

IgE in stools as indicator of food sensitization

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The fragment of the Fc segment of IgE resistant to proteolytic enzymes was determined by a radioimmunologic method in fecal extracts from several groups of patients. IgEs remained undetectable in the 95 healthy subjects studied. IgEs were detected in 16/27 carriers of intestinal parasites (60%), with a mean of 92.4 IU/g dry weight. IgEs were also detected in 236/312 food-sensitization patients, with the sensitizing foodstuffs being identified by searching for the specific IgEs in circulation (75%), with a mean of 63.9 IU/g dry weight. The simultaneous determination of alpha-1-antitrypsin in fecal extracts and in sera from 21 control subjects and 21 food-sensitization carriers demonstrated that extravasation of plasma proteins into the gut lumen cannot be responsible for the presence of IgE in stools. Testing for IgE in stools therefore appears to be a simple and economical means of identifying patients without parasites who present with food sensitization.

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Food allergy is one of the most controversial topics in medicine (7, 19). One explanation for this situation is the confusion which often exists between food allergy and food intolerance. Food allergy is caused by intestinal IgE-mediated hypersensitivity reactions. Food intolerance may mimic this immunologic hypersensitivity but is caused by some psychiatric disorders, certain enzyme deficiencies, bacterial contamination of the small intestine (9), and some pharmacologically active substances, such as histamine (18) and tyramine, which are present in certain foodstuffs.

The list of food-allergy symptoms is very long. It may include symptoms which invoke a life-threatening prognosis, such as anaphylactic shocks and certain severe cases of Quincke's edema, as well as urticaria and atopic dermatitis, rhinitis and asthma, edema of the lips and of the buccal cavity, aphthous stomatitis, abdominal pains and diarrhea, vomiting, and sometimes migraine, nephrotic syndrome, or interstitial cystitis. However, allergy is only one cause of these manifestations, playing a part with a frequency which is doubtless different according to age and symptoms. Food allergy is thus involved in 5% of asthma cases but in 20-30% of cases of atopic dermatitis in children (22).

Patients who have food allergy may be screened by several methods. The single clinical method permits diagnosis to be made only in caricatural situa-

tions, which are obvious and rare. Exclusion regimens for the purpose of diagnosis are applicable only to patients in whom it is highly probable that allergy exists: the method usually requires several weeks of observation before a conclusion can be drawn.

Screening of patients can be effected by skin tests, but, although there is no danger associated with the prick test, it is time-consuming if a wide-ranging exploration is undertaken. The quality of commercial food extracts is not always of the level attained for airborne allergens, and the use of fresh extracts cannot be extended indefinitely. Skin tests lead to responses which are erroneously negative and erroneously positive: the latter are caused by the non-specific capacity of certain foodstuffs to liberate histamine (crude wheat flour, for example), or directly by the histamine content of the food. Radioimmunologic determination of the specific IgEs which are in circulation for each foodstuff very quickly encounters economical constraints. Screening of food-allergy patients may be based on the simultaneous detection of the plasma IgEs directed against the most common food allergens (proteins from cow's milk, egg-white, wheat, peanuts, soy, and fish), such as that effected by RAST fX5 (Pharmacia AB, Uppsala, Sweden). This test identifies three out of four children who have food allergy, particularly in the presence of atopic dermatitis, and identifies one

allergic adult in two (3). Finally, counting the plasmocytes which are IgE producers in the duodenal mucosa may represent an absolute test of sensitization, but the method is invasive and not readily accepted when the patient does not exhibit any digestive symptoms which justify endoscopy and intestinal biopsy (1, 2). Search for IgE in the intestinal juice (4) also runs into sampling difficulties which prevent its use as a screening method. The demonstration of IgEs or IgE fragments in the stools of a limited number of patients who were carriers of intestinal parasitosis (13) or had gastrointestinal allergies (11) showed that a very significant alternative could exist to screening patients suspected of exhibiting problems associated with food allergy. The object of this study was to validate this hypothesis on a large series of patients.

Material and methods

Patients

Three hundred and twelve patients were studied. The group consisted of 156 females and 156 males with an average age of 30 years (the ages ranging from 1 to 74 years). Their symptomatology comprised 139 cases of urticaria, 91 cases of atopic dermatitis, 32 cases of irritable bowel syndrome, 28 cases of asthma or rhinitis, 18 cases of anaphylactic shock, and four cases of nephrotic syndrome. Indeed, food allergy may also be involved in rare cases of nephrotic syndrome (15, 16). The clinical history of these four patients with nephrotic syndrome also included rhinitis in all, asthma in two, and urticaria or atopic dermatitis in one. In all cases, accountability due to one or, more often, a large number of foodstuffs had been strongly suggested when the patients were questioned, and the implication of IgE-dependent mechanisms had been demonstrated by the positive results obtained from skin prick tests performed with Stallergènes extracts (Stallergènes SA, Fresnes, France), or with fresh extracts prepared, as required in the laboratory, and by the subsequent demonstration of the presence of serum antibodies specific to the IgE class by radioimmunologic determination (RAST, Pharmacia AB, Uppsala, Sweden). The list of sensitizations identified in the 312 patients is given in Table 1. The serum IgE concentrations of all the allergic patients were measured with the Phadebas paper disk double antibody radioimmunoassay technique (PRIST, Pharmacia AB).

IgE in stools and food allergy

A double-blind, placebo-controlled food challenge was done in 186 subjects with one or more foods.

Table 1. Sensitization to foodstuffs identified in 312 sufferers from food allergy

Foods	n	Foods	n
Wheat	105	Mustard	36
Peanut	92	Carrot	35
Soy	91	Walnut	32
Crab	90	Almond	31
Celery	78	Egg-yolk	30
Tomato	70	Kiwi	28
Parsley	67	Tuna	27
Rice	64	Beef	24
Hazelnut	63	Banana	22
Yeast	62	Strawberry	22
Egg-white	62	Chicken	19
Pea	61	Mango	13
Orange	61	Pear	13
Onion	59	Peach	10
Milk	58	Oats	9
Rye	55	Gluten	7
Garlic	55	Avocado	6
White bean	54	Mussel	6
Pork	52	Saracen corn	6
Potato	51	Barley	5
Maize	46	Cacao	5
Melon	45	Lobster	4
Apple	41	Salmon	4
Shrimp	39	Malt	3
Cod	37	Lamb	3

The challenge was judged to be negative in 65 and positive to at least one food in 121 patients.

IgE in stools and treatment of food allergy

Forty-seven patients were advised to take daily 800 mg sodium cromoglycate and to reduce the consumption of recognized allergens. All the symptoms of these patients were improved at 6-month follow-up. Fecal IgE was measured before and after the treatment. The same study was performed in 27 patients who did not accept any treatment other than antihistamine.

Controls

The patients were compared with a group of 95 healthy controls. These comprised 63 females and 32 males with an average age of 32 years (the ages ranging from 1 to 76 years). They were either volunteers who were members of the hospital staff, or medical students, or patients presenting with functional digestive problems, the evaluation of which had excluded any allergy and organic lesion. No patient and no control was a carrier of intestinal parasites, as established by parasitologic examination of their feces.

Finally, as a positive control, IgEs were also sought for and determined in fecal extracts from 27 carriers of intestinal parasites; these comprised 12

females and 15 males with an average age of 41 years (the ages ranging from 1 to 69 years). The parasites identified were *Giardia intestinalis* (20 times) *Oxyuris* or *Trichocephalus* species (twice), and *Entamoeba histolytica* (three times).

IgE determination in fecal extracts

Samples of fresh feces were collected and frozen in plastic containers. Blood was not detected in any of the fecal samples (Hemocult, SKD, Gagny, France). Extracts of freeze-dried feces were prepared as described earlier (10). Briefly, a 1-g sample of crushed dry feces was suspended in 10 ml phosphate-buffered saline, pH 7.2, and mixed for 20 min at room temperature. The mixture was centrifuged at 20000 g for 20 min at 4 °C. The supernatant liquids, called extracts, were pipetted off and analyzed for IgE. IgE was determined by the Phadebas paper disk double-antibody radioimmunoassay technique (PRIST, Pharmacia AB).

IgE values were expressed as international units (IU) per gram of dry feces. The lower limit of detection was 5 IU/g dry feces. Fecal IgEs were also determined at the same time for controls and for allergic patients by the following alternative techniques: Quanticlon IgE ERIA (Kallestad Diagnostics, Inc, Chaska, MN, USA), PD IgE RIA (Ventrex Laboratories, Inc, Portland, USA), IgE RIA (Immunotech SA, Marseille, France), IgE RIA Ultra 50 (Pharmacia AB), Phadezym PRIST (Pharmacia AB), Magic Lite® (Ciba-Corning Diagnostics, Cergy-Pontoise, France), and IgE EIA Abbott (Abbott Laboratories Diagnostics Division, Chicago, IL, USA). When using the last method, a protease inhibitor – phenylmethyl sulfonyl fluoride (Sigma Co, St Louis, MO, USA) – was added to the phosphate buffer at a concentration of 1 mg/ml.

Alpha-1-antitrypsin determination

In fecal extracts and in sera, alpha-1-antitrypsin levels were measured by radial immunodiffusion in 21 sensitized patients at the same time as the measurement of IgE in fecal extracts and in sera and in fecal extracts and plasma from 21 control subjects. The immunodiffusion plates, containing monospecific antiserum against alpha-1-antitrypsin, LC-Partigen for the quantitative determination of proteins in low-concentration ranges and NOR-Partigen for the quantitative determination of proteins at the usual concentration in serum, and the appropriate standard preparations, were obtained from Behringwerke AG (Marburg, Germany) and used according to the recommendations of the producer.

Statistical methods

Results were expressed as mean (SD). Comparison between groups was made with Student's *t*-test. Linear regression was used to analyze correlations between the concentrations of IgE and of alpha-1-antitrypsin. All reported significance levels represent two-tailed *P* values.

Results

None of the 95 healthy subjects exhibited detectable IgE in their fecal extracts. In contrast, 16/27 intestinal parasitosis carriers, or 60%, gave a positive reaction, with a mean concentration of 92.4 IU/g dry stool (SD 291.5; range: 5.2–1184).

For the 312 allergic patients in whom sensitizing foodstuffs were identified, IgEs were detected in the stools of 236 patients, or in 75.6%, of cases. The mean concentration observed was 63.9 IU/g (SD 115.9; range: 5.0–1000.0). This group comprised 55 children with an average age of 7 years (range: 1–15 years); for these, the test proved to be positive 45 times, or in 82%, of cases. The mean IgE concentration was 121.6 IU/g (SD 201.8; range: 5.0–1000.0).

For the 312 allergic patients, the mean number of sensitizing foodstuffs identified was seven per patient (range: from one to 35 foodstuffs). The mean number of sensitizing foodstuffs was eight (range: from one to 35) when the stools gave a positive result for IgE, with a mean of three foodstuffs (range: from one to five) when IgEs were not detected. Another analysis showed that when sensitization involved one or two foodstuffs, which was the case for 107 subjects, IgEs were detectable in 71 subjects, or in 66%, of cases, while when sensitization involved three or more foodstuffs, which was the case for 205 subjects, fecal IgEs were detected in 165 subjects, or in 80%, of cases.

In 48 allergic patients who were monosensitized to one of the following foodstuffs: egg-white, protein from cow's milk, crab, celery, wheat, or yeast, fecal IgEs were detected in 31 subjects, but remained undetectable in 17 others. The mean severity of sensitization, determined in the blood by the specific IgE titer expressed in Pharmacia units (PRU), was 1.71 PRU in subjects with positive stools, and 0.54 PRU in subjects with negative stools ($P < 0.001$; Student's *t*-test).

Moreover, the mean serum IgE level was 1275 kIU/l (SD 2216.4; range: 3–11 550) in allergic patients with stools which were positive for IgE, and 270 kIU/l (SD 550.0; range: 2–3000) for allergic patients with stools which were negative for IgE.

Table 2. Frequency of detection and concentration of IgE in stools of 312 allergic patients in relation to type of disease

Symptoms	No. of patients	No. of positive stools	% of positive stools	IgE in IU/g dry weight	
				Mean* (SD*)	Range
Urticaria	139	102	73.4	31.7 (61.4)	5.0–456.0
Atopic dermatitis	91	74	81.3	118.3 (180.0)	5.0–1000.0
Irritable bowel syndrome	32	22	68.8	51.4 (91.8)	6.0–426.0
Asthma or rhinitis	28	23	82.1	43.3 (86.6)	5.0–424.0
Anaphylactic shock	18	11	61.1	80.7 (225.0)	5.8–758.7
Nephrotic syndrome	4	4	100.0	21.3 (11.2)	12.0–36.8
Total	312	236	75.6	63.9 (129.5)	5.0–1000.0

* Values calculated only from IgE-positive fecal extracts.

The correlation between the fecal IgE level and the serum IgE level was significant, with $r = 0.457$ ($P < 0.001$).

Table 2 shows that the frequency of detection of IgEs in the stools of allergic patients for whom the nature of the sensitization had been identified did not vary according to the type of clinical symptom shown. The mean IgE concentration per gram of dry stool was 63.9 IU/g (SD 129.5; range: 5.0–1000.0). The IgE content of the stools was significantly greater for atopic dermatitis patients, than for urticaria, asthma, or rhinitis patients, or for irritable bowel syndrome patients, with a significance of $P < 0.005$, 0.05 and 0.05, respectively (Student's *t*-test).

In 121 subjects sensitized to foods and considered to present food allergy because they reacted to double-blind, placebo-controlled food challenge, the mean concentration of fecal IgE was 48.8 IU/g (SD 135.2), which was nonsignificantly different from the 51.9 IU (SD 136.1) found in sensitized subjects who were not reactive in double-blind, placebo-controlled food challenges.

A 6-month treatment which combined an elimination diet with administration of sodium cromoglycate induced a significant ($P < 0.001$) reduction of the titer of fecal IgE from 61.3 IU/g (SD 116.7) to 17.8 IU/g (SD 40.0). In the patient group with no treatment other than symptomatic, the titer of fecal IgE did not change significantly between 33.6 IU/g (SD 50.8) and 70.0 IU/g (SD 188.9).

As for alternatives to the PRIST Pharmacia method for the determination of fecal IgE, all the techniques used were shown to be defective by the absence of detection of IgEs in all cases and by the observation of false-positive results for the Pharmacia Phadezym method (not shown). However, the EIA method (Abbott), provided it was associated with the addition of a proteolysis inhibitor, was shown to be capable of detecting fecal IgEs. Compared with the PRIST technique (Pharmacia), which detected fecal IgEs in 53 patients, the Abbott EIA

method gave positive results 43 times. The 10 subjects who were not identified showed low values, less than 10 IU/g of dry stool. The mean concentration shown by the PRIST method was 40.7 IU/g of dry weight (SD 78.5), and 23.6 IU/g of dry weight (SD 28.7) by the Abbott IgE EIA ($P < 0.025$; Student's *t*-test). However, there was a significant correlation between the two methods, with $r = 0.981$ ($P < 0.001$). Finally, the Abbott EIA technique was not subject to any false-positive result.

The mean concentration of alpha-1-antitrypsin in stools from sensitized patients was 0.58 mg/g (SD 0.49), with a mean of 0.56 mg/g (SD 0.35) in control subjects. There was also no difference in the ratios of alpha-1-antitrypsin feces/serum, the values being 0.29 (SD 0.25) and 0.28 (SD 0.20), respectively, in sensitized patients and in control subjects. The mean ratio of IgE in feces/IgE in serum was 0.11 (SD 0.26) in the 21 sensitized patients also submitted to alpha-1-antitrypsin determination. In these patients, there was no correlation between the ratios IgE feces/serum and alpha-1-antitrypsin feces/serum ($r = 0.129$).

Discussion

The IgEs detected in the stools were present in the form of fragments (14), mainly comprising the Fc $^{\alpha}$ fragment resistant to proteolysis, corresponding to the D e1 domain. This doubtless explains why detection of fecal IgEs is possible by the PRIST and Abbott systems, which are based on two types of anti-IgE polyclonal antibodies, and not by the other detection systems tested, since these utilize two monoclonal antibodies, or one monoclonal antibody, which are not specific to the Fc $^{\alpha}$ fragment of the IgE. Concentrations of IgE in extracts of small samples of dry feces have been shown to correlate well with the total daily amounts of IgE in feces collected over a 3-day period; therefore, simple small samples of feces can be used to measure the excretion of IgE with feces at that time (12). In patients studied over a 5-week period, the IgE excretion varied somewhat from one day to another, but was largely within a certain range of concentrations (12).

The origin of the IgEs which can be detected in the stools has to be considered. It is obvious that IgEs result from a mucosal synthesis since it has been reported that IgE plasma cells are very numerous in the gut mucosa of patients with food allergy (6, 21, 24–26), but a plasma origin cannot be excluded. Indeed, an animal model of food allergy has shown that endointestinal challenge with a low concentration of allergen produces significant exudation of plasma into the lumen of the ileum without causing damage to the epithelial lining (20). A relationship between plasma IgE and fecal IgE was not identified

in a previous study, yet it holds true for a limited number of patients (11). The observation of a positive correlation between the level of IgE in blood and in the fecal extracts from the food-sensitized patients of the present study might indicate that IgEs in stools have a plasma origin. The absence of correlation between the ratios of IgE in blood/IgE in stools to the ratios of alpha-1-antitrypsin in blood/alpha-1-antitrypsin in fecal extracts and the similarity of alpha-1-antitrypsin content in stools from food-sensitized patients and control subjects clearly shows that in man IgEs in stools have only a mucosal origin.

This was also the conclusion of other authors (23) who showed that the level of copro-alpha-1-antitrypsin was the same in patients with food allergy with presence of copro-IgE, and in control subjects. Furthermore, oral challenge with an allergen increased significantly the level of copro-IgE but did not modify the level of copro-alpha-1-antitrypsin (23). The comparison of the fecal contents in alpha-1-antitrypsin and in the Fc fragment of IgE resistant to proteolytic enzymes is very relevant. The mol. mass of the acute-phase reactant, which is totally nonsusceptible to gut enzymes (8), is 45 KDa, very close to that of the IgE Fc fragment of 40 KDa (5). The following fact also shows the intestinal origin of fecal IgEs in the patients of the present study.

Certain patients exhibit a level of circulating plasma IgE which is particularly low, of the order of a few IgE units, although this does not prevent specific IgEs from being detected in their plasma, but it does mean that the IgE concentration detected in stools may be higher than that observed in the blood (see ranges in Table 2). In general, the detection of fecal IgEs appears to be more frequent, and the levels measured appear to be greater, the greater the number of food sensitizations and the greater the level of each specific antibody. These significant sensitizations are usually associated with a higher total plasma IgE level. This also explains why fecal IgEs are more easily demonstrated in atopic dermatitis patients and in children.

As might be expected, the concentration of fecal IgE does not differ between patients who present a documented food allergy and those with biologic sensitization. The level of fecal IgE is not very different from the circulating level of anti-food-specific IgE. In addition, the fecal concentration of IgE is not reduced in patients who are treated only with antihistamine, but it is reduced in those who undergo elimination diets together with oral sodium cromoglycate. This reduction may be explained in two ways which are not mutually exclusive. There may be reduction of stimulation because of the reduction of exposure, or also a reduction of IgE synthesis due to administration of sodium cromoglycate (17).

This study has validated the detection of fecal IgEs as a method of screening, since the test was regularly negative for healthy subjects, and was positive with acceptable sensitivity for carriers of intestinal parasitosis or sufferers from food sensitization.

In conclusion, the detection of IgEs in the stools of patients presenting with neither bleeding of the digestive system nor intestinal parasitosis appears to be an economical and effective method of screening for patients who are carriers of food sensitization and who justify a deeper etiological evaluation; for example, by evaluation of the circulating food-specific IgE together with an oral double-blind challenge. The method is effective, since it was always negative for the 95 controls studied but was positive for 236/312 sufferers from food sensitization evaluated (75% of cases).

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