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The natural history of shrimp hypersensitivity

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Sera collected sequentially during a 24-month interval from 11 individuals with shrimp hypersensitivity and 10 nonhypersensitive control subjects were evaluated for shrimp-specific IgE, IgG, IgM, and IgA reactivity. Shrimp-hypersensitive subjects underwent double-blind, placebo-controlled shrimp challenges; seven exhibited positive challenges, and four subjects reported the subjective symptom of oropharyngeal pruritus. Shrimp-specific IgE levels in all subjects were relatively constant during the 24 months of this study and not affected by shrimp challenge, although some fluctuation in the shrimp-specific IgG, IgM, and IgA reactivity were noted, apparently unrelated to shrimp challenge. Shrimp-specific IgE and IgG, but not IgM and IgA, were significantly higher in the group with shrimp hypersensitivity as compared to the control subjects. Moreover, the challenge-positive subjects had higher levels of both shrimp-specific IgE and IgG than subjects reporting pruritus. The levels of shrimp-specific IgG correlated directly with shrimp-specific IgE reactivity. These studies indicate that serum levels of shrimp-specific IgE are significantly elevated in shrimp-hypersensitive subjects who exhibit positive food challenges, and these baseline levels did not appear to be altered long term by isolated shrimp challenge. Furthermore, baseline shrimp-specific antibody (IgG, IgM, and IgA) levels noted in normal subjects were not markedly affected by frequent ingestion of shrimp. (J ALLERGY CLIN IMMUNOL 1990;86:88-93.)

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Abbreviations used
DBPC: Double-blind, placebo-controlled
PBS: Phosphate-buffered saline
OD: Optical density

Recent advances have been made in elucidating some aspects of food hypersensitivity reactions, primarily through the use of DBPC food challenges. Previous studies have demonstrated the importance

of IgE-mediated mechanisms in subjects exhibiting positive responses to DBPC food challenges.[1, 2] However, little is known about time- or diet-related fluctuations of food-specific antibodies in food-hypersensitive individuals. Furthermore, it has become clear that food-specific antibodies, specifically IgG, IgM, and IgA isotypes, do exist in the sera of some individuals who have no history of adverse food reactions.[3] As part of our ongoing studies concerning mechanisms of shrimp-hypersensitivity reactions, we have prospectively evaluated shrimp-specific, serum-antibody levels during a 2-year period in a group of shrimp-hypersensitive individuals who participated in oral food-challenge studies. A control group consisted of nonhypersensitive subjects who included shrimp as a regular constituent in their diet.

MATERIAL AND METHODS

Study subjects and challenge protocol

Eleven adult subjects who had participated in previous studies of shrimp hypersensitivity[1, 4] were enrolled in this study; all subjects had definitive histories of objective, adverse reactions within 1 hour of shrimp ingestion. DBPC food challenges were performed on these 11 subjects as part of a larger challenge study that has been previously reported in detail.[1] Briefly, the challenges were preformed in two phases. The first phase was DBPC with either shrimp extract or saline administered at hourly intervals. The shrimp extract or saline was masked in 200 ml of vanilla ice cream containing 40 ml of Syrpalta (Emerson Laboratories, Texarkana, Texas) grape flavoring. Dosages of 1, 4, and 16 shrimp equivalents were administered. In those individuals with a negative DBPC challenge, an open food challenge of 16 medium-sized boiled shrimp (64 gm) was performed. Two of the shrimp-hypersensitive subjects were evaluated with a second shrimp challenge. A positive response was defined as reproduction of objective symptoms during the challenge.

Ten of the 11 shrimp-hypersensitive individuals were designated as atopic by previously established criteria of two or more positive prick skin tets to common inhalant allergens and a personal or family history of respiratory allergy[4, 5]; the one nonatopic subject was in the group with pruritus.

The control group consisted of 10 adult volunteers without any history of reactions after shrimp ingestion. This group reported inclusion of shrimp as a regular constituent of their diet. These individuals were either medical center personnel or patients referred for evaluation of rhinitis or asthma. Seven control subjects were designated as atopic and three subjects were nonatopic.

Informed consent was obtained before all studies, including skin tests, venipuncture, and food challenge.

Study interval

Sera were collected prospectively from shrimp-hypersensitive subjects during a 23.9 ± 5.7-month interval. Most (6/11) shrimp-hypersensitive subjects had two sequential serum samples drawn before oral food challenge; one sample was collected approximately 12 months before the oral food challenge, and the other sample, on the day of challenge (before the start of the challenge procedure). After shrimp challenge, all subjects had at least one serum sample collected an average of 10.6 ± 1.3 months after challenge. Sera were collected from control subjects at similar time intervals during a 25.3 ± 4.9-month period.

Shrimp-allergen extracts

Water-soluble extracts of white shrimp *(Peneus setifecus)* were prepared in PBS (pH 7.4) and used for skin testing, in vitro studies, and provocative challenges as previously described.[1] All extracts were sterile filtered (0.45 μm) before use and were negative for hepatitis B surface antigen.[6]

Skin Testing

Subjects were prick skin tested with shrimp-allergen extract (10 mg/ml of PBS in 50% glycerol) as well as commercial extracts (50% glycerol) of 17 common inhalant and 10 food allergens (Greer Laboratories, Lenoir, N.C., and Hollister-Stier Laboratories, Spokane, Wash.). Inhalant allergens included *Dermatophagoides farinae*, American cockroach, danders of cat and dog, the pollens of live oak and pecan trees, Bermuda, Bahia and Johnson grass, ragweed, English plantain, and mold allergens (*Aspergillus, Alternaria, Cladosporum, Epicoccum, Penicillium*, and *Fusarium*). Food allergens included cow's milk, chocolate, egg, wheat, peanut, soy, shrimp, beef, corn, and rice. Prick skin tests were performed with a straight taper-point surgical needle (Richard-Allan Medical Industries, Richland, Mich.). The positive test was defined as an immediate wheal and flare with a mean wheal diameter 3 mm larger than the control reaction wheal to PBS in 50% glycerol within 15 minutes of application.

Total and specific IgE determinations

Total serum IgE levels were determined in duplicate with a commercially available paper radioimmunosorbent test kit (PRIST, Pharmacia Diagnostics, Piscataway, N.J.) as previously described.[4] IgE serum concentrations were expressed as international units per milliliter.

Shrimp-specific IgE (RAST) was determined on duplicate serum samples by a RAST with shrimp-allergen extract or human serum albumin conjugated to cyanogen bromide-activated disks according to the method of Karr et al.[7] Results, expressed as percent label bound, were calculated as mean counts per minute for shrimp disks divided by total counts per minute (^{125}I-labeled anti-IgE) added to system times 100. In this study, >3% label bound was considered significant. This level of significance had been previously determined[8] by calculating the 99% confidence interval for the percent label bound obtained with a serum panel from skin test-negative, shrimp-tolerant, atopic control subjects (N = 15). The mean percent label bound to HSA conjugated disks was always <2%.

ELISA

Serum levels of shrimp-specific IgG, IgA, and IgM were quantified in an ELISA as previously described.[4] Results were recorded as Δ OD measured at 405 nm where Δ OD = OD experimental serum − OD diluent. Assays were standardized by including a reference serum with

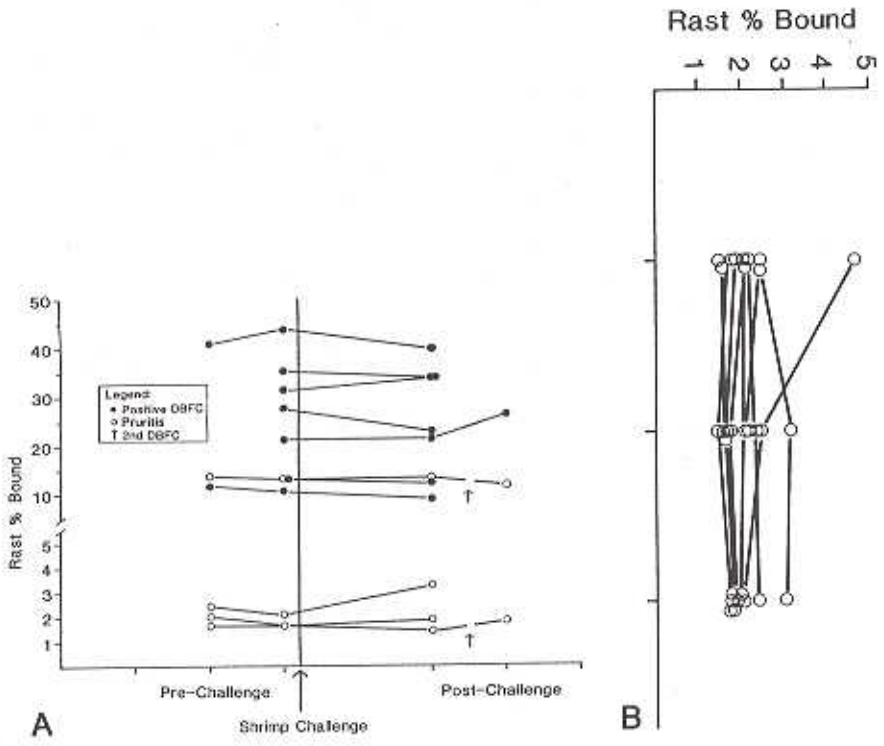

FIG. 1. A, Shrimp-specific serum IgE (RAST) values of shrimp-hypersensitive subjects. Venipuncture for the second prechallenge determination was preformed on the day of, but before challenge. B, Shrimp-specific serum IgE (RAST) values of shrimp nonhypersensitive control subjects.

known reactivity on each plate; the Δ OD of this serum varied <10% among assays.

Statistical analysis

Shrimp skin test end points were compared with the Mann-Whitney U nonparametric test. Total serum IgE (log-transformed values), shrimp-specific IgG, IgM, and IgA (ELISA), and shrimp-specific IgE (log-transformed RAST) of the shrimp-hypersensitive group and the control group were compared by analysis of variance. The differences between the challenge response groups (objective positive versus oropharyngeal pruritus) were analyzed in the same manner. Linear regression analysis was used in testing for an association between the shrimp-specific IgG and shrimp-specific IgE in shrimp-hypersensitive subjects. In all cases, alpha values ≤0.05 were considered statistically significant.

RESULTS

DBPC food challenge results

DBPC food challenges were performed on all shrimp-hypersensitive individuals. Seven individuals had a positive shrimp challenge in that they manifested objective reactions to shrimp within 60 minutes of ingestion. These reactions were similar in quality to reactions reported by history and included wheezing, vomiting, urticaria, and angioedema. The remaining four subjects did not have an objective positive shrimp challenge, although they reported the subjective symptoms of pruritus (predominantly oropharyngeal) after shrimp ingestion. Twenty-nine placebo challenges were all negative. The details of these shrimp-challenge studies have been previously reported.[1]

Shrimp prick skin testing

The shrimp prick skin test was positive in all members of the shrimp-hypersensitive group and was negative in all members of the control group. There were no significant differences noted in the shrimp prick skin test mean wheal diameters or titration end points between the challenge-positive subjects and subjects with oropharyngeal pruritus.

Total serum IgE

The average total serum IgE levels of individuals with a positive shrimp challenge and that of the four subjects reporting oropharyngeal pruritus were similar (338 ± 87 and 290 ± 138 IU/ml, respectively). The average total serum IgE levels of control subjects was somewhat lower (156 ± 45 IU/ml), although most were classified as atopic individuals (7/10 in control group versus 9/11 in shrimp-hypersensitive group).

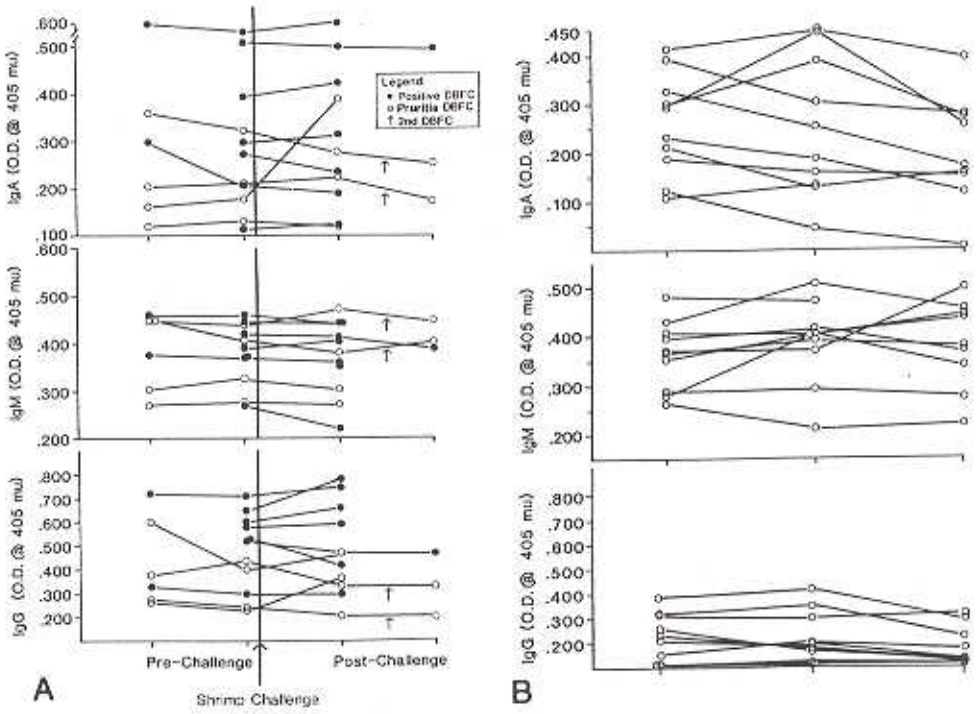

FIG. 2. A, Shrimp-specific serum IgG, IgM, and IgA (ELISA) reactivity of shrimp-hypersensitive subjects. Venipuncture for the second prechallenge determination was performed on the day of, but before the oral challenge. **B,** Shrimp-specific serum IgG, IgM, and IgA (ELISA) reactivity of shrimp-nonhypersensitive control subjects.

The statistical analysis demonstrated that there were no significant differences among these groups. The total serum IgE levels for a given subject did not fluctuate significantly between sequential serum samples (data not presented).

Shrimp-specific IgE

The results of the shrimp RAST determinations in the shrimp-hypersensitive individuals are illustrated in Fig. 1, *A*. All subjects exhibiting a positive challenge had significantly elevated (>3% label bound) shrimp RAST, whereas only one subject reporting pruritus had an elevated shrimp RAST. The RAST percent label bound of the positive challenge subjects, as a group, was significantly higher than that of individuals reporting pruritus (25.9 ± 4.3 versus 4.8 ± 0.2, respectively). Moreover, the shrimp-specific IgE reactivity of a given subject was noted to be remarkably constant during the time course of this study and did not change relative to shrimp challenge.

The shrimp-specific IgE reactivity of the control group is illustrated in Fig. 1, *B*. Significant activity was observed in only one serum sample from one control individual. The mean of sequential control samples was significantly lower ($p < 0.01$) than the mean of shrimp-hypersensitive subjects. This low level of activity was again remarkably constant during the course of this study.

Shrimp-specific IgG, IgA, and IgM

ELISA reactivity of shrimp-specific IgG, IgA, and IgM isotypes in the sera of shrimp-hypersensitive subjects is presented in Fig. 2, *A*. The shrimp-specific IgG demonstrated a significant direct correlation with the shrimp-specific IgE reactivity in shrimp-hypersensitive subjects. Furthermore, the shrimp-specific IgG reactivity was significantly higher in the positive challenge group compared to subjects reporting pruritus. No significant differences in the levels of shrimp-specific IgA and IgM were noted between shrimp-hypersensitive subgroups (positive challenge and pruritus). Although this reactivity did fluctuate somewhat during the course of this study, there was no consistent trend, and the changes appeared to be independent of shrimp challenge.

Variations in the shrimp-specific IgG, IgA, and IgM reactivity of sera from control subjects during the study interval were similar to changes observed in shrimp-hypersensitive subjects (Fig. 2, *B*). Although the levels of shrimp-specific IgG were significantly

lower ($p < 0.001$) in this shrimp-tolerant group as compared to hypersensitive subjects, the levels of shrimp-specific IgA and IgM were similar.

DISCUSSION

Very little is known about the role of time- or diet-related fluctuations of food-specific antibody levels in the immunopathogenesis of food-hypersensitivity reactions. The present investigation was designed as a prospective study of levels of food-specific serum antibodies in groups of both food-hypersensitive and nonhypersensitive subjects. The purpose of this study was to characterize the natural history of food-specific isotypic responses as they related to the ingestion and challenge responses. We have used shrimp hypersensitivity as a model for food-hypersensitivity reactions, and our shrimp-hypersensitive subjects were categorized by their responses to DBPC food challenge.

Evaluation of serum isotypes indicated that shrimp-specific IgE, IgG, IgA, and IgM were detected in all study subjects. There were significant differences in food-specific IgE and IgG reactivity between the entire shrimp-hypersensitive group (independent of challenge response) and control subjects. Furthermore, within the shrimp-hypersensitive subjects, the shrimp-specific IgE and IgG reactivity was also significantly higher in the challenge-positive compared to equivocal-response (pruritus) subgroup. However, no significant longitudinal changes in the food-specific reactivity of any of the isotypes (IgE, IgG, IgA, or IgM) were noted relative to shrimp ingestion in these groups.

Excluding reactions to food additives, such as sulfites and tartrazine, food-specific IgE appears to have a crucial role in the immunopathogenesis of most, if not all, substantiated (DBPC food challenge) immediate food-hypersensitivity reactions.[1, 2, 9] In this study, the shrimp-specific serum IgE levels were significantly higher in the positive-challenge group compared to either subjects with equivocal-challenge responses (subjects reporting the subjective symptom of pruritus) or the control population. These IgE results are in agreement with the conclusions of other investigations based on a single serum sample obtained at the time of challenge[2, 9-11] and extend our previous findings[1] on a longitudinal basis. Furthermore, our data indicate that the shrimp-specific IgE of a particular shrimp-allergic individual is relatively constant during at least a 24-month study interval. Immediate, postchallenge (within 1 to 2 hours) decreases in food-specific IgE levels have been observed in some food-allergic subjects,[12] possibly related to the formation of IgE containing immune complexes. This is a short-term modulation (24 to 48 hours) since the food-specific IgE ultimately returns to prechallenge levels. However, since immediate postchallenge samples were not obtained in the present study, the possibility that short-term reversible fluctuations may occur in our shrimp-hypersensitive subjects remains to be established.

Other studies of normal, food-tolerant individuals have either demonstrated the absence of,[13] or very low levels[14] of, food-specific IgE as in the current investigation. In contrast to the consistently low shrimp-specific IgE levels noted in our control subjects, normal adults chronically ingesting (during a 4-week period) high dietary amounts of soya produced low levels of soya-IgE, which increased significantly during the study interval in female subjects.[14] Perhaps this discrepancy could be explained by the fact that our studies did not involve ingestion of shrimp at sustained or "high" levels. Regardless of the explanation, there appear to be no detectable biologic sequelae to such low-level IgE recognition of dietary antigen/allergen in normal subjects.[1, 14]

Although the relationship of non-IgE (IgG, IgA, and IgM) food-specific antibodies has been the subject of previous investigations, neither the biologic significance nor the natural history of these isotypes is well understood. Non-IgE food-specific antibodies to a variety of dietary antigens have been demonstrated in a substantial proportion of healthy, nonfood-hypersensitive subjects.[3, 10, 13-17] In some instances, these antibodies appear to be primarily of the IgG isotype.[3, 14] However, no predilection for shrimp-specific IgG synthesis was noted in our control subjects, since similar levels of reactivity were noted in IgG, IgM, and IgA isotypes. Furthermore, in agreement with our current study, levels of non-IgE food-specific antibodies did not appear to be influenced by particular food ingestion in adults.[13, 14]

In contrast, shrimp challenge–positive subjects had significantly higher shrimp-specific IgG than either the control group or the group with pruritus. Interestingly, the shrimp-specific IgG levels demonstrated a significant direct correlation with the shrimp-specific IgE reactivity. A similar trend has been noted in children with a history of food intolerance.[15, 18, 19] However, the biologic significance of the persistently elevated shrimp-specific IgG in shrimp-hypersensitive subjects remains to be elucidated.

When contemplating the role of serum antibodies to food proteins (antigens/allergens) in the pathogenesis of hypersensitivity disorders, the initial immune reaction probably occurs in the gut. Therefore, local gut antibody may be more relevant and may not be accurately reflected in the serum. The gastrointestinal "barrier" to antigen/allergen absorption appears to be significantly affected by local gut IgE-mediated anaphylaxis[20] and local secretory IgA,[21] as well as by

malabsorption syndromes[19] and infection.[22] Local gut IgE-mediated food anaphylaxis may enhance intestinal permeability to food proteins. With enhanced entry, more widespread antigen processing and immune response could occur and ultimately lead to enhanced synthesis of food-specific serum IgG. This would result in a generalized enhanced immune responsiveness to shrimp antigens in persons with elevated shrimp-specific IgE levels. Such a scenario would explain the relationship of shrimp-specific IgE and IgG in shrimp-hypersensitive subjects. Furthermore, our data do not indicate that shrimp-specific non-IgE antibody is related to tolerance per se, as has previously been suggested in children with food allergy.[18, 19] Whether such antibodies are involved in the formation of circulating immune complexes and production of symptoms, as suggested by other investigators,[23] remains to be established. Possible covariables of immunopathogenic importance include IgG subclass, as proposed by Halpern and Scott,[24] as well as the affinity and clearance potential of such non-IgE antibodies.

In our previously reported DBPC food challenges in shrimp-hypersensitive subjects,[1] a positive shrimp prick skin test (immediate wheal and flare) combined with an elevated shrimp RAST (>11% bound) demonstrated an 87% correct predictive value of a positive-challenge response. Therefore, the most significant serologic aspect predictive of positive challenge was the presence of elevated shrimp-specific IgE that, in this study, appears to be a persistent phenomenon (at least during 24 months). Furthermore, most (8/11) of our shrimp-hypersensitive subjects had voluntarily excluded shrimp from their diet for several years before this DBPC food challenge. This would also indicate that the persistent nature of the immune response to dietary antigens in hypersensitive adult subjects is independent of continued antigen/allergen exposure. However, the exact duration of such long-term IgE immunologic responsiveness remains to be established. Moreover, whether or not such elevated shrimp-specific IgE reactivity constitutes a "life-long stigma" of shrimp allergy must be determined.

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