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EDITORIAL

What can we learn from measuring IgE to allergens and allergen components in tropical and subtropical settings in Brazil?☆

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There are few multicenter studies on patterns of allergen sensitization among patients with allergic diseases, particularly from low and middle-income countries (LMICs) in tropical and subtropical regions. Understanding patterns of sensitization are important for research and clinical practice reasons—they may help us understand differences in geographic variability in allergic diseases prevalence and severity as well as informing clinicians on which allergens and allergen components are most relevant for clinical screening of atopic patients and for immunotherapy.

The study by Aranda et al. helps fill this knowledge gap in Brazil.[1] The aim of the study was to characterize the pattern of sensitization in allergic patients treated at pediatric allergy referral centers in Brazil. The authors analyzed data from 470 children and adolescents (aged 6 months to 18 years), attending 11 allergy clinics in cities in subtropical and tropical localities across Brazil. Subjects were sampled over the period 2015–2016, a period that covered all seasons. They measured the presence of specific IgE to a wide range of allergens and allergen components using the highly standardized ImmunoCAP assay and a threshold for positivity of 0.1 KUA/L. Pediatric patients included in the survey had respiratory allergy (predominantly asthma), atopic dermatitis, or food allergy. In addition, children aged 6 years or younger with wheezing illness were included as well as asymptomatic controls with no history of allergy. They observed high rates of sensitization to any type of allergen and polysensitization (3 or more allergens) in all study groups including controls (respiratory allergy – 92.0% vs. 75.7%; atopic dermatitis – 97.1% vs. 85.9%; food allergy – 95.9% vs. 85.3%; wheezing illness – 57.6% vs. 26.3%; and controls – 70.6% vs. 45.9%). Unsurprisingly for these settings, the dominant allergens in all subject groups were dust mite allergens with significant titers among those with respiratory allergy and atopic dermatitis. Among children with a food allergy, significant geometric mean titers were also seen for cow's milk (21% sensitized) with similar titers (geometric mean $\geq$ 1.5 kUA/L) as observed for *Dermatophagoides pteronyssinus*. IgE titers for all sensitizations among wheezing infants and controls were low with geometric mean titers of 0.2 kUA/L or less.

The significance of high frequencies of sensitization with low titers is difficult to interpret especially as high rates were seen also in the control group. Low IgE titers can be clinically relevant, particularly when it is a significant proportion of total IgE but are less easy to interpret in populations exposed to endemic helminth infections which induce elevated levels of polyclonal IgE.[2] No data for total

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IgE levels were provided. Sensitization rates to *Ascaris* were high (>35% in all groups except wheezing infants, who were younger) indicating high rates of exposure to helminths in these populations. What then do these high rates of sensitization to a wide range of allergens and allergen components actually mean?

If we consider only those allergens and allergen components with geometric mean titers of specific IgE with RAST II or greater ($\geq$0.7 kUA/L) as being clinically meaningful, then a simpler pattern emerges with mite allergens being relevant for respiratory allergy; mite, dog, *Ascaris*, and shrimp for atopic dermatitis; and mite, cow epithelium and cow's milk for food allergy. In terms of allergen components, elevated geometric mean titers were observed as follows: Der p 1 and Der p 2 for respiratory allergy and atopic dermatitis; and Der p 1, Der p 2, ovalbumin, alpha-lactalbumin, beta-lactoglobulin, and casein for food allergy, all consistent with what might be expected for these allergic diseases. In clinical practice, much lower titers of specific IgE are likely to be relevant in individual patients (where sensitizations to specific allergen components or extracts constitute a high proportion of total IgE) but among children living in conditions of poverty and exposed to endemic helminths such as *Ascaris lumbricoides*, high frequencies of sensitizations to multiple allergen components are to be expected using such a low threshold for positivity.

There is extensive IgE cross-reactivity between molecules derived from *A. lumbricoides* and a wide variety of aeroallergens including dust mites.[3–5] For example, molecules such as the panallergen tropomyosin show extensive IgE cross-reactivity between helminths, arthropods (e.g. Der p 10 of *D. pteronussinus*), and crustaceans and it would be difficult to attribute the high rates of sensitization to tropomyosin, seen in the study for all groups except wheezing infants, to any particular organism. Further, helminths are known to induce IgE to carbohydrate determinants that can cross-react with serological tests for allergens and allergen components.[6] Cross-reactive carbohydrate determinants such as galactose-a1,3-galactose (alpha-gal) cause delayed allergic reactions to mammalian meat called the alpha-gal syndrome in high-income settings[7] and are associated with tick bites. The alpha-gal syndrome seems to be less relevant in LMICs where the presence and titers of anti-alpha-gal IgE are increased by *A. lumbricoides* infections.[8] Anti-alpha-gal IgE causes, for example, false-positive reactions to the cat allergen Fel d 5.[9]

The study used convenience samples of the different patient groups making it more difficult to make comparisons across the patient groups because of differences in age and potential selection biases. Further, we are not provided with information on whether the patients were derived from private or public clinics although the latter is assumed and would be expected to represent a poorer segment of the population. The study samples come from a variety of climatic settings at different latitudes within Brazil, including sub-tropical to tropical settings each of which might be expected to vary with respect to the range of allergens to which the different populations are exposed.

The range of allergens examined was clearly limited by those available from the manufacturer and is therefore heavily biased towards those most relevant in more temperate settings in Europe and North America. Thus, limited information is provided on relevant pollens that might be present in Brazil and be related to respiratory allergies or even other potential sensitizers such as biting insects that could be relevant to the skin[2] and food allergies.[8] It would have been interesting to measure the mite allergen, Der p 23, which may have a role in allergic diseases in tropical settings.[10] The study data emphasizes the dominance of mite sensitization in allergic patients (particularly among those with respiratory allergy and atopic dermatitis) as has been observed in a variety of tropical and subtropical settings.[11,12] House dust mites thrive in the high temperature and humidity of tropical regions causing high levels of allergen exposure throughout the year.[2]

Future studies on the patterns of sensitization in such Latin American settings could usefully provide data on socioeconomic and other relevant factors including endemic helminths among the population and patient samples—one might expect that data on patterns of IgE sensitizations in wealthier populations not exposed to helminths would be easier to interpret even at low titers. Future studies could expand also the range of allergens tested to include those that might be relevant in specific geo-climatic settings within Brazil.

Overall, this study provides an extremely useful reference source for clinical allergists practicing in Brazil and allergy researchers interested in patterns of allergen sensitization in the region. The study represents an excellent resource for future comparative analyses within Latin America and beyond. More work is needed to define patterns of sensitization and their role in the development of allergic diseases in the Latin American region where some of the highest rates of respiratory allergy have been reported worldwide.[13] Such studies will need to be longitudinal, where possible, and should examine the link between patterns of sensitization in early life and the later development of well-defined allergic disease outcomes in the context of relevant environmental modifiers. The present analysis provides an excellent starting point for such studies.

Conflicts of interest

The author declares no conflicts of interest.

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