a second oligoantigenic diet, with no foods in common with the first diet. Seventy-eight children recovered completely on the first or second oligoantigenic diet, and four improved markedly (total recovery rate, 93%). Of the 82 patients who improved, 74 developed symptoms after one or more individual food challenges. Forty of these 74 patients participated in double-blind, placebo-controlled food challenges, which confirmed the etiologic role of food allergy. Most patients reacted to several foods. Fifty-five different foods provoked symptoms, the most common of which were (number of patients in parentheses): cow's milk (27), egg (24), chocolate (22), orange (21), and wheat (21).

Grant studied 60 patients with a history of frequent and recurrent migraines.[11] The mean duration of illness was 18 years for women and 22 years for men. Each patient consumed an oligoantigenic diet for five days, consisting only of two low risk foods (usually lamb and pears) and drank only bottled spring water. Migraines disappeared by the fifth day in most cases, after which foods were tested individually. The mean number of symptom-provoking foods was ten per patient (range, 1-30). The foods most frequently causing symptoms and/or pulse changes (a presumed indicator of allergy) were wheat (78%), orange (65%), egg (45%), tea and coffee (40% each), chocolate and milk (37% each), beef (35%), corn, cane sugar and yeast (33% each), mushrooms (30%), and peas (28%). When the offending foods were avoided, all patients improved. The number of headaches in the group fell from 402 to 6 per month, and 85 percent of the patients became headache-free.

Monro et al provided evidence that at least some food-induced migraines are true allergic reactions (as opposed to being mediated by vasoactive compounds).[11] Nine patients with food-induced migraines were treated in double-blind fashion with sodium cromoglycate (a drug which blocks mast-cell degranulation and allergic reactions) or a placebo, along with foods previously identified as symptom provokers. Sodium cromoglycate was significantly more effective than placebo in preventing the development of migraines. Challenge with offending foods resulted in the appearance of IgE-containing immune complexes; this was prevented by pretreatment with sodium cromoglycate, but not placebo.

Arthritis

Food allergy was mentioned by Kaufman in 1953 as a causative factor in some cases of arthritis.[12] O'Banion reported three patients with rheumatoid arthritis in whom removal of allergenic foods from the diet was followed by complete elimination of arthritis pain.[13] Ratner et al, reported the case of a 14-year-old female with a six-year history of juvenile rheumatoid arthritis who recovered after elimination of all cow's milk protein from her diet.[14] Dietary provocation on four occasions (two inadvertent and two planned) reproduced the signs and symptoms of her illness.

Hicklin et al administered an elimination diet to 22 patients with rheumatoid arthritis.[15] Twenty of the patients (91%) noted an improvement in their symptoms, and 19

found that certain foods repeatedly caused exacerbations. The mean number of food sensitivities per patient was 2.5.

Ratner et al, studied 15 women and eight men with rheumatoid (n=19) or psoriatic (n=4) arthritis.[16] The patients were instructed to remove dairy products and beef from their diet. Seven patients became asymptomatic within 3-4 weeks after starting the diet, and these patients had an exacerbation of symptoms after reintroducing dairy products into their diet. The other 16 patients did not improve. The seven patients who improved were all women, seronegative, and lactase deficient. These results suggest a diet free of dairy products and beef is of value in lactase-deficient women with seronegative rheumatoid arthritis or psoriatic arthritis.

In another study, 27 patients with rheumatoid arthritis underwent a partial fast, followed by individual food challenges.[17] Foods which provoked symptoms were avoided, as were animal foods, refined sugar, citrus fruits, preservatives, coffee, tea, alcohol, salt, and strong spices. A control group of 26 patients ate an ordinary diet. After four weeks, the diet group showed a significant improvement in the number of tender joints, Ritchie's articular index, number of swollen joints, pain score, duration of morning stiffness, grip strength, sedimentation rate, and C-reactive protein. In the control group, only pain score improved significantly. The benefits in the diet group were still present after one year. These results suggest a partial fast, followed by a lactovegetarian diet that omits symptom-provoking foods, is of value in treatment of rheumatoid arthritis.

Beri et al prescribed an elimination-and-rechallenge diet to 27 patients with rheumatoid arthritis.[18] Of the 14 patients who completed the diet program, 10 (71%) showed significant clinical improvement.

Darlington treated 70 patients with rheumatoid arthritis by identifying and eliminating symptom-provoking foods.[19] Of these 70 patients, 19 percent remained well and did not require any medications during follow-up periods ranging from 1.5-5 years (mean, 37 months). The foods that most commonly caused symptoms were: corn (56%), wheat (54%), bacon/pork (39%), oranges (39%), milk, oats (37% each), rye (34%), egg, beef, coffee (32% each), malt (27%), cheese, grapefruit (24% each), tomato (22%), peanuts, cane sugar (20% each), and butter, lamb, lemon, and soy (17% each).

In a 10-week, double-blind trial, 26 patients with chronic, progressive rheumatoid arthritis consumed an experimental diet which excluded additives, preservatives, fruit, red meat, herbs, egg yolks, and dairy products, or a "placebo diet," which excluded selected foods from the major food groups.[20] Two of the 11 patients consuming the experimental diet improved significantly; however, there were no significant differences between the two groups in terms of clinical improvement or changes in laboratory parameters. The lack of significant benefit in this study may have been due to the fact that the experimental diet did not exclude a number of common allergens, such as wheat, corn, egg whites, sugar, and coffee.

Irritable Bowel Syndrome

Some 189 patients with irritable bowel syndrome consumed an elimination diet for three weeks.[21] The diet prohibited dairy products, cereals, citrus fruits, potatoes, tea, coffee, alcohol, additives, and preservatives. Ninety-one patients (48.2%) improved. Subsequent challenges with individual foods provoked symptoms in 73 of the 91 responders; of these, 72 remained well on a modified diet during a mean follow-up period of 14.7 months. Of the 98 patients who did not improve on the elimination diet, only three were well at follow-up. The number of food intolerances ranged from 1 to 19. The most

commonly implicated foods were: dairy products (40.7%), onions (35.2%), wheat (29.7%), chocolate (27.5%), coffee (24.2%), eggs (23.3%), nuts (18.0%), citrus fruits (17.8%), tea (17.6%), rye (17.6%), potatoes (15.4%), barley (13.3%), oats (12.1%), and corn (11.1%).

In another study, 21 patients with irritable bowel syndrome limited their diet for one week to a single meat, a single fruit, and distilled or spring water.[22] In 14 of the 21 patients, symptoms disappeared on the elimination diet. Individual food challenges identified the following symptom-provoking foods (number of patients in parentheses): wheat (9), corn (5), dairy products (4), coffee (4), tea (3), and citrus fruits (2). Six patients underwent food challenges through a nasogastric tube, in double-blind fashion. In each case, double-blind testing confirmed the food intolerance. Changes in plasma histamine, immune complexes and eosinophil counts were similar after challenge with symptom-provoking foods and control foods, indicating that these food reactions were probably not immunologically mediated.

Inflammatory Bowel Disease

In 1942, Andresen studied 50 patients with ulcerative colitis. Food allergy was found to be the cause in 67 percent of the patients, all of whom showed a satisfactory response to dietary modification.[23] Rowe and Rowe reported that 49.4 percent of 170 patients with ulcerative colitis could be successfully managed with anti-allergy therapy alone, without the need for corticosteroids or other medications.[24]

Rider and Moeller injected extracts of wheat, egg and milk into the rectal mucosa of 20 patients with ulcerative colitis.[25] Some 80 percent of the patients showed a positive reaction (edema, erythema, capillary engorgement) to at least one of the food extracts. Fifteen patients who had a positive intramucosal test were prescribed diets free from the offending food or foods. Fourteen of these patients (93%) experienced complete remission or significant improvement.

Rudman et al maintained four patients with regional enteritis (Crohn's disease) on a gluten-free, lactose-free diet for 12 days, after which they were challenged with 5-20 g/day of gluten for up to 12 days. Various reactions, including melena, fever, abdominal pain, diarrhea, steatorrhea, and nausea developed in all cases, within 4-9 days of beginning the gluten challenge. In all cases, these reactions subsided within 2-4 weeks after discontinuation of gluten.[26]

In another study, 50 patients with ulcerative colitis were randomly assigned to a milk-free diet or a control diet for one year.[27] During the follow-up period, 38 percent of the patients on the milk-free diet remained free of relapses, compared with 21 percent of those on the control diet. Three or more relapses occurred in 12 percent of patients on the milk-free diet, and in 33 percent of those on the control diet (statistical analysis not presented).

Jones et al induced remission in 20 consecutive patients with active Crohn's disease by administering an elemental diet or total parenteral nutrition.[28] After the patients had achieved remission, they were randomly assigned to receive a control diet (high in fiber and unrefined carbohydrates) or to perform individual food challenges and to exclude from the diet those foods which provoked symptoms. Seven of the 10 patients on the exclusion diet remained in remission for 6 months, compared with none of 10 patients on the control diet ($p < .05$). In an open trial, 51 of 77 patients on the exclusion diet alone remained well for periods of up to 51 months. After 2 years, 65 percent of those patients were still in remission. The most frequent symptom-provoking foods were wheat, dairy products, Brassicas (cabbage, broccoli, cauliflower, etc.), corn, yeast, tomatoes, citrus fruits, and eggs.

In another study, 21 patients with an acute exacerbation of Crohn's disease were randomly assigned to receive either 1) prednisolone or 2) an elemental diet followed by gradual reintroduction of foods after four weeks.[29] Assessment of disease activity after 4 and 12 weeks showed that the group receiving the elemental diet improved as much as, and by some criteria more than, the steroid-treated group. These results suggest that elimination of food antigens from the diet can induce remission in patients with active Crohn's disease.

In a 1993 study, 136 patients with active Crohn's disease were given an elemental diet.[30] Of the 93 patients who continued the diet for 14 days, 78 (84%) achieved clinical remission and were then randomly assigned to receive corticosteroids or dietary treatment. The diet group was instructed to introduce one new food daily, and to exclude any food that precipitated symptoms. The median length of remission was 7.5 months in the diet group, compared with 3.8 months in the corticosteroid group. Of the patients who followed the diet, 45 percent remained disease-free for at least two years.

Asthma

In 1959, Rowe and Young described 95 patients in whom asthma was successfully treated by eliminating allergenic foods from their diet.[31] Among patients over the age of 55 years, food allergy alone appeared to be the cause of asthma in 40 percent. Sensitivity to food additives such as metabisulfites, tartrazine (FD&C Yellow Dye #5), sodium benzoate, and sulfur dioxide have also been implicated as triggering factors for asthma.[32-34]

In another study, 188 children under one year of age with allergic rhinitis and/or bronchial asthma were placed on an elimination diet for six weeks.[35] Sixty-two percent of the patients had total symptom relief, and an additional 28 percent had partial relief. Forty percent of the children who had improved experienced a recurrence of symptoms upon reintroduction of specific foods.

Hoj et al randomly assigned 41 patients with severe asthma to an antigen-free elemental diet or to a control diet for two weeks, in a double-blind trial.[36] Improvement was observed in 1 of 16 patients in the control group, compared with 9 of 21 patients consuming the elemental diet ($p < 0.05$). In another study of 107 patients with perennial asthma, 60 (56%) had an asthmatic response to ingestion of one or more foods.[37]

Other investigators have failed to find an important relationship between food allergy and asthma. In one study, only 9 percent of 300 asthmatic patients had either a positive history or positive skin or IgE-radioallergosorbent tests (RAST) for food allergy.[38] However, practitioners who work with hidden food allergies have found that reliance on history, skin tests and IgE RAST can result in many clinically significant allergies being overlooked.

In another study, 18 children and adults with asthma consumed in random order each of two different diets during two separate three-week periods.[39] Diet 1 (based on Rowe's Cereal-Free Diet) consisted of foods reported to cause asthma only rarely. Diet 2 contained foods reported to cause asthma commonly, including cereal, milk, eggs and seafood. The amount of wheezing and the requirement for medication were similar during the two diet periods, and most patients failed to benefit from either diet.

Aphthous Ulcers

Twenty patients who had suffered from recurrent aphthous ulcers for a mean duration of 11.2 years followed a gluten-free diet.[40] A complete remission of ulcers occurred in five patients (25%), and each of these five patients had a recurrence of ulcers after gluten challenge. In another study, 17 patients with recurrent aphthous ulcers that had been

unresponsive to conventional therapy were prescribed an elimination diet.[41] Of the 12 patients who followed the diet for six to eight weeks, four became asymptomatic and one had marked improvement. In four of these five patients, a particular food was identified which, when eliminated from the diet, led to marked improvement or complete resolution of aphthous ulcers. Similar results were reported by other investigators.[42]

Nolan et al studied 21 patients with recurrent aphthous ulcers. Each patient was tested for allergies to foods, food additives, flavoring agents and essential oils.[43] Twenty of the 21 patients showed positive patch-test reactions to one or more of the following (number of patients reacting in parentheses): benzoic acid (11); cinnamaldehyde (8); nickel, dichromate, fragrance mix, methyl methacrylate (2 each); parabens, sorbic acid, phosphorus, mercury, colophony, and balsam of Peru (1 each). Avoidance of the allergens which had tested positive resulted in improvement in 18 patients, during a follow-up period of six months to six years.

Nephrotic Syndrome

Six children (aged 10-13 years) with steroid-responsive idiopathic nephrotic syndrome were studied.[44] Prednisone was discontinued and an elemental diet was given. After proteinuria had decreased to 500 mg/24 hours or less on consecutive days (usually within 3 to 10 days), patients were challenged with cow's milk. Milk challenge resulted in a return of significant proteinuria and edema in four patients. An acute alteration of plasma C3 complement component accompanied milk challenge in all six patients. These results suggest that milk allergy may play a role in the pathogenesis of idiopathic nephrotic syndrome.

In another report, a six-year-old girl with dermatitis herpetiformis, celiac disease, and nephrotic syndrome showed a complete resolution of all three conditions after commencing a gluten-free diet.[45] Other investigators have confirmed the role of food allergy in idiopathic nephrotic syndrome.[46-48]

Gallbladder Disease

Animal studies have demonstrated that the gallbladder can be a target organ for allergic reactions.[49] In a clinical study, 69 patients with symptomatic gallstones or post-cholecystectomy syndrome were placed on an elimination diet consisting of beef, rye, soy, rice, cherry, peach, apricot, beet, and spinach. No fat restrictions were imposed. All 69 individuals were relieved of their symptoms after one week on the diet, with improvement usually occurring in three to five days. Egg, pork, and onion were found to be the most frequent symptom-provoking foods, with reactions occurring in 93 percent, 64 percent, and 52 percent of patients, respectively. The mean number of food sensitivities per patient was 4.4 (range, 1 to 9).

Recurrent Otitis Media

One hundred-four children with recurrent serous otitis media were evaluated for food allergy by means of skin testing, specific IgE tests, and food challenges.[50] Children who had evidence of allergy eliminated the suspected offending foods for 16 weeks, after which individual food challenges were done. Eighty-one (78%) of the children had evidence of food allergy. Elimination of the suspected allergens resulted in significant improvement in otitis media in 86 percent of those patients (documented by tympanometry). Seventy children underwent individual food challenges; among those, addition of the suspected offenders provoked a recurrence of serous otitis media in 94 percent of cases. Other investigators have also reported that control of food and environmental allergies reduced the recurrence rate of otitis media in children.[51,52]

Attention Deficit-Hyperactivity Disorder (ADHD)

Twenty-three hyperactive children eliminated milk, wheat, egg, cocoa, corn, sugar, and food coloring from their diet for seven days.[53] Twelve of these children (52%) showed moderate or marked improvement. Specific foods and food dyes which reproduced hyperactive behavior in challenge tests were removed from the diet permanently. With this selective dietary restriction, symptom relief persisted for at least 12 weeks in 11 of 17 patients.

In another study, 26 children with ADHD went on a comprehensive elimination diet. Improvement was seen in 19 patients (73%). Upon retesting, all of the children who improved reported reactions to three or more foods or additives. These reactions were repeatedly confirmed by double-blind food challenges, indicating that the results were not due to a placebo effect.[54] Another double-blind study[55] and two open trials[56,57] have produced similar results.

The importance of artificial food dyes and other food additives in the etiology of ADHD was first suggested by Feingold.[58] However, studies that investigated the "Feingold hypothesis" have produced equivocal results, ranging from minor adverse reactions to no effect at all. [59-63] It should be noted that much of the research on food additives and ADHD suffered from methodological weaknesses. For example, in one study, a chocolate cookie was used as the placebo, an inappropriate choice since many hyperactive children react to chocolate.[64] In other studies that tested the effect of food dyes, major allergens were allowed to remain in the diet. The failure to exclude these common allergens may have masked an adverse effect of the additives.

Other Allergy-Related Conditions

Other conditions which may respond to avoidance of allergenic foods include fatigue, enuresis, frequent urination, epilepsy, bruxism, infantile colic, eczema, psoriasis, urticaria, purpura, thrombocytopenia, obesity, chronic bronchitis, rhinitis, and IgA nephropathy. These conditions have been discussed elsewhere.[1, 2, 65]

Diagnostic Tests for Allergy

Food allergies usually can be identified by means of an elimination diet, followed by individual food challenges.[5,66] Although double-blind, placebo-controlled challenges are preferable, they may not be feasible in the typical outpatient setting. Fortunately, open challenges are usually reliable.

Several blood tests are available which measure antibodies to individual food extracts. Measuring IgE-antibody levels may be helpful for identifying classical allergic reactions (such as those that result in acute asthma or urticaria). IgE levels do not appear to be reliable indicators of hidden food allergy. Tests which measure food-specific IgG4 antibodies are also commercially available. However, while there is evidence that antibodies within the IgG4 fraction act as symptom-provoking antibodies, the IgG4 fraction also appears to contain blocking antibodies, which might prevent allergic reactions.[67] Consequently, the theoretical basis for measuring IgG4 antibodies is open to question. At the present time there are no adequate data addressing the incidence of false positives and false negatives with these tests.

Another test, known as ALCAT, measures platelet aggregation and changes in white blood cells after mixing whole blood with various food extracts. ALCAT has been shown to be fairly reliable for identifying reactions to food additives.[68] However, in tests for allergy to foods, 18 (24.3%) of 74 positive results were found to be false positives and 21 (30.9%) of 68 negative results were false negatives.[69]

Provocative testing is used by some practitioners to diagnose food allergies.[2] This

procedure involves intradermal or sublingual administration of various dilutions of food extracts. A similar procedure is used to "neutralize" or desensitize allergies. Although the efficacy of food extract injection therapy has been demonstrated in a double-blind study,[70] others have failed to find a beneficial effect,[71] and provocative testing and neutralization remain controversial techniques.

Conclusion

Food allergy is an important and frequently overlooked cause of (or triggering factor for) a wide range of chronic physical and mental disorders. Routine use of elimination diets in clinical practice can greatly increase the response rate in many difficult-to-treat medical conditions.

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