

Quantitative aspect of specific IgE levels

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SUMMARY

Quantitation of specific IgE antibodies can be performed in a few systems available on the market. Such quantitative results enable evaluation and prediction of clinical allergic reactions and improved patient management. Requirements for quantitation of IgE antibodies are given.

KEY-WORDS: IgE antibodies. – Predictive value. – Quantitation methods.

RÉSUMÉ

Intérêt des dosages quantitatifs des IgE spécifiques. – Très peu de systèmes de dosages des IgE spécifiques sont capables de produire des résultats quantitatifs. De tels résultats quantitatifs permettent l'évaluation et la prédiction des réactions cliniques allergiques et contribuent à améliorer la prise en charge des patients. Cet article décrit les exigences requises pour des dosages quantitatifs d'IgE.

MOTS-CLÉS: Immunoglobuline E. – Valeur prédictive. – Méthodes de dosage.

INTRODUCTION

There is a vast experience with IgE antibody determinations *in vitro* as a measure of allergen sensitization of allergic patients. The relation to clinical disease of the presence of such IgE antibodies has been appreciated during the years [1], in particular converting the old paper disc RAST technology to modern Immuno CAP technology with significantly higher sensitivity [2, 3]. Using good allergen extracts the Pharmacia CAP System has been found to correlate exactly to quantitative skin testing [4]. However, reports of the levels of specific IgE antibodies are mostly given as posi-

tive (above cut-off of 0.35 kU/L) or negative, and also in what is known as RAST classes. The question may be raised whether there would be advantages for management of allergic patients when using quantitation of specific IgE antibodies in particular clinical situations.

SENSITIZATION EARLY IN LIFE

The IgE antibody formation starts early in life and can often be seen before clinical symptoms have evolved. Thus IgE antibody determination can be used not only to identify the causative

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allergen for current symptoms, but also as a predictor of allergy development in individuals having risk through heredity and environmental allergen exposures. The IgE antibody specificities above 0.35 kU/L develop in a specific order and change over time. This shows food allergen specific IgE as the earliest indicator, while antibodies to inhalant allergens arrive later [5, 6]. Thus to monitor such specific IgE antibody responses over time, quantitation of the antibodies needs to be incorporated.

Early sensitization to food allergens was demonstrated as predictors for sensitization to inhalant allergens like house dust mite and to subsequent asthma like disease [7, 8]. Positive predictive value of hen's egg IgE antibodies at 6 months of age was reported to be 85 % [8]. Extended studies were performed confirming the view that hen's egg IgE antibodies are good predictors, particularly at increased levels of 2.0 kU/L at 12 months of age with subsequent sensitization to the inhalant allergen, house dust mite at 3 years of age [9]. Thus the antibodies need to be quantified to establish this different «clinical cut-off».

Degree of allergen exposure

There is a dose-response relationship between the frequency and level of sensitization and IgE antibody formation on the one hand and the amount of allergen in the environment exposed to the individual on the other. Thus if the individual has been exposed to higher allergen levels at longer times the likelihood to become sensitized increases. This principle holds true for all allergens like dust mite, cat dander although the frequency of sensitization and degree of IgE antibody formation may vary in different studies.

Amount and length of allergen exposure have important impact on the frequency of individual allergen sensitization [10]. Similar conclusion was achieved in other studies of childhood development of asthma, where allergen amounts, age of exposure and time of exposure were important in the evolving disease [11]. Using CAP-RAST classes it has been found that the asthma patients with the worse symptoms had the highest antibody levels of IgE antibodies to relevant allergens. A similar observation has been made also when using quantitation of specific IgE antibodies to grass pollens [12]. The question is thus justified to what extent quantitation of IgE antibodies would provide more information than just a yes/no or class response in the dynamic of an evolving allergic disease.

Value of allergen avoidance

Individuals not already having been sensitized may delay or decrease the magnitude of their sensitization by avoiding the allergen in question. Accordingly, attempts have been made to decrease and delay allergen sensitization by minimizing allergen exposure [13, 14]. The allergic symptoms and hyperresponsiveness in the airways also show less deterioration in an allergen free milieu.

In individuals suffering from asthma there is very good evidence that avoidance can decrease asthma symptoms and bronchial hyperresponsiveness as well as subsequent IgE antibody levels over time [15]. The IgE antibody levels will not disappear completely, however, even if they may be significantly decreased and accurate quantitation is necessary to document the changes. The most effective means to reach an efficient avoidance is to change environment, e.g. from the low, warm and humid altitude where the mites grow to cold, dry and high altitude where they do not grow, like from the low land in Italy to the Italian Alps. Since this is not possible for most people there are tools like chemicals (tannic acid, acaricides as well as mattress and pillow covers) to reduce the exposure. Such measures may also be helpful and efficient both to prevent sensitization and asthma symptoms. Since allergen minimization measures are not easily achieved, quantitation of IgE antibodies may help to document the efficacy of the measures undertaken.

Food allergens may be more difficult to avoid since they may have been mixed into the final dish as substitute or as part of the cooking procedure. Recently it was also found that in such risk individuals having IgE antibodies to food allergens, by use of mattress encasing, minimization of exposure to mite allergens from levels well above 2.0 µg/gm dust to below that level during one year time resulted in a decreased IgE antibody formation to the mite allergens from 2.5 kU/L to 0.7 kU/L [16]. Thus the antibody levels had to be quantified to appreciate the allergen avoidance effects and documenting to the patients the benefit of such many times inconvenient measures.

In children with IgE antibodies to hen's egg, the antibody levels associated with positive challenge reactions of urticaria and angioedema to reexposure was analyzed [17]. An IgE antibody level of 1.2 kU/L resulted in 92 % probability of reactions to rechallenge, whereas 0.70 kU/L gave 83 % and 0.35 kU/L 78 % probability to react with allergic reactions to oral exposure to hen's egg. This concept was extended by Sampson and collaborators [18], who calculated the threshold IgE levels

to hen's egg, cow's milk, soy, peanut, fish and wheat. They established IgE antibody level for 95 % Positive Predictive value for reactions as well as for 90 % Negative Predictive Value, clearly demonstrating a clinical benefit of having a system which can quantify the IgE antibody levels.

REQUIREMENT ON THE *IN VITRO* IgE DETERMINATION SYSTEM TO MEET THE CRITERIA OF QUANTITATION OF IgE ANTIBODIES

To enable quantitation of IgE antibodies all components in a test system have to be standardised separately and in combination. An IgE antibody assay needs to determine specifically IgE antibodies. The assay must give the same result from time to time which shall be related to reference curve. To be able to give results in true quantitative terms they need to be calibrated quantitatively against an international standard, preferably against the WHO standard. The systems shall be sensitive and have capacity enough not to get disturbed by the presence of blocking substances like antibodies of IgG class.

Allergen sources should be utilised which are representative, and which do not contain contaminating allergens or toxins of other sources. The allergen extracts must contain all important components in sufficient quantities not to get affected by the presence of high IgG antibody levels.

Variation of the relative concentrations of allergen in the test solutions can be used to shift the results from more specific and less sensitive to more sensitive and less specific [19]. Similar exercises can be undertaken with the *in vitro* tests. If carefully standardised and performed, a good

sensitivity and specificity can be obtained with the *in vitro* determination of IgE antibodies, even better than for skin tests. Variation in relation to allergen species can be seen, however [20, 22].

All *in vitro* systems are not standardized and do not possess the capacity to evaluate high levels of IgE. There must be linearity and parallel slopes between standard curve and dilution curve of the unknown serum sample; the high capacity of the systems not allowing much influence by specific IgG antibodies; and low background not being interfered by high total serum IgE levels. To achieve fully quantitative results, dilution of the test samples must be parallel to the standard curve. This is accomplished for some but not for all *in vitro* IgE antibody determination systems.

The accuracy and reproducibility of Pharmacia CAP System and UniCAP has been reported to be extraordinary [23]. Compared with other systems higher sensitivity and specificity of determination of IgE antibodies have been revealed [24]. Thus, presence of specific IgG antibodies does not seem to affect the results obtained with Pharmacia CAP System whereas other systems seemed to have insufficient allergen concentration. Further more high levels of total IgE did not affect the results in the Pharmacia CAP system whereas again it may cause elevated results in other systems. However, one should be very clear about that the variability of a certain system is influenced by the type of allergen analyzed, and concentration of antibodies in the serum sample. Such a devoid function between different systems may be easily demonstrated by allergens like Latex, where similarities between the antibody spectrum may be seen, whereas in the lower end of the concentration curve the competitor accuracy is not very good [25].

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