

Prevalence of adverse reactions to food in patients with gastrointestinal disease

Bischoff SC, Herrmann A, Manns MP. Prevalence of adverse reactions to food in patients with gastrointestinal disease. *Allergy* 1996; 51: 811–818. © Munksgaard 1996.

The role of allergic reactions in the pathogenesis of inflammatory bowel disease and irritable bowel syndrome has been disputed. This study aimed to determine the prevalence of adverse reactions to food in patients with gastrointestinal disease. A total of 375 adult patients of a gastroenterologic outpatient clinic were examined by history, skin tests, measurements of laboratory parameters, and intestinal provocation with food allergens by colonoscopy. Some 32% complained of adverse reactions to food as a cause of their abdominal symptoms. In 14.4%, the diagnosis of intestinal food allergy could be suspected according to several criteria such as elevated total IgE, specific IgE against food antigens, eosinophilia, responsiveness to cromoglycate, and clinical signs of atopic disease. In 3.2%, the diagnosis could be confirmed by endoscopic allergen provocation and/or elimination diet and rechallenge. In conclusion, the data suggest that allergic reactions to food antigens may be a causative factor in a subgroup of patients with inflammatory and functional gastrointestinal disease.

**S. C. Bischoff, A. Herrmann,
M. P. Manns**

Department of Gastroenterology and
Hepatology, Medical School of Hanover,
Hanover, Germany

Key words: Crohn's disease; eosinophil cationic protein; food allergy; IgE; ulcerative colitis.

Dr Stephan C. Bischoff
Department of Gastroenterology and Hepatology
Medical School of Hanover
D-30623 Hanover
Germany

Accepted for publication 16 May 1996

The cause of inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and other chronic, noninfectious diseases of the intestinal tract such as eosinophilic enteritis or celiac disease is largely unclear, and the options for treatment are unsatisfactory (1, 2). However, uncharacterized infectious agents, abnormal immunologic reactions against endogenous or exogenous antigens, environmental factors, and psychosomatic mechanisms have been thought to play a role in the pathogenesis of such diseases. The hypothesis that allergic reactions to food antigens may be involved in a subgroup of such patients has been disputed (2–8).

The existence of intestinal allergic reactions to food in children and adults is generally accepted, but the prevalence is largely unknown (9–11). It has been estimated that, depending on the methods of diagnosis, 2–5% of the general population suffer from food allergy or food intolerance reactions (12, 13). A recent population study of food intolerance in adults reported a prevalence of 1.4% based on a questionnaire involving 20 000 respondents and oral food-challenge tests (14). Of subjects testing positive in the food-challenge test, 28% had intestinal symptoms. However, it has to be considered that 20–45% of the adult population believe that

they suffer from adverse reactions to food, indicating the necessity of objective diagnostic means (12–14). Several studies have suggested that the prevalence of adverse reactions to food is even higher in patients with gastrointestinal symptoms, possibly indicating an association between intestinal diseases and food allergy (3–6).

The manifestations of food allergy are variable, since different organ systems such as the skin, the respiratory system, and the gastrointestinal tract may be involved (9–12). The factors determining the site of manifestation are unknown. The clinical symptoms of intestinal allergy, IBD, and IBS are strikingly similar and include abdominal pain, cramps, flatulence, irregular bowel movements, and other unspecific symptoms (1, 2, 9–12). Moreover, laboratory parameters or endoscopic findings do not usually allow us to distinguish between intestinal allergic disease and other disorders. The lack of appropriate diagnostic means is a major problem in intestinal food allergy. Skin tests and IgE measurements are known to be of limited value for the diagnosis of intestinal food allergy (10–13). The double-blind, placebo-controlled oral challenge with food and the methods of elimination diet and rechallenge have been suggested as “gold stand-

ards" to confirm the diagnosis of food allergy (15–17). Both methods may be of high theoretical value, but, in practice, they have several limitations. We developed a new test, the colonoscopic allergen provocation (COLAP) test, which allows the identification of antigens capable of inducing a mucosal reaction in the intestine when administered under endoscopic view. Our previous experiments provided evidence that the COLAP test is a valuable diagnostic tool and is useful for the study of mechanisms of intestinal food allergy (Bischoff et al., paper submitted).

This study aimed to determine the prevalence of adverse reactions to food in patients with gastrointestinal disease of unclear origin by the COLAP test and classical allergologic means such as history, skin tests, measurement of IgE, and elimination diet. We examined 375 patients and proposed criteria which may be helpful to identify patients with suspected intestinal food allergy. The results support the hypothesis of an association between IBD, IBS, and intestinal hypersensitivity reactions to food, as can be demonstrated in a subgroup of patients.

Material and methods

Patients

Between 1992 and 1995, 375 unselected patients (255 with Crohn's disease, 82 with ulcerative colitis, and 38 with other diseases) of the gastroenterologic outpatient clinic for IBD of the Medical School of Hanover were included in the study. Usually, the patients were repeatedly seen in the clinic. The time intervals between the consultations varied from 3 to 12 months (mean: three consultations per patient, 1029 consultations total). For each consultation, patient history, clinical data (bowel movements, drug treatment, extraintestinal manifestations of the disease, etc.), and laboratory findings (routine parameters, total IgE in serum, and specific IgE) were monitored.

The diagnosis of IBD was based on clinical, endoscopic, and histologic data. Infectious disease was excluded by microbiologic examinations of blood and feces in all patients. Disease activity was assessed by the Crohn's disease activity index (CDAI), according to Best et al. (18). In addition, patient global assessment was recorded on a scale of 1–6 (1 = very good, 2 = good, 3 = moderate, 4 = sufficient, 5 = poor, and 6 = very poor). Extraintestinal manifestations of IBD (perianal and other fistulae, arthritis, iritis, uveitis, erythema nodosum, and stomatitis) were monitored. Nutritional status was examined by calculating the body mass index (BMI) according to the formula $BMI = \text{body weight in kg} / (\text{height in m})^2$. Most of the

patients received drugs such as corticosteroids and/or 5-amino-salicylates (5-ASA); a few were also treated with disodium cromoglycate (DSCG). The data were collected in a database (Access, Microsoft Corporation).

The patients were distributed among three groups:

- 1) patients with suspected intestinal food allergy
- 2) patients with confirmed intestinal food allergy
- 3) patients with no evidence of intestinal food allergy according to the criteria shown in Table 1.

The criteria were chosen according to their practicability in clinical routine work and their validity for the diagnosis of other forms of allergic disease. In 50 patients belonging to groups 1 and 2, additional tests were performed such as skin prick tests (Scherax, Hamburg, Germany), measurement of specific IgE by the radioallergosorbent test (RAST) using the Pharmacia CAP System, classes 0–6 (Kabi-Pharmacia, Uppsala, Sweden), and measurement of inflammatory mediators. The detailed clinical data of these 50 patients with suspected or confirmed intestinal food allergy, and of all patients are summarized in Table 2.

Measurement of ECP, EPX, and methylhistamine

Eosinophil cationic protein (ECP) and eosinophil protein X (EPX) were measured in serum by immunoassay, following the manufacturer's instructions (Kabi-Pharmacia). Blood was centrifuged 30–60 min after venous puncture, and the serum was stored at -80°C until the measurement was performed. Methylhistamine was measured by immunoassay (Kabi-Pharmacia) in urine samples, which had been stored at -20°C . The methylhistamine data were expressed as μmol per mol creatinine, as determined by standard methods in the same samples. For comparison, the three inflammatory mediators were also measured in 20 healthy controls (age: 33 ± 10 years, range: 25–58 years, male:female = 10:10) with no evidence of any atopic disease (negative history, normal clinical examination, and normal routine laboratory parameters).

Colonoscopic allergen provocation (COLAP) test

To confirm the diagnosis of intestinal food allergy, we performed intestinal provocation of the cecal mucosa in 13 selected patients with suspected intestinal food allergy. In these patients, an elimination diet did not clearly confirm the diagnosis or could not be done for practical reasons (too many allergens, allergens difficult to avoid, or insufficient compliance). Three allergens (selected according to patient history and RAST), a negative control buffer (NaCl 0.9%), and a positive control (histamine at $3.4 \mu\text{g/ml}$) were administered

Table 1. Clinical definition of intestinal food allergy

A) "Suspected intestinal food allergy"
● History of gastrointestinal symptoms related to food
● Increased total serum IgE (> 150 U/ml)
● Specific IgE against food antigens
● Eosinophilia in peripheral blood (> 400/ μ l) and/or tissue (> 8% of lamina propria cells)
● Improvement of symptoms after treatment with disodium cromoglycate
● Clinical signs of atopy (e.g., extrinsic asthma, seasonal rhinoconjunctivitis, atopic dermatitis, atopic disease of first-degree relatives)
At least three out of six criteria must be fulfilled
B) "Confirmed intestinal food allergy"
● Positive response in the colonoscopic allergen provocation (COLAP) test
● Improvement of symptoms after elimination diet
At least one out of two criteria must be fulfilled in addition to A

endoscopically by intramucosal injection (250 μ l each). The mucosa was observed on a video screen for 20 min. Afterward, the mucosal reaction (wheal

and flare reaction) was classified on a scale of 0–4: 0 = no reaction, 1 = questionable reaction, 2 = moderate reaction (<1 cm diameter), 3 = strong reaction (1–2 cm), and 4 = maximal reaction (>2 cm). The reaction was classified as "positive" if the grade of reddening or swelling was ≥ 2 . The mucosal reaction was assessed by two observers: the endoscopist, who was not informed about patient history and the content of the given solutions, and a second investigator who administered the solution. The patient was also not informed which antigens were administered. After 20 min, biopsies were taken from each site of application. Mast-cell and eosinophil numbers and activation grades were examined by immunohistochemistry and electron microscopy as described (19; Bischoff et al., paper submitted).

Elimination diet and rechallenge

Patients with evidence of intestinal food allergy were advised by a dietitian to follow an elimination

Table 2. Clinical data

	All patients	Patients with intestinal allergy
Patients	375	50
Consultations	1029	143
Sex (M:F)	42:58%	58:42%
Age (years)§	37 $\pm$ 12 (16–73)	35 $\pm$ 10 (16–61)
Duration of disease (months)§	119 $\pm$ 88 (0–499)	98.4 $\pm$ 82.7 (1–267)
Body mass index <20 kg/m ² (%)	19%	24%
Diagnosis		
Crohn's disease	68%	46%
Ulcerative colitis	22%	16%
Celiac disease	1%	2%
Eosinophilic enteritis	1%	8%
Unclassified intestinal disease	8%	28%
Disease activity (CDAI)#		
0–150	73%	79%
150–250	19%	19%
>250	8%	2%
Stool frequency (per week)		
1–14	43%	49%
15–35	41%	46%
>35	16%	5%
Extraintestinal manifestation (%)	39%	29%
Patient global assessment (scale 1–6)	7/44/34/12/2/1%	6/51/33/9/1/0%
Drug treatment		
Local steroids	3%	3%
"Low-dose" prednisolone (≤ 10 mg/d)	21%	24%
"High-dose" prednisolone (> 10 mg/d)	11%	8%
5-Amino-salicylates	42%	34%
Sulfasalazine	19%	13%
Disodium cromoglycate	1%	8%
History of food intolerance	32%	56%
Atopic disease	22%	61%

§ Mean $\pm$ SD (range).

diet for diagnostic and/or therapeutic reasons. Food allergens were eliminated according to history, RAST (class ≥ 2), and/or COLAP test. The elimination diet was judged positive if the symptoms could be clearly reduced and/or were restored after challenge. Patients who could not follow an elimination diet were treated with disodium cromoglycate (DSCG), or, if necessary, temporarily with corticosteroids and parenteral nutrition. The indication for treatment with corticosteroids and parenteral nutrition was ineffectiveness of diet and DSCG, or severe intestinal inflammation with mucosal bleeding.

Results

Prevalence of intestinal food allergy in patients with gastrointestinal disease

A total of 120/375 patients (32%) with IBD or gastrointestinal symptoms of unclear origin complained of adverse reactions to food as the cause of their symptoms. In the selected subgroup of patients with suspected or confirmed intestinal allergy, the prevalence of adverse reactions to food according to history was 56%. Almost 2/3 of the patients with suspected food allergy suffered from atopic diseases such as seasonal rhinoconjunctivitis, extrinsic asthma, atopic dermatitis, or urticaria. The pattern and the severity of symptoms were similar in unselected patients with gastrointestinal disease and the subgroup of patients with evidence of intestinal allergy (Table 2). According to the criteria of Table 1, the prevalence of "suspected intestinal food allergy" was 14.4%. The diagnosis could be confirmed by intestinal provocation (COLAP test) or elimination diet in 3.2% of all patients (Fig. 1). The prevalence of intestinal food allergy was lower in patients with IBD than in patients with other intestinal diseases (eosinophilic enteritis, celiac disease, hyper-IgE syndrome, unclassified disease, or functional disorders).

Laboratory findings in patients with intestinal food allergy

Some routine laboratory findings unspecifically related to inflammatory processes (erythrocyte sedimentation rate, leukocyte count, protein, albumin, c-reactive protein, immunoglobulins, iron, transferrin, and ferritin) were altered in many patients, but significant differences were not observed between unselected patients with gastrointestinal disease and the subgroup of patients with evidence of intestinal allergy (Table 3). Only the number of eosinophils in peripheral blood and total serum IgE levels (measured in 286/375

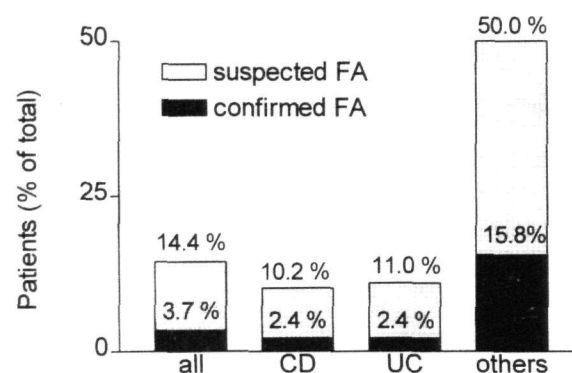


Fig. 1. Prevalence of intestinal food allergy (FA) defined according to criteria listed in Table 1 in 375 patients with gastrointestinal disease (all), of whom 255 had Crohn's disease (CD), 82 had ulcerative colitis (UC), and 38 had other diseases (others) such as celiac disease, eosinophilic enteritis, and irritable bowel syndrome.

patients) were increased in patients with evidence of intestinal allergy ($P < 0.05$, two-tailed t -test). However, almost all patients with IBD and 57% of the patients with suspected intestinal food allergy had normal IgE levels (< 150 U/ml, Table 4). Fig. 2 shows that ECP (19.2 ± 27.8 $\mu\text{g/l}$, mean $\pm$ SD) and EPX (58.1 ± 107.2 $\mu\text{g/l}$) levels in peripheral blood were elevated in patients with evidence of intestinal allergy compared to healthy controls (ECP: 6.8 ± 3.2 $\mu\text{g/l}$; EPX: 14.5 ± 6.0 $\mu\text{g/l}$). However, no significant differences were found in urinary levels of methylhistamine between the group of patients with intestinal food allergy and controls (102.4 ± 87.3 versus 77.5 ± 29.1 $\mu\text{mol/mol}$ creatinine).

Skin tests and RAST

Skin prick tests with food allergens were negative in 92% of the patients with suspected intestinal food allergy. RAST was performed in 36/50 patients with suspected intestinal food allergy. Allergens were selected according to history, and, in addition, most common group tests (milk proteins, egg proteins, cereals, seafood, nuts, vegetables, fruits, and spices) were tested in each subject. In 13/36 patients (36%), RAST was completely negative for all tested food allergens (Pharmacia CAP System, classes 0–1). Most of the patients had low levels of specific IgE (class ≤ 2). In only 5/540 determinations (1%) could high levels of specific IgE be detected (classes 3–6). The relevance of particular food allergens according to history and RAST is summarized in Table 5.

Endoscopic challenge with food allergens

The COLAP test was performed in 13 patients with suspected food allergy. The response to histamine challenge was positive in 12/13 patients. In contrast, no reactions were observed in response to buffer

Table 3. Laboratory findings

	Normal values	All patients (<i>n</i> = 375)			Patients with intestinal allergy (<i>n</i> = 50)		
		Mean $\pm$ SD	< Norm	> Norm	Mean $\pm$ SD	< Norm	> Norm
ESR (1 h)	M: <20 F: <30	17 $\pm$ 13		21%	14 $\pm$ 9		13%
Leukocytes (Tsd/ μ l)	4.3–10	8.7 $\pm$ 3.7	3%	27%	8.7 $\pm$ 3.5	4%	29%
Hemoglobin (g/ μ l)	M: 13.0–17.5 F: 12.0–16.0	13.6 $\pm$ 1.5	18%	1%	13.8 $\pm$ 1.7	20%	1%
Platelets (Tsd/ μ l)	150–300	317 $\pm$ 104	1%	48%	324 $\pm$ 125	1%	38%
Eosinophils (%)	0–10	2.4 $\pm$ 3.1		2%	4.7 $\pm$ 6.5		9%
Basophils (%)	0–2	0.8 $\pm$ 0.6		5%	0.9 $\pm$ 0.7		6%
Protein (g/l)	65–80	71 $\pm$ 6	16%	4%	70 $\pm$ 5	17%	4%
Albumin (g/l)	37–51	39 $\pm$ 6	34%	1%	39 $\pm$ 6	38%	2%
C-reactive protein	$\leq$ 8	12.6 $\pm$ 17.3		27%	10.9 $\pm$ 13.3		25%
IgG (g/l)	8–18	13.8 $\pm$ 3.5	3%	13%	13.6 $\pm$ 2.8	1%	4%
IgM (g/l)	0.6–2.8	2.1 $\pm$ 1.2	3%	18%	1.9 $\pm$ 0.9	3%	8%
IgA (g/l)	0.9–4.5	3.0 $\pm$ 1.3	3%	13%	2.6 $\pm$ 0.9	1%	2%
IgE (U/ml)	< 150	163 $\pm$ 2778		9%	859 $\pm$ 7077		43%
Iron (μ mol/l)	M: 14–27 F: 11–25	14.2 $\pm$ 7.9	47%	6%	14.7 $\pm$ 7.7	45%	6%
Transferrin (μ mol/l)	M: 54–73 F: 45–63	76 $\pm$ 17	3%	92%	79 $\pm$ 21	4%	59%
Ferritin (μ mol/l)	M: 30–284 F: 6–186	47 $\pm$ 68	23%	2%	40 $\pm$ 50	24%	1%

Table 4. Serum IgE level in patients with chronic intestinal disease

	Patients (<i>n</i>)	Measurements (<i>n</i>)	IgE in serum (U/ml)				
			Mean $\pm$ SD	0–150	150–300	300–1000	> 1000
Crohn's disease	164	449	29 $\pm$ 74	97%	1.8%	1%	0.2%
Ulcerative colitis	53	135	20 $\pm$ 33	99%	1%	0%	10%
Food allergy	50	115	144 $\pm$ 592	57%	23%	17%	3%
Other diseases	19	53	859 $\pm$ 7077	92%	0%	4%	4%

control. Positive reactions to food antigen were obtained in response to 18/34 applications (53%). Eleven of the patients who underwent COLAP testing had negative skin tests for the most common food antigens. The results of the RAST were not significantly correlated with patient history or with the COLAP test (chi-square test, both $P > 0.1$). The relation between the COLAP test and patient history of food intolerance was somewhat closer than that between the COLAP test and RAST, but it also failed to reach statistical significance (chi-square test, $P > 0.1$). In 56%, the results of the COLAP test agreed with history of food intolerance (50% both positive, 6% both negative). In 3%, patient history was negative but the COLAP test yielded a positive response. However, in 41%, the positive history could not be confirmed by the COLAP test. The detailed responses to different food antigens are summarized in Table 5.

Discussion

The functional significance of food-allergic reactions in the origin and pathogenesis of IBD has been disputed. One of the first authors on the subject was Truelove, who put forward in 1961 the hypothesis that ulcerative colitis may be due to allergic reactions to food allergens such as those of milk (4). In selected patients with ulcerative colitis, he found that removal of particular food allergens from the diet was followed by marked improvement in the clinical course of the illness and that reintroduction of the allergens caused a relapse. Furthermore, he suggested that the induced relapses were unlikely to be immediate-type anaphylactic reactions, since the responses upon rechallenge were greatly delayed. Further observations supporting the hypothesis that ulcerative colitis and proctitis are related to food allergy have

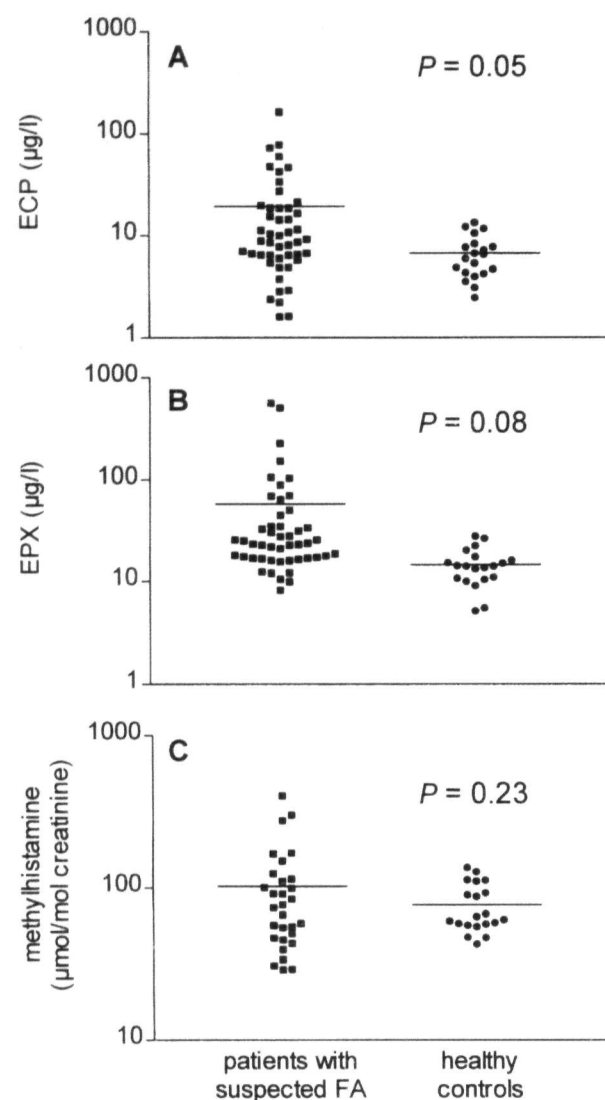


Fig. 2. Serum levels of eosinophil cationic protein (ECP, *n*=48, panel A), eosinophil protein X (EPX, *n*=48, panel B), and methylhistamine (*n*=30, panel C) in patients with evidence of intestinal food allergy (FA) according to criteria listed in Table 1. For comparison, these three inflammatory mediators were also measured in 20 healthy control subjects with no evidence of allergic or intestinal disease.

been published for both children and adults in the following years (5, 6). In particular, it has been repeatedly reported that the elimination diet or elemental diet is an effective treatment regimen in many patients with Crohn's disease (20, 21).

These reports conflict with other studies showing that only in a minor number of patients can adverse

reactions to food be confirmed as a cause of gastrointestinal symptoms by objective means such as the "low allergenicity diet" and double-blind challenges (7, 8). However, it has to be considered that the methods used to confirm the diagnosis may not be appropriate to identify all forms of adverse reactions to food. The observation that an elimination diet can reduce the symptoms, and even the extent of intestinal inflammation, may be more important than the outcome of particular tests, although it cannot be excluded that psychosomatic factors are involved. Another reason for the discrepancies in the literature may be that most studies of the relation between allergy and gastrointestinal disease have been based on unselected patient groups (7, 8, 20, 21). However, it is known that both IBD and IBS represent a heterogeneous group of patients with variable symptoms, and, probably, different causes (1). Since intestinal allergy may be only one mechanism among others which are involved in the pathogenesis of IBD and IBS in a subgroup of patients (2, 4, 7, 8), studies will lack statistical significance if unselected patients are examined.

At present, we do not know whether adverse reactions to food are a cause or a result of intestinal inflammation, or whether allergic reactions to food antigens occurring in the intestinal tract are IgE-mediated or not (4, 22). Therefore, we have to take into account different possibilities when developing a strategy to identify patients with intestinal food allergy. We proposed several criteria which should be applied to patients with suspected intestinal food allergy. Some (total and specific IgE in serum and history of atopic disease) will favor type I hypersensitivity; others (history of food intolerance, eosinophilia, and improvement by DSCG) may also reflect IgE-independent mechanisms.

Using the proposed criteria, we defined a subgroup of 54 patients (approximately 1/7 of all) for which the diagnosis of intestinal food allergy has to be considered. These patients were subjected to

Table 5. Major food allergens

	According to history – all patients (<i>n</i> =375)	According to history – selected patients (<i>n</i> =50)	According to RAST – selected patients (<i>n</i> =50)	According to COLAP test – selected patients (<i>n</i> =13)
Milk/milk products	9.2%	20%	15%	15%
Fruits (except apple)	4.7%	24%	8%	8%
Pulse, cabbage, etc.	12.3%	14%	8%	–
Walnuts/hazelnuts	4.1%	20%	42%	46%
Apple	3.4%	16%	6%	31%
Cereals	3.3%	12%	15%	15%
Spices	2.2%	14%	25%	–
Citrus fruits	3.2%	4%	2%	–
Coffee	2.6%	0%	–	–
Wine/beer	1.5%	6%	–	–
Any food antigen	32.2%	55.9%	97%	85%

further examinations such as measurement of inflammatory mediators (ECP, EPX, and methylhistamine), the COLAP test, and an elimination diet. The results derived from these examinations as well as from the IgE measurements show that the diagnosis could be confirmed in 14/54 patients (26%), by either the COLAP test (six patients), elimination diet (three patients), or both (five patients). However, a detailed diagnostic procedure including elimination diet or COLAP test was performed in only 18 patients in whom the diagnosis was highly suspected, and who agreed to undergo further examinations.

The prevalence of confirmed food allergy could be even higher, if the additional diagnostics had been performed in all patients belonging to the subgroup of 54 patients with suspected intestinal food allergy. Most of these patients believed that they suffered from adverse reactions to food. However, it has to be considered that food allergy may also exist in some patients who do not mention adverse reactions to food (10). These patients may not recognize the food dependency of their symptoms because the allergens are ubiquitous and therefore difficult to identify by experience. "Exotic allergens" such as those of shrimp, hazelnuts, or kiwi, which are rarely consumed, will be recognized more easily by the patient.

On the other hand, our study shows that not all patients with a history of adverse reaction to food fulfill the criteria of "suspected food allergy". Therefore, patient history is necessary but not sufficient to select the patients. The fact that the COLAP test yielded positive results for at least one food allergen in 35/45 patients (78%) indicates that the diagnosis of intestinal food allergy can be frequently confirmed if the patients are carefully selected on an objective basis. These findings emphasize the clinical value of the criteria, which may help to improve the cost-effectiveness of the diagnostic means. Of course, the diagnosis of food allergy is not confirmed when these criteria are fulfilled, but the probability of the diagnosis "intestinal food allergy" may be increased.

The limited value of skin tests and measurement of total or specific IgE is well known, and is confirmed by our study. Therefore, several attempts have been made to improve the diagnosis of intestinal food allergy by establishing new laboratory methods such as measurement of IgE-Fc fragments in stool samples (23, 24), measurement of specific IgG and IgA against food antigens in serum (3), measurement of *in vitro* mediator release by peripheral blood basophils or intestinal mast cells upon challenge with food antigens (25–28), or measurement of intestinal permeability (29). Most of these tests are either too complicated

to perform clinically, or they have not yet been validated by clinical studies, but some of the tests provide new insights into the mechanisms of intestinal allergy or may be useful for future clinical studies. Our study shows that measurement of inflammatory mediators such as ECP and EPX may be useful to identify patients with allergic inflammation. Elevated levels of these mediators were found only in patients with suspected intestinal allergy, but not in all of them. Therefore, the diagnosis of intestinal allergy cannot be excluded by normal ECP/EPX. Own preliminary data indicate that measurement of ECP and EPX in feces yields even more accurate results (Bischoff et al., unpublished data). Parameters such as ECP, EPX, and IgE in serum and feces, respectively, should be considered useful as selection criteria for patients with suspected intestinal allergy, and may be added to the proposed "A criteria" in Table 1.

Provocation tests are acknowledged as the "gold standard" to confirm the diagnosis of allergic disease. The only established provocation test for food allergy is the oral food challenge (15–17). However, the major disadvantage of this test is that the read-out system depends on the patient's subjective symptoms; therefore, despite the fact that it can be performed in a double-blind, placebo-controlled fashion, this test remains subjective (17). Since the recordings of nonvisible and nonmeasurable intestinal reactions such as pain, cramps, and flatulence can hardly be standardized, discrimination between unspecific variability of symptoms and significant changes in response to food challenges will be very difficult. Moreover, this test entails considerable risk of anaphylactic reaction, because an amount of antigen is required which can induce gastrointestinal symptoms (15, 17). Because of these limitations, we did not perform oral food challenge tests in patients with abdominal symptoms.

Compared to oral challenges, mucosal provocation tests have several advantages such as low risk because the amounts of allergens used for provocation are smaller, and the fact that the read-out system is faster and more objective, since the reaction can be directly visualized. Such tests are established for the bronchial, nasal, or conjunctival mucosa, and have been performed also in the stomach by endoscopic means (30–33). However, we could not completely confirm these findings. In our hands, the results of intragastral challenges were much more variable than those of intestinal provocation, possibly because of the acidity of the stomach, which may destroy most of the antigens in an uncontrolled manner. Therefore, we developed a colonoscopic allergen provocation (COLAP) test. The COLAP test, like other provocation tests, is not appropriate for screening but

may be useful to confirm doubtful cases with clear evidence of intestinal food allergy according to history and laboratory findings. The finding that neither skin tests, IgE measurements, nor patient history clearly correlated with the results of the COLAP test was confirmed by another study performed in 45 patients with unclear intestinal disease (Bischoff et al., paper submitted). Both the present study and the previous one show that the COLAP test is safe and specific. The validity of the COLAP test cannot be definitely confirmed yet, although there is a body of evidence suggesting that the mucosal reaction correlates with intestinal allergic disease.

In conclusion, we demonstrated that among patients with gastrointestinal disease of unclear cause, a subgroup, in which allergic reactions may play a pathophysiologic role, can be defined by the use of the COLAP test and other diagnostic means. Further studies are required to elucidate the mechanisms of intestinal allergy and to establish appropriate therapeutic strategies.

Acknowledgments

We thank Monika Olesch, registered nurse, for her untiring support in the care of patients in the gastroenterologic outpatient clinic. Part of this work was supported by a grant from the Deutsche Forschungsgemeinschaft (SFB 280-C8) to S. C. B.

References

- Podolsky DK. Inflammatory bowel disease. *N Engl J Med* 1991;325:928-1016.
- Zwetchkenbaum JF, Burakoff R. Food allergy and the irritable bowel syndrome. *Am J Gastroenterol* 1988;83:901-4.
- Knoflach P, Park BH, Cunningham R, Weiser MM, Albin B. Serum antibodies to cow's milk proteins in ulcerative colitis and Crohn's disease. *Gastroenterology* 1987;92:479-85.
- Truelove SC. Ulcerative colitis provoked by milk. *BMJ* 1961;3:154-60.
- Rosekrans PCM, Meijer CJLM, van der Wal AM, Lindeman J. Allergic proctitis, a clinical and immunopathological entity. *Gut* 1980;21:1017-23.
- Jenkins HR, Pincott JR, Soothill JF, Milla PJ, Harries JT. Food allergy: the major cause of infantile colitis. *Arch Dis Child* 1984;59:326-9.
- Farah DA, Calder I, Benson L, Mackenzie JF. Specific food intolerance: its place as a cause of gastrointestinal symptoms. *Gut* 1985;26:164-8.
- Pearson M, Teahon K, Levi AJ, Bjarnason I. Food intolerance and Crohn's disease. *Gut* 1993;34:783-7.
- Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-4.
- Food intolerance and food aversion. A joint report of the Royal College of Physicians and the British Nutrition Foundation. *J R Coll Physicians Lond* 1984;18:83-123.
- Bruijnzeel-Koomen C, Ortolani C, Aas K, et al. Adverse reactions to food. *Allergy* 1995;50:623-35.
- Crowe SE, Perdue MH. Gastrointestinal food hypersensitivity: basic mechanisms of pathophysiology. *Gastroenterology* 1992;103:1075-95.
- Shanahan F. Food allergy: fact, fiction, and fatality. *Gastroenterology* 1993;104:1229-31.
- Young E, Stoneham MD, Petrukevitch A, Barton J, Rona R. A population study of food intolerance. *Lancet* 1994;343:1127-30.
- Sampson HA. Immunologically mediated food allergy: the importance of food challenge procedures. *Ann Allergy* 1988;60:262-9.
- Bock SA. Food challenges in the diagnosis of food hypersensitivity. In: De Weck AL, Sampson HA, editors. *Intestinal immunology and food allergy*. New York: Raven Press, 1995:105-17.
- Goldman AS, Kantal AG, Ham Pong AJ, Goldblum RM. Food hypersensitivities: historical perspectives, diagnosis and clinical presentation. In: Brostoff J, Challacombe SJ, editors. *Food allergy and intolerance*. London: WB Saunders, 1987:797-805.
- Best WR, Beckett JM, Singleton JW, Kern F. Development of a Crohn's disease activity index. *Gastroenterology* 1976;70:439-44.
- Bischoff SC, Wedemeyer J, Herrmann A, et al. Quantitative assessment of intestinal eosinophils and mast cells in inflammatory bowel disease. *Histopathology* 1996;28:1-13.
- Alun Jones V, Dickinson RJ, Workman E, Wilson AJ, Freeman AH, Hunter JO. Crohn's disease: maintenance of remission by diet. *Lancet* 1985;1:177-80.
- Giaffer MH, North G, Holdsworth CD. Controlled trial of polymeric versus elemental diet in treatment of active Crohn's disease. *Lancet* 1990;1:816-19.
- Halpern GM, Scott JR. Non-IgE antibody mediated mechanisms in food allergy. *Ann Allergy* 1987;58:14-27.
- André F, André C, Cavagna S. IgE in stools as indicator of food sensitization. *Allergy* 1995;50:328-33.
- Kolmannskog S, Haneberg B. Immunoglobulin E in faeces from children with allergy. Evidence of local production of IgE in the gut. *Int Arch Allergy Appl Immunol* 1985;76:133-7.
- Selbekk BH. A comparison between *in vitro* jejunal mast cell degranulation and intragastric challenge in patients with suspected food intolerance. *Scand J Gastroenterol* 1985;20:299-303.
- Nolte H, Schiotz PO, Kruse A, Stahl Skov P. Comparison of intestinal mast cell and basophil histamine release in children with food allergic reactions. *Allergy* 1989;44:554-65.
- Baenkler HW, Lux G. Antigen-induced histamine release from duodenal biopsy in gastrointestinal food allergy. *Ann Allergy* 1989;62:449-52.
- Bischoff SC, Schwengberg S, Wordelmann K, Weimann A, Raab R, Manns MP. Effect of *c-kit* ligand, stem cell factor, on mediator release by human intestinal mast cells isolated from patients with inflammatory bowel disease and controls. *Gut* 1996;38:104-14.
- André C, André F, Colin L, Cavagna S. Measurement of intestinal permeability to mannitol and lactulose as a means of diagnosing food allergy and evaluating therapeutic effectiveness of disodium cromoglycate. *Ann Allergy* 1987;59:127-30.
- Pollard HM, Stuart GJ. Experimental reproduction of gastric allergy in human beings with controlled observations on the mucosa. *J Allergy* 1942;13:467-73.
- Romanski B. The pathology of food allergy studied by gastric allergen challenge. In: Brostoff J, Challacombe SJ, editors. *Food allergy and intolerance*. London: WB Saunders, 1987:917-31.
- Reimann HJ, Lewin J. Gastric mucosal reactions in patients with food allergy. *Am J Gastroenterol* 1988;83:1212-19.
- Bagnato GF, Di Cesare E, Caruso RA, et al. Gastric mucosal mast cells in atopic subjects. *Allergy* 1995;50:322-7.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.