

ARE LOW LEVELS OF SPECIFIC IGE USEFUL IN DIAGNOSING CLINICALLY RELEVANT FOOD SENSITIZATION?

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INTRODUCTION

The ability to detect low levels of specific IgE using Immunocap Phadia® (formerly Pharmacia®) has been shown recently to be feasible (lower limit: 0.10 kU/l). After taking account of variability, the clinically significant threshold now proposed is 0.17 kU/l. Allergists must now question the benefit of this increased sensitivity when screening for food allergy (FA). In short, is a low level of specific IgE (0.17 to 0.35kU/l) clinically relevant? If this is the case, it will be necessary to study this level in the context of positive diagnoses, and differential ones (to rule out FA). It will also be necessary to discover whether it improves predicting recovery from FA. To answer the first question concerning clinical relevance, we present here a retrospective study of data collected by the Circle of Clinical and Biological Investigations in Food Allergy (CICBAA).

Method

The CICBAA data base records all cases of confirmed food allergies (FA), including data on prick-in-prick tests, atopy patch-tests, biological tests (Pharmacia-Phadia®: Immuno-Cap System) and oral challenges double blind or simple blind placebo controlled food challenges: DB or SBPCFC. We identified cases of FA, confirmed by positive DBPCFC: 95 FA to cow's milk, 154 to egg and 156 to peanut. Of these, 74 FA to milk, 138 FA to egg and 146 FA to peanut had undergone a specific IgE assay.

Results

5.4%, 3.6%, 2.7% of cases of milk, egg and peanut allergies had an IgE level below 0.35 kU/l: four cases

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of cow's milk allergy, five egg allergy, four peanut allergy (tables 1 and 2).

Three of four patients with allergy to cow milk protein were under one year of age. Patients with egg allergy were older: three between one and three years, one between three and six years, and one older child. The age profile was identical for peanut allergy: three children between one and three years and one older child (table 2). Only one case concerned an adult who was allergic to milk.

Ten of 14 presented with atopic dermatitis (AD), either isolated (1) or associated with gastrointestinal disorders (3), or with urticaria (3) or asthma (2). There was one case of anaphylactic shock to egg.

Prick-tests were positive in seven of 14 cases. Eight children were negative to labial challenge carried out before oral food challenge.

Nothing particular was noted for these children with regard to cumulative doses, which ranged from 100 mg to 7110 mg for egg and peanut, and from 6 ml to 1000 ml for milk (1000 ml corresponds to the cumulative intake for two days of bottle feeding.)

However, the reactions in ten children with AD were stereotypic: one presented with rash on eczema in the hours following oral food challenge, nine had a delayed-onset of exacerbated eczema, after 24 hours. The child under three years who suffered anaphylactic shock with egg, reacted immediately to 100 mg of egg-white, with vomiting, moderate tachycardia (no change in blood pressure; tachycardia may have been caused by vomiting).

Food allergies	n	Specific IgE	
		0.35 to 0.70 kU/l (%)	< 0.35 kU/l (%)
Milk	74	22.9	5.4
Egg	138	14.5	3.6
Peanut	146	4.7	2.7

Table 1: Specific IgE levels (%) for 358 cases of FA.

DISCUSSION

Currently, the diagnosis of FA is based on two steps. The first identifies sensitization by prick-tests and screening for specific IgE. Recently, atopy patch-tests have been proposed as complementary tests. It has been shown that although these are often positive in the presence of IgE-mediated sensitization, isolated positive patch-tests characterize only 7% of all FA (1). The second step uses DBPCFC (2). At present, two points are of particular interest. First, can FA be predicted from the size of the prick-test wheals and the levels of specific IgE? If so, DBPCFC would no longer be needed. Second, can the severity of later allergic reactions be estimated from skin tests and RAST? Several studies have tried to propose both positive and negative predictive values (3-6). However, these values are influenced by the allergen and the population.

In this series, we had a child who suffered anaphylactic shock to egg with specific IgE below 0.35 kU/l and an immediate reaction to a low dose (100 mg) during food challenge. Prick-tests were positive for 50% of subjects; whereas specific IgE levels were below 0.35 kU/l. The better sensitivity of prick-tests has been reported (7). However no prick-test re-

acted the positive predictive value defined by Hill (8 mm). A more sensitive assay of specific IgE would therefore be of great interest.

In proven FA, confirmed by DBPCFC, the number of patients with possible specific IgE levels between 0.17 and 0.35 kU/l is certainly very low. Figures could correspond to low levels of specific IgE between 0.35 and 0.17 kU/l (using the new technique) or to negative RAST (less than 0.17 kU/L). It would therefore be a maximum of 5.4% for milk, 3.6% for egg and 2.7% for peanut. According to a recent study by Desai in Chicago and presented in a poster at the AAAAI Meeting in Miami (March 2006), levels could reach 6%, 14%, and 25%.

Oral food challenge triggered a delayed-onset exacerbation of eczema after 24 hours. These results differ from those of Desai et al., who reported that reactions to food challenges were mainly immediate, with 22% requiring epinephrine (8).

Ten out of 14 patients with specific IgEs below 0.35 kU/l had atopic dermatitis. So it is not surprising that only half of the cases had positive prick-tests. A delayed type of food hypersensitivity may be postulated. Atopy patch-tests had not been carried out.

Food	Sex	Age	Clinical features	Prick-test (mm)*	CRD on SBPCFC/DBPCFC	Symptoms elicited by SBPCFC/DBPCFC
Milk						
	M	<1 year	AD+ GI S	2mm N	50 ml	EE
	M	<1 year	AD+ GI S	2mm N	6 ml	EE
	F	<6 months	AD	0 N	1000 ml	EE
	F	15-30 years		0 N	300 ml	asthenia, bloating
Egg						
	F	1-3 years	Anaphylactic shock	2 mm P pos(=cod)*	100 mg	vomiting + tachycardia
	M	1-3 years	AD +Urt+Asth	6 mm P	320 mg	rash
	M	6-15	AD+Asth	4 mm P	7110	EE
	M	1-3 years	AD	0 neg	7110mg	eczema
	F	3-6 years	Urt+AO	5 mm P	965 mg	rash
Peanut						
	M	1-3 years	AD+GI S	2 mm N	965 mg	EE
	F	1-3 years	AD	2 mm P (=cod)	7110 mg	EE
	F	6-15 years	AD + Urt	5 mm P	7110 mg	rash + EE
	M	1-3 years	AD	4 mm P	965 mg	EE

Table 2: Cases of FA with specific IgE less than 0.35 kU/L.

Legend: CRD: cumulative reactive dose - SBPCFC/DBPCFC: single-blind oral food challenge/double-blind oral food challenge - AD: atopic dermatitis - GI S: gastro-intestinal symptoms - urt: urticaria - asth: asthma - AO: angio-edema - EE: exacerbation of eczema.

* The criteria for positivity is currently 3 mm.

In young children with a codeine control inferior to 3 mm, the positivity is estimated for a size of the test equal to the size of codeine control.

CONCLUSION

More sensitive methods for detecting specific IgE at a threshold of 0.17 kU/L might have improved the diagnosis in 14 out of 358 cases, i.e. in at most 3.9% of cases (by assuming that levels under 0.35 were over 0.17 kU/L).

As far as we know, a level of 1.5 kU/l anti-CM IgE is good predictor of allergy to cow's milk in children between 13-18 months (9). It is likely that the increased sensitivity of the Immunocap technique from Phadia will improve the diagnosis of CMA in infants under one year of age, and specially in those under six months, inasmuch as most cases of CMA in infants occur between two and four months. In these young infants, prick-tests may be negative, oral challenges are uncommon, biological tests for specific IgEs are negative, and most often, the diagnosis of CMA is only proved when the milk formula has been replaced by casein hydrolysate. However, in certain cases a diagnosis is not obtained because a partial milk hydrolysate has been prescribed and the child is allergic to it. In such cases symptoms, either digestive or cutaneous, are unchanged over several months.

As well as improving diagnosis, the new technique could help to rule out suspected CMA, giving a better negative predictive value. At present, an IgE level below 0.35 kU/l in infants of mean age 6.5 months corresponds to a negative predictive value of 81% (9). This is insufficient for clinical practice.

No such specific data have been obtained in the case of egg allergy (10).

A third consideration is the possibility of predicting recovery from FA. At present, recovery seems to be more likely after the rapid decrease in specific IgE bet-

ween two assays than from the absolute level of specific IgE (3-6, 9). It now seems necessary to try the new technique for predicting recovery from allergy to milk and egg.

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