

Letter to the editor

IgE antibody in the serum – The main problem is cross-reactivity

I read with great interest the review by Dolen about immunoglobulin E (IgE) antibody in the serum (1). Albeit already published for the most part (2), this paper clearly delineates the use and limits of serum specific IgE (sIgE) measurements as a diagnostic tool. It timely recalls that one must not interpret any sIgE result independently of the whole clinical picture and that a quantitative sIgE result cannot give the probability of allergic symptoms in most cases, contrary to recent suggestions (3–5).

Many drawbacks limit the meaning of quantitative sIgE results, especially cross-reactions. The extent of these cross-reactions is much larger than the cross-reactive carbohydrate determinants (CCD) highlighted by Dolen: a wide array of peptide homologies have been demonstrated too, leading to a classification of allergens into molecular families and to the understanding of many clinical allergic associations (6).

What is basically different between *in vitro* cross-reactions and a clinical

cross-reactivity? During a sIgE assay, serum IgE molecules are free: they can bind to all available (and compatible) epitopes. This binding is monovalent and each IgE molecule bound to one epitope generates a signal in the assay cup. This is valid for genuine as well as for cross-reacting epitopes. But once linked to their target cells (e.g. mast cells), IgE are no longer free to move and they must locally cooperate to lead to a degranulation: thus (at least) two adjacent IgE molecules must simultaneously bind to adjacent epitopes on a single allergen molecule. As a result, compatible epitopes should be on the same side of the allergen, at the right distance from each other, etc. This would not matter if the presence of repeated identical epitopes along the allergen was the rule. But this is the opposite: three-dimensional strictly identical epitopes are probably extremely rare, if any exist. So, adjacent IgE must be 'different' (exhibit different specificities) to obtain a degranulation. Whatever the level of sensitization, a clin-

ical response (e.g. a positive skin test) is thus always more difficult but more specific than a positive serum sIgE reaction.

When the reaction implies a cross-reactive allergen/epitope, the situation is further complicated: two different but cross-reactive IgE molecules must simultaneously bind to the cross-reactive allergen. One can easily understand as to why cross-reactions are far more frequent during serum sIgE assays than in cell-based situations (clinical reactions, challenges, skin tests, and even *ex vivo* tests with basophils).

Compared with skin tests, serum sIgE assays thus lack specificity. In daily practice, they are more reproducible, however.

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References

1. DOLEN WK. IgE antibody in the serum – detection and diagnostic significance. *Allergy* 2003;**58**:717–723.
2. DOLEN WK. Skin testing and immunoassays for allergen-specific IgE. *Clin Rev Allergy Immunol* 2001;**21**:229–239.
3. AHLSTEDT S. Understanding the usefulness of specific IgE blood tests in allergy. *Clin Exp Allergy* 2002;**32**:11–16.
4. SAMPSON HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;**107**:891–896.
5. SÖDERSTÖRM L, KOBER A, AHLSTEDT S, et al. A further evaluation of the clinical use of specific IgE antibody testing in allergic diseases. *Allergy* 2003;**58**:921–928.
6. STEINMAN HA, Lee S. Concomitant clinical sensitivity and cross-reactivity. *Allergy Clin Immunol Int* 2003;**15**:18–29.

Reply to letter from Dr Malandain

As physicians, we should be disturbed by a tendency, increasingly seen in modern medicine, to rely more on results of laboratory tests than on a skillful assessment performed by a trained, experienced clinician. However, a recent article by Williams et al. (1) affirms the concept that history and examination alone will not successfully distinguish those patients with IgE-mediated allergic sensitization from those who do not have sensitization. Thus, carefully performed allergy testing is essential for a complete diagnosis, and allergists need to be experts on the relative advantages and pitfalls of the different testing methods.

Certainly if an IgE antibody nonspecifically binds to an immunoassay solid phase, or specifically binds (perhaps with low affinity) to a cross-reacting epitope,

the outcome will be a test result reported as positive – that is, IgE detected. Dr Malandain clearly describes a mechanism by which a specific IgE immunoassay might (on the basis of *in vitro* crossreactivity) report a positive result when skin testing is negative. It is not clear how commonly this phenomenon occurs in clinical medicine, so it would be interesting to design a method for detecting such cross reactions when they occur, and then to determine their prevalence. For sure, the field of medical informatics will help us understand practical aspects of crossreactivity in a meaningful way, but developing an evidence-based database at the epitope level for all allergens will be an enormous task.

Two statements quoted by Cohen in a review article on skin testing apply also to specific IgE immunoassays: 'Skin testing,

aimless, excessive, and misunderstood, has done more than its share in bringing allergy into disrepute,' and 'We permitted entrance into the field of some men who took the attitude that allergy consisted of needles, syringes, and a patient's extremity; men who failed to appreciate the fact that to first know allergy one must first know medicine.'(2).

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References

1. WILLIAMS PB, AHLSTEDT S, BARNES JH, SODERSTROM L, PORTNOY J. Are our impressions of allergy test performances correct? *Ann Allergy Asthm Immunol* 2003;**91**:26–33.
2. COHEN SG, KING JR. Skin tests: a historic trail. In: DOLEN WK, editor. *Skin Testing, Immunol Allergy Clin NA*. Philadelphia: WB Saunders, May 2001.