

Specific IgE to food and inhalant allergens in intestinal washings of children affected by atopic eczema

F. MARCUCCI, L. G. SENSI and G. BIZZARRI

Department of Paediatrics, Perugia University, Perugia, Italy

(Received in original form 23 July 1984 and in revised form 10 December 1984; accepted for publication 15 January 1985)

Summary

Serum and rectal total and specific IgE were measured in eleven children with atopic dermatitis and eight with atopic dermatitis and associated wheezing. Specific IgE to food and inhalant allergens in rectal washings were found in fourteen patients. Of the seventy-six allergens which gave positive results, twenty were positive in both serum and intestine, thirty in serum alone and twenty-six in intestines alone. Specific intestinal IgE were confirmed by food challenge in three out of four patients whose skin-prick test and serum RAST were both negative. Local production of these antibodies was demonstrated by the 'double ratio' of Deuschl and Johansson [1], and the 'specific activity ratio' of Platts-Mills [2]. Positive ratios (> 1) were obtained with both formulas for twelve of fourteen allergens tested. These data suggest that gut-associated lymphoid tissue may play a role in the pathogenesis of atopic disease.

Introduction

Despite intensive studies, the pathogenesis of atopic dermatitis, a disease that affects between 1.1% and 4.3% of the paediatric population, is still poorly understood.

The high incidence of raised serum IgE levels [3], a positive response to immediate-type skin tests [4,5] and, in many cases, a positive radioallergosorbent test (RAST) [6] seem to indicate that immediate hypersensitivity plays a role in the aetiology of this disorder. On the other hand, the prick test is often negative in children under 4 years old and the specific IgE assay does not always aid diagnosis [7,8].

Several immunological mechanisms could be implicated in the pathogenesis of atopic dermatitis. Circulating IgE immune complexes have been shown in children with atopic dermatitis [9] and food allergy [10]. Studies on IgE concentrations in intestinal juices has led to debate as to whether the antibodies were produced locally or otherwise [11]. In some situations high IgE concentrations have been reported in atopic dermatitis, but not to the extent seen in patients with food allergy [12].

Correspondence: Dr F. Marcucci, Istituto di Pediatria-Policlinico, Montelucente 06100, Perugia, Italy.

The results of investigations on IgE plasma cells of the intestinal mucosal membrane in atopic dermatitis and food allergy patients are also conflicting [13,14]. Studies on rectal washings are based on two pre-suppositions: (i) the functional unity of the mucosa-associated lymphoid system [15] and (ii) the direct involvement of the large intestine in food allergy disorders [16].

Because of the possible role of the intestinal mucosa in atopic diseases and the relationship between food allergy and atopic eczema, we evaluated local IgE production by studying both total and specific levels of this immunoglobulin in rectal washings from children with atopic dermatitis with and without associated wheezing.

Patients and methods

Nineteen patients with atopic dermatitis, of whom eight had associated wheezing, and ten healthy non-atopic controls between 4 months and 6 years were entered in the study after obtaining informed consent for the rectal washings. All patients had a family history of atopic diseases (i.e. one or both parents were affected) and all had characteristic lesions of atopic dermatitis for at least 2–5 months. As defined by Clendenning *et al.* [17], the condition was moderate in seventeen and severe in two patients. No patient took medication or followed an elimination diet either before or during the study. None had evidence of intestinal parasites.

Eight parents were of the opinion that the atopic dermatitis was aggravated by milk and/or eggs (Nos. 1,6,7,9,16,17) and tomatoes (Nos. 10,14). In four patients (Nos. 1,6,16,17) these foods were also suspected of causing gastrointestinal symptoms. Some patients (Nos. 1,2,9,11) experienced worsening of the skin manifestations and onset of wheezing in spring. In patient No. 2 there was association of wheezing with skin rash on exposure to wool, and patient No. 1 the same association was reported on exposure to dog epithelium.

Four other patients had occasional non-seasonal respiratory symptoms (Nos. 8,10,17,19). No patient with wheezing received any specific desensitization therapy. After clinical examination, all patients were tested by the prick test with the same panel of allergens and assayed for specific serum and intestinal IgE. Total serum and intestinal IgE was also determined. Patients with negative serum RAST and prick tests were subsequently challenged with foods.

Food challenge

Food challenges were carried out, according to the McEwen and Constantinopulous [18] method, after an exclusion diet that lasted for 1 month or until a symptom-free day. Symptoms were recorded for the 2 h immediately following the ingestion of food. A positive reaction was confirmed by rechallenge 2 weeks later.

Skin test

After admission to the study, children were tested with a wide panel of foods and inhalants, which included both allergens suggested by, and unrelated to, the case history (grass pollen, house dust, mites, *Parietaria* off., *Alternaria*, *Candida*, animal danders, milk, eggs, cheese, tomato, potato, cod, tuna, chicken, oats), by the prick technique with standard glycerinated extracts (Hollister-Stier).

Total and specific serum IgE

Total serum IgE was determined by monoclonal antibody radioimmune assay

(Gammadab-M J¹²¹ IgE RIA, Clinical Assays); specific serum IgE by the immuno-enzymatic assay (Phadezym RAST, Pharmacia) to the same allergens as used in the prick test.

Total and specific intestinal IgE

Samples for IgE determination were collected by rectal washings after a 12-hr fast and 2 hr thorough entero-cleaning with 200 ml physiological saline solution as previously described [19]. The rectal washings were performed with a syringe equipped with a 0.5 × 15 cm tygon tubing, delivering 40 ml of a 9% NaCl solution then promptly aspirated. This procedure was repeated with physiological saline solution and the pooled aspirated liquid containing the intestinal secretions was immediately mixed with phosphate buffer solution (0.1 M, pH 7.5) containing 0.2% w/v sodium azide and 10 000 U/ml of antitrypsin (Trasylol, Bayer) in a proportion of 0.1:10 ml of sample [12]. After a centrifugation at 10 000 g - 4°C for 15 min, the supernatant was placed in visking tubes (8/32) and after dialysis against two changes of 100 ml each of 0.9% NaCl solution concentrated 30-fold by dialysis against polyethylene glycol 6000 (BDH Chemicals Ltd.) solution. The concentrated intestinal secretions were centrifuged at 3000 rpm at 4°C for 5 min. The resulting supernatant was stored at -20°C until used for determining the protein content by the Lowry method, and the transferrin values by radial immunodiffusion on LC-Partigen plates (Behringwerke). Monoclonal antibody radioimmune assay (Gammadab-M J¹²¹ IgE RIA, Clinical Assays) was adopted for estimating total intestinal IgE.

Specific IgE was measured in the rectal washings to the range of allergens used in the skin tests by a double-controlled immuno-enzymatic assay. Normal controls were tested for the same allergens. The results of both serum and intestinal RAST were calculated in PRU taking 0.35 PRU/ml as the lowest positive values.

The assessment of local production of intestinal specific IgE was done according to Deuschl and Johansson [1], examining the double ratio of the concentrations of IgE antibody and transferrin between the intestinal washings and the serum:

$$\frac{\text{IgE antibody (PRU/ml) intestines/serum}}{\text{Transferrin (}\mu\text{g/ml) intestines/serum}}$$

The Platts-Mills formula of the specific activity ratio was also applied [2] dividing the ratio of intestinal specific and total IgE by the ratio of serum specific and total IgE:

$$\frac{\text{Intestinal specific IgE (PRU/ml)/intestinal total IgE (IU/ml)}}{\text{Serum specific IgE (PRU/ml)/serum total IgE (IU/ml)}}$$

The ratios greater than 1:0 indicated the local production of IgE.

Results

Eight patients had a positive skin-prick test; six to inhalant allergens and two against food allergens. Of the six patients with a positive response to inhalant allergens, four had atopic dermatitis with wheezing and two had atopic dermatitis alone, and total serum IgE was raised (>2s.d.) in twelve cases (Table 1). Specific serum IgE (>0.35 PRU/ml) were detected in fourteen patients. There were no significant differences between the two groups with atopic dermatitis (i.e. with or without wheeze). The total protein content in the intestinal washings from atopic dermatitis patients was

Table 1. Prick tests, serum and intestinal total and specific IgE in children affected by atopic dermatitis with and without wheezing

	Positive prick test			Total IgE IU/ml (> 2 s.d.)		Specific IgE (> 0.35 PRU/ml)	
	Total	Food	Inhalant	Serum	Intestine	Serum	Intestine
A.D. (eleven cases)	4	2	2	6	6	7	8
A.D. + wheezing (eight cases)	4	—	4	6	7	7	6
Total (nineteen cases)	8	2	6	12	13	14	14
Controls (ten cases)	0	0	0	0	0	0	0
				(0.94 $\pm$ 0.9) (< 0.35 PRU/ml) (< 0.35 PRU/ml) IU/ml: mean $\pm$ s.d.)			

A.D. = atopic dermatitis.

reasonably constant (1.8 ± 0.31 g %/ml) and similar to control values (1.24 ± 0.59 g %/ml). Transferrin was present in the washings from twelve out of nineteen patients, but in only one control sample. Total intestinal IgE were raised (> 2 s.d.) in thirteen patients with respect to controls (0.94 ± 0.9 IU/ml). Specific intestinal IgE were positive in fourteen (> 0.35 PRU/ml; maximum 1.87 PRU/ml, mean 0.67 ± 0.35) and negative in controls (< 0.35 PRU/ml) (Table 1).

In those children with positive prick tests, in the case of thirteen allergens both serum and intestinal specific IgE were raised; with fourteen allergens only serum specific IgE was raised; and with nine allergens only intestinal specific IgE was raised (Table 2).

In those children with negative skin tests but positive serum tests, in the case of seven allergens both serum and intestinal specific IgE were raised; with sixteen allergens only serum specific IgE was raised; and with four allergens only intestinal specific IgE was raised (Table 3).

Of the five children with negative prick tests and serum RAST, specific intestinal IgE could be detected in four of them (Table 4). Food challenge elicited a positive skin reaction to a total of six out of nine foods in three of these four children. A positive was manifest by puritus, erythema and/or macular rash within few minutes to 2 hr. Vomiting and abdominal pain were also documented in one case (Table 4).

In total, specific intestinal and serum IgE were both raised for twenty allergens (fourteen inhalants, six foods); there was a positive only intestinal response to twenty-six (three inhalant, twenty-three food); and thirty allergens (fourteen inhalant, sixteen food) that were positive in serum, were negative in the intestine (Table 5).

The double ratio, used to assess the local production of intestinal specific IgE, was applied in five patients where intestinal transferrin values were detectable and intestinal and serum specific IgE both raised.

The specific activity ratio was applied in nine cases. Positively correlated results

Table 2. 'Double ratios' and 'specific activity ratios' in A.D.-affected children with positive skin tests and serum specific IgE

Patient No.	*Positive allergens	Positive skin tests	Specific IgE (PRU/ml)		Transferrin (μ g/ml)		Total IgE (IU/ml)		'Double ratios' Intestine		'Specific activity ratios' Intestine	
			Serum	Intestine	Serum	Intestine	Serum	Intestine	Serum	Intestine	Serum	Intestine
1	<i>Lolium perenne</i> Dog epithelia Egg white β -lactoglobulin Cheese	++ ++ ++ ++ ++	14.1	1.21	3500	0	730	38			1.6	
			0.57	0.6							20.1	
			0.61	1.4							44	
			0.35	1.54							84.4	
			<0.35	0.6								
2	<i>Lolium perenne</i> <i>Phleum pratensis</i> <i>Poa pratensis</i> Sheep epithelia	++ ++ ++ ++	1.23	0.77	3400	4	23	3	532		4.8	
			2.42	0.66					231.8		2.1	
			2.5	1.05					357		3.2	
			<0.35	1.45								
3	<i>Dermatophagoides teronyssinus</i> <i>Alternaria</i> Egg white Egg yolk	++ ++ ++ ++	8.8	0.75	2900	10	353	39	24.7		0.8	
			3.3	0.66					58		1.8	
			<0.35	0.79								
			0.39	<0.35								
			<0.35	0.35								
4	<i>Parietaria off.</i> Egg white Tomato Potato	++ ++ ++ ++	0.94	<0.35	3400	10	164	1				
			<0.35	0.48								
			<0.35	0.55								
			<0.35	0.52								
11	<i>Phleum pratensis</i> <i>Parietaria off.</i> Egg white Tomato	++ ++ ++ ++	11	<0.35	2900	120	140	144				
			4.4	<0.35								
			0.44	<0.35								
			<0.35	0.81								
14	<i>Phleum pratensis</i> Tomato Potato	++ ++ ++	0.41	<0.35	3400	64	104	0.5				
			2.97	<0.35								
			0.41	<0.35								
16	<i>Phleum pratensis</i> House dust <i>Dermatophagoides pteronyssinus</i> Egg white β -lactoglobulin Fish Tomato	++ ++ ++ ++ ++ ++	0.35	0.44	3400	21	67	1	203.5		84.2	
			0.39	<0.35								
			0.88	0.35								
			5.5	0.57					64.3		26.6	
			3.08	0.44					16.7		6.9	
19	<i>Cynodon dactylon</i> <i>Poa pratensis</i> House dust <i>Permatophagoides pteronyssinus</i>	++ ++ ++ ++	<0.35	0.88					128.7		53.2	
			0.74	<0.35	3000	0	362	11				
			1.32	<0.35								
			5.72	<0.35								
			17.6	<0.35								

* Positive allergens in serum and/or in intestine. The negative values in both are not reported.

Table 3. 'Double ratios' and 'specific activity ratios' in A.D.-affected children with serum positive specific IgE and negative skin tests

Patient No.	*Positive allergens	Specific IgE (PRU/ml)		Transferrin (μ g/ml)		Total IgE (IU/ml)		'Double ratios' Intestine		'Specific activity ratios' Intestine	
		Serum	Intestine	Serum	Intestine	Serum	Intestine	Serum	Intestine	Serum	Intestine
8	<i>Dermatophagoides pteronyssinus</i>	11	0.35	3400	0	160	16				0.31
	<i>Alternaria t.</i>	7.7	<0.35								
	β -lactoglobulin	0.35	<0.35								
	Casein	<0.35	0.4								
9	<i>Poa pratensis</i>	2.3	0.35	3200	0	117	0.6				29.7
	α -lactalbumin	0.35	<0.35								
	β -lactoglobulin	0.35	<0.35								
	Tomato	<0.35	0.52								
10	<i>Dermatophagoides pteronyssinus</i>	11	0.97	3400	85	16	14	3.52			0.1
	Egg white	1.2	<0.35								
	Egg yolk	<0.35	0.44								
	β -lactoglobulin	<0.35	0.44								
	Fish	0.44	0.7							63.6	1.8
	Tomato	0.79	0.75							37.9	1.1
15	<i>Phleum pratensis</i>	1.98	0.63	2800	120	14	3.5	7.4			1.27
	<i>Dermatophagoides pteronyssinus</i>	0.44	<0.35								
	<i>Candida alba</i>	1.1	0.35								
	Egg white	0.44	<0.35								
	α -lactalbumin	0.35	<0.35							7.4	1.28
17	<i>Lolium perenne</i>	1.2	<0.35	3500	0	443	29.8				
	House dust	13.2	<0.35								
	<i>Dermatophagoides pteronyssinus</i>	17.5	<0.35								
	Egg white	1.32	<0.35								
	Tomato	0.44	<0.35								
18	Egg white	0.44	<0.35	3200	0	201	34				
	Egg yolk	0.7	<0.35								
	Tomato	0.35	<0.35								

* Positive allergens in serum and/or in intestine. The negative values in both are not reported.

Table 4. Food challenge in A.D.-affected children with intestinal positive specific IgE and negative prick test and serum RAST

Patient	*Positive allergens	Specific IgE (PRU/ml) Intestine	Transferrin (μ g/ml) Intestine	Total IgE (IU/ml) Intestine	Food challenge	Symptoms elicited
6	Egg white	0.66	15.5	9	*+	Cutaneous
	Egg yolk	0.77			*+	
	α -lactalbumin	1.1			*+	
	β -lactoglobulin	0.55			*+	Cutaneous and gastrointestinal
	Casein	1.87			*+	
	Cheese	0.55			*+	Cutaneous
7	<i>Dermatophagoides pteronyssinus</i>	0.59	33	14		
	Egg white	0.35			*+	Cutaneous
	Chicken	0.66			*+	Cutaneous
12	Tomato	0.41	—	1	—	
13	Egg white	0.35	64	0.5	*—	
	Cheese	0.35			*+	Cutaneous
	Tomato	0.35			*—	

* The negative values in intestine are not reported.

Table 5. RAST results in serum and rectal washings using inhalant and food allergens

	Positive only in serum	Positive RAST only in intestine	RAST concordantly positive in serum and in intestine
Inhalant allergens	14	3	14
Food allergens	16	23	6
Total	30	26	20

(ratio > 1) were obtained for all food allergens (four out of four) and eight out of ten inhalants in the five cases (Nos. 2,3,16: Table 2; Nos. 10,15: Table 3), where both formulas were evaluated. In the other three cases, where only the specific activity ratio could be calculated (No. 1: Table 2; Nos. 8,9: Table 3) two out of two food allergens and three out of four inhalants gave a positive ratio.

Discussion

Sixty-eight per cent of our patients had higher total IgE levels in their rectal washings than controls and this agrees with the findings in various mucosal surfaces of allergy patients reported by other investigators [20–23].

IgE determination by the competitive monoclonal antibody radioimmune assay, like the radioimmunosorbent test (RIST) [12] allowed us to detect both digested and

undigested intact 1/2 FcE₁-bearing IgE molecules. Unlike IgA, IgE has no secretory component and can easily be digested by proteolytic enzymes in secretions.

Specific IgE to foods and inhalants were detected in rectal washings of a high number of patients (74%), including the four with negative serum RAST and skin tests. Our data, therefore, agrees with the reports on specific IgE in nasal washings and tears of patients with negative serum RAST and skin tests [22,24], supported by specific provocation tests [25,26].

The high number of inhalant allergens found in intestinal washings, often in concordance with serum RAST and skin tests, may be explained in two ways: firstly, by the deposition of the inhalants in oropharynx and successive passage into the gastrointestinal tract [27]; and secondly, that the gut and bronchus associated lymphoid tissues are two functionally united systems [28].

The reliability of our data was supported by the high number of allergens which were positive in both the results of the intestine and serum, as well as the prick test, and by the absence of specific IgE in controls.

The response of four patients, positive for specific intestinal IgE but negative for both serum RAST and skin test, to food challenge further confirmed the specificity of the results. Moreover, in the two patients (Nos. 1 & 2) whose parents had reported a clear causal relationship between the appearance of skin rash and wheezing and contact with wool or dog epithelium, the specific IgE values for these allergens were higher in intestinal washing than serum. Confirmation of this association was obtained by double-exposing these children to the antigens in question at an interval of 2 weeks and on both occasions and in both cases obtained a respiratory symptomatology characterized by wheezing accompanied by a significant reduction of PEFR, as well as an immediate skin rash in case No. 2.

The absence of specific intestinal IgE in some patients with a positive specific serum IgE response to foods and inhalants may be caused by a more rapid clearance of IgE from the intestine than from the serum.

The prick test to inhalant allergens was significantly positive, particularly in subjects who wheezed. However, the data obtained in the two pure atopic eczema patients with a positive reaction to inhalants (Nos. 3,4) support the causal role for such allergens in atopic dermatitis proposed by Ohman and Johansson [29] and Chapman *et al.* [30].

The surprisingly high specific serum IgE levels revealed in skin test negative subjects (Nos. 8,10,17) is probably because of their particularly young age.

Despite the fact that immunohistochemical studies on IgE in intestinal mucosa surface have so far proved to be conflicting [13,14,31], we attempted to assess the local production of these antibodies by the double ratio method and the specific activity ratio. The positive correlation (ratio > 1) with both formulae for twelve out of fourteen allergens tested and the general good agreement between the two methods, suggest that locally produced antibodies were mainly responsible for the RAST values, although very low intestinal PRU levels were registered for some allergens in three cases. The markedly higher double ratio values with respect to the specific activity ratio could be due to either false low transferrin values caused by enzymatic degradation of the transferrin antigenic component, or to greater total than specific levels of intestinal IgE being detected. In fact, provided that the digested molecules bear 1/2 Fc E₁ they can be detected by RIA, whereas, because both and Fc and a FAB determinant are required for RAST, only more or less intact immunoglobulin E can be revealed by this method.

Although we cannot attribute any diagnostic value to our data, they do suggest that the mucosa-associated lymphoid tissue may play an important role in the pathogenesis of atopic disorders. The lack of transferrin in almost all normal controls is interesting in this respect, as it supports the concept of a major serum leakage from patients intestinal mucosa, probably due to the presence of an inflammatory bowel reaction.

Such a finding agrees well with the presence of IgE in the intestines. Animal studies [32,33] have demonstrated that over-production of IgE may act on intestinal mast cells and, although these degranulate with great difficulty [34], they induce a mediator release that is responsible for the persisting mucosa permeability to the allergens. Further studies on mucosa permeability and on the response of other immunoglobulin classes to specific antigenic stimuli are now required to better define the role of mucosa surface-associated lymphoid tissue in atopic diseases.

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