

CORRESPONDENCE

Egg allergy: the relevance of molecular-based allergy diagnostics

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Hen's egg allergy (HEA) accounts for most of the diagnosed allergy to foods, mainly in the first years of life, as its prevalence ranges between 1.6% and 8% [1]. Thus, HEA represents a relevant issue for the paediatrician. Moreover, HEA can cause severe anaphylaxis [2]. HEA management is based essentially on strict avoidance and rescue medication prescription [3]. On the other hand, accidental ingestion may occur and strict avoidance is difficult to be maintained in the course of time. For these reasons, strategies able to induce immunologic tolerance to food have been developed. Oral immunotherapy (OIT) for HEA has been used with interesting outcome [4, 5]. However, safety perspective represents a relevant concern, because reactions to OIT may affect up to 100% of treated children [3–5]. Therefore, defining potential biomarker predicting safety of OIT should be a relevant target. In this regard, Vazquez-Ortiz and colleagues performed a relevant study from a practical point of view [6]. In fact, they demonstrated that allergen-specific IgE (sIgE) showed excellent performance in predicting belonging to resolved reactions phenotype, such as the subgroup that better tolerated OIT. In particular, levels above the optimal cut-off (ovomucoid-sIgE 8.85 kU_A/L) indicated 95% probability of early discontinuation or ongoing reactions over time.

On the other hand, molecular-based allergy diagnostics have been recently available in the clinical practice [7]. This method allows to define and to characterize the sensitization profile, so identifying potential dangerous proteins and suggesting a more precise prognosis [7]. D'Urbano and colleagues reported that protein microarray had a good ability to predict food challenge test results [8]. In particular, sIgE to Gal d 1 was the best predictor for FCT positivity.

It is well known that egg contains 24 proteins, including ovomucoid, ovalbumin, conalbumin, and lysozyme, identified as major egg allergens [3]. Ovomucoid (Gal d 1) sensitization characterized patients less likely to outgrow their HEA [9]. Ovalbumin (Gal d 2) is the most abundant protein in egg white, and sensitization to Gal d 2 is associated with tolerance to well-cooked egg, as it is thermolabile [10]. Conalbumin (Gal

d 3) is a thermolabile protein associated with allergic reaction after ingestion of raw egg. Chicken serum albumin (Gal d 5) has a role in the bird-egg syndrome, as it is present in chicken feathers, meat, and egg [11].

Ando and colleagues defined a positive decision point, based on 95% clinical specificity, 7.4 kU_A/L of Gal d 1 that was useful in the diagnosis of allergy to raw egg white, whereas for the heated egg white, the cut-off was 10.8 kU_A/L [12].

As the study of Vazquez-Ortiz did not consider the molecular profile of egg-allergic children, we believe that it could be interesting to evaluate also the sensitization profile in children with HEA. In this regard, we retrospectively considered a group of children visited in the last year at the Istituto Giannina Gaslini, a third-level children hospital. We subdivided the patients in two groups on the basis of the history of anaphylaxis after ingestion of egg. Diagnosis of egg anaphylaxis was based on validated criteria [2] such as (i) suggestive clinical history, (ii) allergen-specific IgE detection for suspected food, and (iii) symptoms consistent with sensitization, that is, the demonstration of a cause/effect dependence between ingestion of sensitizing food allergen and occurrence of anaphylaxis clinical features (*post hoc ergo propter hoc*). HEA diagnosis was performed on suggestive history, documented egg sensitization, and food challenge test. Specific IgE to raw egg allergens, such as egg white and egg yolk, was measured by ImmunoCAP method (Thermo Fisher, Milan, Italy). Specific IgE to molecular component of egg, such as Gal d 1, Gal d 2, Gal d 3, and Gal d 5, was assayed by the semiquantitative ISAC method (Thermo Fisher).

Globally, 54 patients were visited: 17 with anaphylaxis and 37 with HEA. The Table 1 shows clinical and immunologic characteristics of the two groups. The age (at the visit) was significantly lower in anaphylaxis group. Specific IgE levels to raw egg allergens (white and yolk) were significantly higher in anaphylaxis group. Similarly, children with anaphylaxis had higher IgE levels to Gal d 1 and Gal d 2 than HEA children. On the other hand, median values of IgE to Gal d 3 and Gal d 5 were under the positivity; thus, the significant difference between groups for Gal d 5 was without clinical relevance.

Receiver operating characteristic analysis showed that egg white ImmunoCAP had a very good sensitivity

Table 1. Clinical and immunological characteristics of patients with or not anaphylaxis.

	Anaphylaxis: yes Median (1st–3rd q)	Anaphylaxis: no Median (1st–3rd q)	P	Cut-off*	AUC	TP/Ana+	TN/Ana–	Sensitivity %	Specificity %
Age (months)	10 (6–15)	35.4 (22.1–94.9)	< 0.0001						
Total IgE (kU/L)	942 (578–2010)	259 (134–1371)	0.06						
Egg white (kU _A /L)	20.3 (3.3–70.5)	3.1 (0.9–10.6)	0.04	> 0.97	0.70	14/14	12/33	100	36.4
Egg yolk (kU _A /L)	4.7 (1–42.8)	0.9 (0.3–9.4)	0.04	> 0.46	0.70	11/12	16/33	94.4	59.3
Gal d 1 (ISU)	1.3 (0.1–5.6)	0.2 (0.2–0.5)	0.44	> 1	0.56	10/16	30/37	62.5	81.1
Gal d 2 (ISU)	1 (0.6–4)	0.2 (0.2–0.5)	0.02	> 0.5	0.70	12/15	28/37	80.0	75.7
Gal d 1 or Gal d 2						14/15	28/37	93.3	75.7
Gal d 3 (ISU)	0.1 (0.1–1.4)	0.2 (0.2–0.5)	0.09	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Gal d 5 (ISU)	0.1 (0.1–0.1)	0.2 (0.2–0.2)	< 0.0001	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

*Cut-off values were determined by means of the ROC curve analysis.

P, P-values refer to the Mann–Whitney U-test; TP, true positive; Ana+, anaphylaxis: yes; TN, true negative; Ana–, anaphylaxis: no.

(100%), but weak specificity (36.4%). Also egg yolk ImmunoCAP had a good sensitivity (94.4%), but weak specificity (59.3%). Gal d 1 ISAC cut-off > 1 ISU had good specificity (81.1%), but weak sensitivity (62.5%), as well as Gal d 2 ISAC cut-off > 0.5 ISU had 75.7% of specificity and 80% of sensitivity. Considering Gal d 1 and Gal d 2 together, the sensitivity improved up to 93.3%.

Therefore, we believe that molecular-based allergy diagnostic should be performed in children with HEA, mainly with anaphylaxis, for better defining the

sensitization profile and improving the prognosis and the management of HEA children.

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