

# Food Intolerance in Patients with Chronic Fatigue

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*Intolerance to various foods is reported often by patients seeking evaluation for chronic fatigue, a common symptom in primary care practice. To assess the prevalence and significance of this phenomenon we studied 200 consecutive patients with chronic fatigue who were given a comprehensive medical and psychiatric evaluation. Intolerance to foods from at least three different groups was reported by 27 patients (13.5%). We compared these patients with 27 age- and gender-matched patients from the same cohort of fatigued patients. Physical examination and laboratory testing showed few abnormalities in either group. The two groups were similar with respect to the duration and severity of fatigue, lifetime depressive symptoms, and prevalence of current depressive disorders (67% vs. 63%) and anxiety disorders (11% vs. 15%). Patients with multiple food intolerance had more lifetime functional somatic symptoms ( $p < .05$ ) and a significantly higher (33% vs. 7%) prevalence of somatization disorder ( $p < .025$ ). These data suggest that intolerance to multiple foods is probably not a cause or the effect of chronic fatigue, but rather one of the manifestations of the somatization trait expressed in these patients. © 1993 by John Wiley & Sons, Inc.*

Symptoms of fatigue, lassitude, and malaise are frequently reported by individuals with food intolerance seeking evaluation in allergy clinics, particularly by those in whom immunologic and biochemical testing fail to reveal the mechanism for the production of their food-related symptoms (Pearson, Rix, & Bentley 1983; Rix, Pearson, & Bentley, 1984; Parker, Leznoff, Sussman, Tarlo, & Kronld, 1990). Likewise, intolerance to multiple foods is quite common among patients seeking evaluation for chronic fatigue (Manu, Lane, & Matthews 1989). The present study was prompted by a detailed review of the available literature which revealed that important questions about the relationship between food intolerance and chronic fatigue remain unanswered. First,

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what is the prevalence of food intolerance among patients with chronic fatigue? Second, are there any historical, physical, or laboratory features that can distinguish those patients who report intolerance to multiple foods from other patients with chronic fatigue who do not have multiple food intolerance? Third, are the medical and psychiatric diagnoses of patients with multiple food intolerance different from those of patients without such a history?

## METHODS

In November 1986, we began the Connecticut Chronic Fatigue Study by opening a clinic for patients with chronic fatigue in the medical outpatient unit at the University of Connecticut Health Center. Any patient over the age of 18 years with a history of fatigue for more than one half of the time for more than 1 month, and who had not been hospitalized within the past 3 months was eligible for evaluation in the clinic. Details of our study methods have been previously published (Manu, Matthews, & Lane, 1988).

From November 1986 to December 1988, we gave the first 200 patients (128 women; mean age of cohort = 39 years) entering the study a comprehensive examination consisting of (1) a complete history and physical examination, (2) a structured psychiatric interview, the Diagnostic Interview Schedule of the Public Health Services's National Institute of Mental Health (Robins, Helzer, Croughan, Williams, & Spitzer, 1981), which enables reliable diagnoses according to the accepted standards (American Psychiatric Association, 1987), and (3) an extensive battery of laboratory investigations. Multiple food intolerance was assessed during the administration of the Diagnostic Interview Schedule by the answer given to the question: "Have you found that there were any foods that you couldn't eat because they made you ill?" If the answer was yes, the patient was asked to name the foods and describe the symptoms produced by their ingestion. The patients were then carefully questioned with regard to associated symptoms and the medical evaluation performed to establish the cause of their food-related symptoms. Multiple food intolerance was diagnosed if the patient had symptoms occurring predictably following the ingestion of food from at least three different food groups. Patients with objectively confirmed food allergies or gastrointestinal enzymatic deficiencies were excluded.

A total of 27 patients fulfilled these criteria for multiple food intolerance. A control group was assembled by randomly selecting gender- and age-matched (within 5 years) subjects from the remaining cohort of patients with chronic fatigue. The two groups of patients were compared with regard to characteristics of their fatigue illness, the physical and laboratory findings on standardized evaluation, the presence of psychiatric and medical disorders, including the newly defined chronic fatigue syndrome (Holmes et al., 1988).

Two indices of psychopathology were calculated. The first index took into account the lifetime occurrence of nine major depressive symptoms (dysphoria, anhedonia, change in appetite or weight, sleep disturbance, lack of energy, psychomotor retardation or agitation, low self-esteem, difficulty with concentration or thinking, and morbid preoccupation). The second index assessed the presence during the patients' life of 34 somatic complaints (abdominal pain, nausea, vomiting, diarrhea, back pain, chest pain, joint pain, pain in extremities, painful menstrual periods, other pain, irregular menstrual periods, excessive menstrual bleeding, blindness, deafness, muscle weak-

ness, paralysis, loss of voice, difficulty swallowing, amnesia, diplopia, blurred vision, dizziness, fainting, dyspnea at rest, palpitations, seizures, pain on urination, burning pain in sexual organs, pain during intercourse, impotence, sexual indifference, vomiting throughout pregnancy, temporary anuria, and ataxia). The score for these symptoms took into account only the complaints that remained unexplained (or were considered functional or psychogenic) after competent medical evaluation.

Statistical significance was assessed by using chi-square analysis for proportions, and Student's two-tailed *t* test for interval data.

## RESULTS

Twenty of the 27 patients with multiple food intolerance were women (74.1%), and all patients were white. The average duration of fatigue in this group was shorter than that of the control group (11.9 years vs. 13.7 years), but the difference did not reach statistical significance. The severity of fatigue at the time of examination, assessed by patients on a scale of 1 to 10, were similar for the two groups. No significant differences between the two groups were noted for the depressive symptom scores. The average of the functional somatic symptom scores of patients with multiple food intolerance was significantly greater than the corresponding control figure (Table 1).

Statistics for each of the 34 symptoms revealed a greater prevalence of irregular menstrual periods ( $\chi^2 = 6.1, df = 1, p < .02$ ), dizziness or lightheadedness ( $\chi^2 = 4.1, df = 1, p < .05$ ), and diarrhea ( $\chi^2 = 4, df = 1, p < .05$ ) among patients with multiple food intolerance.

Only 2 of the 27 patients with multiple food intolerance were found to have medical disorders that were considered the cause of their chronic fatigue, and only 1 patient fulfilled all the criteria required for the diagnosis of chronic fatigue syndrome. One patient had temporal lobe epilepsy, the other moderately severe obstructive airway disease. None of the patients in the control group had serious medical disorders.

Psychiatric morbidity was common in both groups. Active psychiatric disorders were considered a major cause of the chronic fatigue for 70.3% of the patients in both groups. Major depressive disorders explained the chronic fatigue of 66.6% of patients with multiple food intolerance, a prevalence only slightly higher than that recorded for the control group. The prevalence of anxiety disorders was also similar in both groups. A significant statistical difference was present in comparing the prevalence of somatization disorder, diagnosed in 33.3% of the patients with multiple food intolerance, but in only 7.4% of the control patients with chronic fatigue (Table 2).

Table 1. Main clinical features of patients with chronic fatigue and food intolerance

Feature	Study Group		Control Group		p Value
	M	SD	M	SD	
Age	40.0	6.5	40.4	7.79	NS
Duration of fatigue	11.9	10.1	13.7	12.5	NS
Severity of fatigue	5.9	2.5	6.0	1.7	NS
Functional complaints	8.7	4.6	6.2	4.3	<.05*
Depressive symptoms	5.8	2.3	6.1	2.1	NS

\**t* = 2.08, *df* = 60.

Table 2. Diagnoses of attribution of patients with chronic fatigue and food intolerance

Diagnostic Group	Study Group		Control Group		p Value
	N	%	N	%	
Psychiatric diagnoses	19	70.3	19	70.3	NS
Depressive disorders	18	66.6	17	62.9	NS
Somatization disorder	9	33.3	2	7.4	<.025*
Anxiety disorders	3	11.1	4	14.8	NS
Medical diagnoses	2	7.4	—	—	NS
Chronic fatigue syndrome	1	3.7	1	3.7	NS
No diagnosis	5	18.5	7	25.9	NS

\* $\chi^2 = 5.59$ ,  $df = 1$ .

An analysis of the distribution of foods producing symptoms among the traditional food groups indicated that the majority of patients with multiple food intolerance reacted to vegetables and fruits (81.4%), meats, including fish, eggs, and nuts (70.3%), and dairy products (62.9%). The prevalence of reported intolerance to foods from these and three other food groups (spices, prepared and preserved foods, and sugar and sweets) was significantly higher among the patients with multiple food intolerance. Reactions to fats and oils, breads and cereals, and nonalcoholic beverages were more rarely reported, and no significant differences were noted between the two groups (Table 3).

The symptoms produced by food ingestion were varied and sometimes difficult to explain. One patient reported painful abdominal distension after eating tomatoes, severe tiredness after red meat, persistently unpleasant bad taste in mouth after eggs, and diarrhea and shortness of breath after eating chocolate. Another patient had chills after eating fish, nasal and chest congestion after consuming peas, and could not tolerate milk. A feeling of malaise and aches after eating crabmeat was reported by a patient who also complained of headaches produced by tomatoes, and nasal congestion that followed any milk drinking. On occasion, traditional atopic reactions were reported together with more unusual reactions to foods. For example, a patient with urticarial eruptions caused by eating tomatoes also reported severe nausea produced by eggs, burritos, and by frozen dinner food for weight watchers.

Foods of intolerance included most of the standard staples of the American diet,

Table 3. Foods of intolerance in chronic fatigue

	Study Group		Control Group		p Value
	N	%	N	%	
Vegetables and fruits	22	81.4	7	25.9	<.001*
Meats, fish, and eggs	19	70.3	4	14.8	<.001*
Dairy products	17	62.9	3	11.1	<.001*
Spices	13	48.1	1	3.7	<.001*
Preserved foods	10	37.0	—	—	<.001*
Fats and oils	8	29.6	3	11.1	NS
Sugar and sweets	8	29.6	1	3.7	<.02**
Breads and cereals	3	11.1	—	—	NS
Nonalcoholic beverages	3	11.1	—	—	NS

\* $\chi^2 > 10.2$ ,  $df = 1$ .

\*\* $\chi^2 = 6.1$ ,  $df = 1$ .

such as milk, ice cream, eggs, poultry, hot dogs, seafood, peanut butter, pickles, tomatoes and tomato-based sauces, onions, apples, bananas, and carbonated soft drinks. Many patients also described intolerance to groups of foods characterized by some common denominator such as fatty foods, fried foods, smoke-flavored foods, spicy foods, foods containing monosodium glutamate, foods preserved with nitrites, and acidic foods.

## DISCUSSION

Intolerance to multiple foods was reported by 13.5% of a sample of patients with a chief complaint of chronic fatigue. The 27 patients with food intolerance were compared to age- and gender-matched control subjects with a similarly severe chief complaint. Patients with multiple food intolerance had a significantly higher prevalence of functional somatic complaints other than those associated by them with reactions to food and a higher prevalence of somatization disorder. These data appear quite robust on account of three distinctive features of our study. First, we conducted a comprehensive examination of each patient in a prospective, longitudinal manner, according to a detailed, standardized protocol that minimized problems with performance and detection bias. Second, the control group for chronic fatigue patients with multiple food intolerance consisted of other patients with chronic fatigue. Third, we established psychiatric diagnoses using a reliable and extensively validated diagnostic instrument.

With the caveat that no provocation tests or elimination diets were used to confirm the food-related symptoms of our patients, we believe that our findings support and confirm other data generated by studies of patients with food-related complaints.

Research on patients with adverse food reactions that could not be confirmed by double-blind food challenge who were compared with patients with IgE-mediated food hypersensitivity showed that the former were significantly more likely to report symptoms occurring on daily or weekly basis that either interfered with or prevented them from continuing with their usual activities. Their food-related symptoms included fatigue, depression, mood swings, loss of concentration, sluggishness, difficulty sleeping, memory loss, burning mouth, constipation, mood swings, hearing impairment, muscle aches, joint stiffness, chills, and headache. On the other hand, they reported much fewer instances of eczema, hay fever, or episodes of wheezing (Parker et al., 1990). The patients with nonallergic food-related complaints were also more likely to score higher for hypochondriasis and for global indices of distress on standardized psychological testing (Parker et al., 1991).

Similar trends were noted in a study that sought objective evidence of food hypersensitivity by using exclusion diets and provocation tests in patients who attributed a wide variety of symptoms to food allergy (Pearson et al., 1983). All of the patients with objectively confirmed hypersensitivity to foods presented with typical atopic symptoms, reported no psychological symptoms related to food, and had no active psychiatric disorders. In contrast, all of the patients in whom food sensitivity was not confirmed were polysymptomatic, with an average of more than six symptoms per patient. Lethargy was the most common presenting complaint and the most common symptom being reported by more than 80% of these patients. Other common complaints were depression, poor concentration, sleep disturbance, irritability, mood swings, anxiety attacks, headache, chest pain, breathlessness, palpitations, dizziness, abdominal swelling and pain, nausea, and bowel disturbance. On psychiatric evalua-

tion, more than half of these patients were diagnosed to have neurotic depression. Further evaluations compared the patients with unconfirmable food allergy with new referrals to the psychiatric outpatient clinic (Rix et al., 1984). No significant differences were found in terms of psychiatric diagnoses, personal history of psychiatric disorder, and familial loading for psychiatric disorder. Most of the patients with food-related symptoms were hostile to the psychological findings produced by their evaluation, and some rejected the results of double-blind provocation tests. A number of patients continued to believe that they must have a hidden food allergy, and most patients refused to consider referral for psychiatric treatment.

Of interest are also the data presented with regard to the functional somatic syndromes diagnosed among women with pseudo-food allergy (Pearson, 1985). Irritable bowel syndrome with or without associated urethral syndrome was diagnosed in 50% of the patients studied, chronic hyperventilation syndrome in 40%, and somatic features of depression were prominent in 35% of patients.

Case studies have also shed light on the clinical characteristics of patients with multiple food intolerance. Among six female patients presenting with long history of multiple food-related symptoms, and in whom the diagnosis of food allergy was not confirmed, weight problems such as obesity or anorexia during adolescence were followed by abnormal eating behaviors during adulthood, when their lives centered around complicated rotational and elimination diets and the avoidance of artificial food additives (Terr, 1986). Depression, fatigue, and joint pains without objective evidence of synovitis were commonly reported and attributed by the patients to their intolerance of foods. In another recent report (Seggev & Eckert, 1988) concerning three patients with unconfirmable allergies to multiple foods, one patient was diagnosed to have major depression with psychotic features and was able to tolerate a regular diet after treatment with perphenazine and amitriptyline. Another patient was found to have schizoaffective disorder with a psychotic belief fixated on food allergies; she gained weight and tolerated foods to which she thought she was allergic after treatment with imipramine. In the third case, the patient showed a tendency to conceptualize psychological distress in terms of physical symptoms; a thorough medical and psychiatric evaluation seemed to resolve completely the food-related symptoms.

We conclude by reiterating that other than a higher prevalence of somatization disorder, we were unable to detect a constellation of symptoms or a presentation of the fatigue illness that was consistent and unique for patients with multiple food intolerance. Because our data and those available in the literature offer no evidence to suggest that food intolerance is part of the causation of chronic fatigue, we believe that physicians evaluating patients complaining of fatigue and multiple food intolerance should carefully investigate the possible presence of depressive, anxiety, and somatization disorders. When present, these conditions should be aggressively treated. Exclusion diets and provocation testing should be reserved for patients with atopic symptoms and for those with persistent food-related complaints after appropriate psychiatric intervention.

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