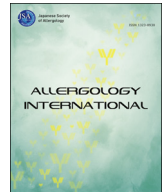




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Letter to the Editor

Par j 2 IgE measurement for distinguishing between sensitization and allergy

Dear Editor,

Allergic rhinitis is characterized by IgE-mediated allergic inflammation consequent to the contact between IgE and allergen.¹ IgE may be considered the hallmark of allergy, as IgE negativity excludes the allergic causality. However, IgE positivity may mean both mere sensitization and true allergy. Sensitization is documented by the presence of allergen-specific IgE in the serum or by positive skin prick test. Conversely, allergy is demonstrated by the correspondence between proved sensitization and symptom occurrence after exposure to the sensitizing allergen. Unfortunately, many people consider a positive test as an evidence of allergy. Moreover, poly-sensitization, such as sensitization to two or more allergens, is very common: up to 80% of allergic patients.² This phenomenon has clinical implications mainly concerning allergen immunotherapy (AIT), as there are allergists who prefer to not prescribe AIT in poly-sensitized patients. However, it has been demonstrated that poly-sensitization should not be considered an obstacle for AIT, as it is effective also in such patients.³ As a consequence, it is crucial to distinguish sensitization from allergy, mainly in poly-sensitized patients. For this purpose, a cause-effect link between IgE evidence and clinical feature should be demonstrated, but it is not always easy to differentiate sensitization from allergy: for example the pollination periods of different pollen species may frequently overlap. Previously, it has been reported that serum allergen-specific IgE measurement is better than skin prick test in managing poly-sensitized patients.⁴ Serum IgE assessment is a standardized quantitative measurement that is commonly used in the allergy practice. In addition, molecular-based allergy diagnostics allows to precisely define and to characterize the sensitization profile in order to define AIT prescription.⁵ In fact, positivity to major allergens excludes false reactivity to pan-allergens. Parietaria allergy is the most common in our area. Par j 2 is a lipid transfer protein (LTP) that usually does not cross-react with other LTP, such as Pru p 3. Par j 2 is the genuine and major molecule of Parietaria judaica family allergens.⁶ Therefore, Par j 2 positivity confirms true sensitization to Parietaria.

This retrospective study aimed to evaluate whether the serum IgE to Par j 2 assessment could differentiate between sensitization and allergy in a group of 101 subjects (51 females, mean age 43 years) with serum IgE positivity only to Par j 2, such as >0.35 kUA/L, and history of nasal symptoms, including itching, sneezing, watery rhinorrhea, and nasal obstruction. The study was performed according to the Review Board rules.

Patients were subdivided in two groups: sensitized subjects (without symptoms after exposure to *Parietaria* pollen) and allergic patients (with symptoms occurring after *Parietaria* pollen inhalation). The *Parietaria* pollen season usually has two periods: from April till June and from September till October in our geographic area.

Serum levels of specific IgE were detected by the IFMA procedure (ImmunoCAP Thermo Fisher Scientific, Uppsala, Sweden) in peripheral blood samples from patients. Serum was collected into gel-separator tubes, centrifuged and stored at -20°C until analysis for Par j 2. Measurement of circulating specific IgE antibodies was performed according to manufacturer's instructions.⁷ Specific Ig E concentrations were expressed in kUA/L according to the traceable calibration to the 2nd IRP WHO for Human IgE and 0.35 kUA/L has been considered as a cut-off.⁸

Medians (md), and percentiles (25th and 75th, IQR) were used as descriptive statistics. The non parametric Wilcoxon's test was used to compare samples. In addition, a receiver operating characteristic (ROC) curve analysis was performed in order to determine a cut-off for sIgE that could optimize both the sensitivity and the specificity of the test, for predicting the probability for true allergy, such as symptoms occurrence after *Parietaria* pollen inhalation in relation to specific immunoglobulin E (sIgE) levels. A p-value ≤ 0.05 was considered statistically significant. All data were analyzed using the Stata statistical package, Release 13.1 Statistical Software. (StataCorp, College Station, TX, USA).

Fig. 1 shows the main findings. Firstly, 71 patients were allergic, whereas 30 were only sensitized. Par j 2 IgE were significantly ($p < 0.0001$) higher in allergic patients (md 24.2 kUA/L; IQR = 16.1–61.2 kUA/L) than in sensitized subjects (md = 2.9 kUA/L; IQR = 1.4–5.9 kUA/L). ROC methodology pointed out a high overall accuracy for Par j 2 IgE (AUC = 0.93, 95% C.I. = 0.86–0.97). On the basis of Youden Index, a cut-off value was estimated: >6.52 kUA/L (sensitivity 100%, specificity 86.7%). The PPV was 94.7 and NPV 100.

The diagnosis of allergic rhinitis is based on the concordance between history of typical nasal symptoms and documented sensitization, such as the demonstration of the consistency between the exposure to sensitizing allergen and the resulting symptom occurrence.^{9,10} Sensitization may be documented by SPT and/or serum IgE assay. However, there may be an overlapping concerning the pollination period so it is difficult to differentiate the most relevant allergen on the basis of symptom period. Therefore, there is the need to have the possibility of easily distinguish between sensitization and allergy, mainly in particular context such as poly-sensitization or presence of confounding factors (overlapped pollen seasons).

This study showed that more than 2/3 of considered subjects was allergic to *Parietaria* pollens, so it confirms the concept that not

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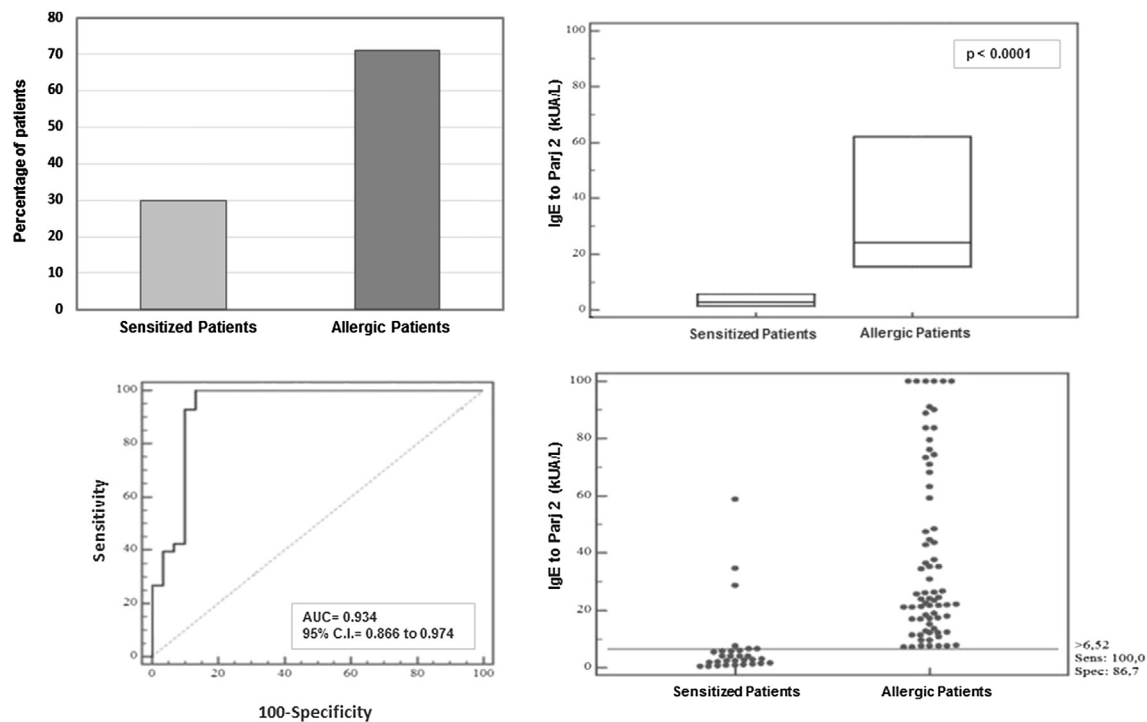


Fig. 1. Upper left quadrant = percentages of sensitized subjects and allergic patients to Parietaria 2. Upper right quadrant = serum IgE to Parietaria 2 levels in sensitized subjects and allergic patients. Lower left quadrant = ROC curve to define cut-off level. Lower right quadrant = distribution of IgE levels to define cut-off level.

necessarily all sensitized subjects are really allergic. In effect, there was a significant difference of serum Parietaria 2 IgE levels between allergic patients and sensitized subjects. The statistical analysis defined a reliable cut-off able to predict Parietaria allergy: >6.52 kU/L. Therefore, serum specific-IgE measurement might significantly improve the diagnostic capability of the clinician, even though the main limitations of this study were that: it was cross-sectional, we included only patients with mono-positivity IgE, thus excluding patients with local allergic rhinitis and/or poly-sensitization, we did not evaluated also Parietaria 1, the other major component of Parietaria, as this molecule was not available in our lab.

However, these findings support the relevance of serum IgE measurement as it is a precise and quantitative methods to evaluate IgE and may be useful in the allergy workup.

In conclusion, serum Parietaria 2 IgE measurement is a precise and quantitative method to evaluate IgE, and may be useful in the allergy workup, as could differentiate sensitization from allergy in subjects sensitized to Parietaria pollen.

Conflict of interest

The authors have no conflict of interest to declare.

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