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A pilot study to assess relationship between total IgE and 95% predictive decision points of food specific IgE concentration

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Summary
Background*. False positive test results in children who are tested for food allergies may lead to inappropriate dietary restrictions.* ***Objective.*** *The aim of this study was to report our experience with a 3 year-old boy, who presented with "multiple food allergies" and, however, passed the food challenges, and to review our experience regarding management of children with high specific food IgEs with high total IgE.* ***Methods****. Medical records of 16 children with food challenges were reviewed. Median age of subjects was 39 months, with a history of adverse clinical reaction to a food, a specific IgE greater than the decision point, and an elevated total serum IgE level of 500 IU, underwent challenges to the offending food.* ***Results.*** *13 out of 16 subjects were successfully re-exposed to the suspected foods and continued to tolerate these foods well.* ***Conclusion.*** *Our finding suggests a much lower clinical risk with previously defined specific IgE decision points in children with very high levels of total IgE (> 6000 IU/ml).*

The prevalence of food allergy approaches 8% in children in the United States. It poses a significant morbidity and mortality burden with 30 000 anaphylactic reactions, 2000 hospitalizations, and 200 deaths reported (1). While double-blind, placebo-controlled food challenges remain the gold standard for food-allergy diagnosis, their use is limited by the risk of severe reactions as well as time, cost, and patient anxiety. Skin testing has a high negative predictive value but a poor positive predictive value, so its use is limited (2). Elimination diets, while vital in the management of true food allergy, can have significant and sometimes devastating consequences, which underscores the need for accurate predictive tools. Daily clinical practice calls for tools in assessing the risk-benefit ratio before making recommending double-blind, placebo-controlled food challenges.
Previous investigators have attempted to investigate correlation between specific and total IgE levels (8-9). Some researchers have established 90% and 95% positive predictive values for milk, egg, peanut, and fish, and 73-74% predictive values for wheat and soy that serve as decision points (3-7).
The utility of these values in a population with markedly elevated serum IgE is not clear, which poses a clinical dilemma. Purpose of our study was to investigate if very high level affects previously established predictive decision points of food-specific IgE antibody concentration.

Methods

Case Report

A 3 years old boy presented for evaluation of multiple food allergies and eczema. His medical history was significant for severe eczema since the age of 6 months with a remission and relapse course. He was avoiding dairy, egg, soy and wheat in his diet due to history of "severe eczema flare ups" after consuming these foods. Child was

seen by his primary care physician who obtained specific IgE testing. Result of Immuno CAP RAST for the suspected foods revealed high values; 56 KU/L for milk, 78.8 KU/L for egg, 56 KU/L for soy and 76 KU/L for wheat. He was given a diagnosis of "food allergies" and referred to a local allergist. He had skin testing done at the allergist's office. Skin prick testing revealed positive reactions to the above mentioned 4 foods plus several other foods. Considering positive skin testing and specific IgEs above "90-95% values for predicted challenge failure", the allergist decided to continue with suspected food avoidance and advised to carry Epinephrine injection for emergency needs. He was also placed on amino acid based formula however; it was changed to almond milk due to high cost. Mother also started giving him "Gluten free diet", some fruits and vegetables. Child started losing weight and was referred to a nutritionist who put him on hydrolyzed formula, adjusted his diet based on required daily caloric intake and referred him to an allergy practice at a tertiary care center where total IgE was obtained in addition to the specific IgE. His total IgE was 6229 IU. There was no significant change in specific IgEs levels. Although his specific IgE levels were "way higher" than "90-95% values for predicted challenge failure", however, considering poor nutritional status, significantly high total IgE level and history of mild reaction to the suspected foods (eczema flare up / mild urticaria) it was decided to proceed with food challenge in a controlled setting. He passed challenges to all 4 major foods (milk, soy, wheat and egg). Eczema management was revised with significant improvement in his skin condition. He continued to tolerate these foods without urticaria, eczema or any other reactions.

Retrospective study to determine the relationship between total IgE and previously established 95% predictive decision points of food specific IgE concentration

The finding in this case led us to perform a retrospective medical records review study approved by our Nemours institutional review board. We identified sixteen children and adolescents, median age 39 months, with a history of adverse clinical reaction to a food, a specific IgE greater than the decision point, and an elevated total serum IgE level of 500 IU, underwent challenges to the offending food.

Inclusion criteria

All patients had a history of food allergy based on the following criteria: 1) adverse reaction to one or more common foods (egg, milk, peanut, fish, soybean, wheat and tree nuts) and 2) food-specific IgE levels greater than previously defined positive predictive value to the food.
3) The patient should have both a food-specific IgE and a total IgE within 6 month preceding challenge.
4) Documented evidence of re-exposure (home challenge, office food challenge) with documented outcome. The target dose for re-exposure was determined based on previously established target doses (8-10 gram for dry foods and 100 ml for wet foods (10). Food challenge was considered positive if one or more was noted: urticaria, angioedema, cough, wheezing, abdominal pain, emesis, shock or worsening of atopic dermatitis (AD) lesions. We followed our subjects for up to 2 years and confirmed that continued ingestion of previously suspected foods in the diet of these children was well tolerated.

Exclusion criteria

Increased total IgE due any other conditions besides atopic conditions. Patient serum was analyzed for concentrations of total

Table 1 *- Demographics of the study population.*

Characteristic	**Study Population (n = 16)**
Male sex	10 (62.5)
Median age at challenge (months)	39
Race	
Caucasian	4 (25)
African American	11 (68.7)
Asian	1 (6.25)
Atopic History	
Atopic dermatitis (Physician diagnosed)	14 (87.5)
Asthma (Physician diagnosed)	12 (75)
Allergic rhinitis (Physician diagnosed)	14 (87.5)

IgE and sIgE to wheat, soy, cow's milk, hen's egg, or peanut as per history of food allergy using the Pharmacia CAP-System FEIA® (Pharmacia-Diagnostics, Uppsala, Sweden). The upper and lower detection limit of the CAP-System was 100 and 0.35 kU/L respectively.
A total of 16 challenges were completed: 6 to wheat, 4 to soy, 4 to milk, 1 to egg and peanut. Study demographics are listed in **table 1**.

Results (table 2)

All of the 6 wheat challenge patients had specific IgE levels greater than 26 kU/L with a mean value of 44.7 kU/L and a mean total IgE of 8460 IU/ml. None of these challenges were positive. The 4 soy challenge patients had specific IgE levels greater than 30 kU/L with a mean value of 47.4 kU/L and a mean total IgE of 16,144 IU/ml. None of these challenges were positive. Similarly, all of the 4 milk challenge patients had specific IgE levels greater than 15 kU/L with a mean value of 73.7 kU/L and a mean total IgE of 4,444 IU/ml. Two of the 4 milk challenges were positive. One patient with an egg specific IgE > 100 kU/L and a total IgE of 6,229 IU/ml had a negative egg challenge. Finally, one patient with a peanut specific IgE > 100 kU/L and a total IgE of 663 IU/L had a positive challenge.
For soy, wheat, and egg, the observed PPV of the previously defined cut-off values of 30, 26, and 7 kU/L, respectively, was "zero" rather than 73-98%. For milk, the observed PPV of the previously defined cut-off of 15 kU/L was 50% rather than 95%. For peanut, the observed PPV of the previously defined cut-off value of 14 kU/L was 100%, consistent with previous findings (**table 2**).

Table 2 *- Study results.*

Type of Food	**Factors at the time of Diagnosis**		**Factors at the time of Challenges**	
Wheat	Initial reaction	Skin rash	# of positive challenges	0
	Skin test	5 mm (mean)	Skin test	4 mm (mean)
	SIgE	50.1 (kU/L) (mean)	SIgE	44.7(kU/L) (mean)
	Total IgE	5518 (IU/ml) (mean)	Total IgE	8460 (IU/ml)
Soy	Initial reaction	AD /Skin rash	# of positive challenges	0
	Skin test	5 mm mean)	Skin test	3 mm (mean)
	SIgE	43.51 (kU/L) (mean)	SIgE	47.4 (kU/L) (mean)
	Total IgE	12,372 (IU/ml) (mean)	Total IgE	16,144(IU/ml) (mean)
Milk	Initial reaction	Skin rash/Eczema flare	# of positive challenges	2
	Skin test	13 mm mean)	Skin test	10 mm (mean)
	SIgE	64.2 (kU/L) (mean)	SIgE	73.7 (kU/L) (mean)
	Total IgE	1458 (IU/ml) (mean)	Total IgE	4444(IU/ml) (mean)
Egg	Initial reaction	AD/Urticaria	# of positive challenges	0
	Skin test	n/a	Skin test	0 mm
	SIgE	78.8 (kU/L)	SIgE	>100 (kU/L)
	Total IgE	3154 (IU/ml)	Total IgE	6229 (IU/ml)
Peanut	Initial reaction	anaphylaxis	# of positive challenges	1
	Skin test	30 mm	Skin test	20 mm
	SIgE	27.8 (kU/L)	SIgE	>100 (kU/L)
	Total IgE		Total IgE	663 (IU/ml)

Discussion

There is significant confusion on the topic of relationship between total and food specific IgEs, specifically among the non Allergy / Immunology (A/I) physicians. Allergists often see children who underwent a specific IgE immune cap tests run by their primary care physicians and other non A/I specialists. Often the results reveal 8-9 foods that are positive in vitro, and automatically these provides advice to them to avoid those foods. This could lead to malnutrition due to unnecessary exclusion of all the foods that are positive on in vitro testing. While the previously established decision points would have predicted challenge failures in 73-95% of these subjects, in our study only 3/16 (18.75%) failed the challenge, indicating a noticeable lower clinical risk than predicted. We observed much lower clinical risk with previously defined specific IgE decision points in our small sample population. This may be attributed to the total IgE level confounding these values.

Most of our successful challenges were in patients with relatively mild food reactions (i.e., AD flare) rather than life threatening reactions yielding conclusions that may not be applicable in patients with a history of anaphylaxis to foods. Also, it is quite possible that our observation regarding the lower clinical risk with previously defined specific IgE decision is applicable only to a subset of patients with AD. We found the greatest discordance from expected outcomes in soy and wheat challenges. Prior studies noted that the predictive power of specific IgE for these foods was weak compared to other foods (4).

Interestingly, the patient with a positive peanut challenge had the lowest total IgE level in our sample and a history of a severe reaction (anaphylaxis). Our findings suggest a much lower clinical risk with previously defined specific IgE decision points in children with very high levels of total IgE > 6000 IU/ml).

Conclusions

Our findings suggest a possibility of link between total serum IgE levels and specific food IgEs and how the serum total IgE affects true predictive specific IgE values in patient with possibility of food allergy. Further investigation in a larger population may support less restrictive use of decision points in a subset of the population with markedly elevated serum IgE levels. Further data focusing on relationship between total IgE, specific IgE and the persistence / transience of food allergy may aid in the use of decision points and identify subsets of patients that are more likely to be clinically tolerant of certain foods.

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