Reactions to Shrimp Including Severe Anaphylaxis in Mite- and Cockroach-Allergic Patients Who Have Never Eaten Shrimp: Clinical Significance of IgE Cross-Reactivity to Tropomyosins From Different Sources

Martins TF[1], Mendonça TN[2], Melo JML[2], Moreno AS[1], Januário YC[1], DaSilva LLP[1], Dias MM[1], Meireles PR[3], Santos KS[3], Yang AC[4,5], Arruda LK[1,2]

[1]*Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, SP, Brazil*

[2]*Clinical Hospital of Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, SP, Brazil*

[3]*Disciplina de Imunologia Clínica e Alergia, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil*

[4]*Disciplina de Imunologia Clínica e Alergia, Hospital da Clínicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil*

[5]*University of Campinas, São Paulo, Brazil*

J Investig Allergol Clin Immunol 2019; Vol. 29(4): 302-305
doi: 10.18176/jiaci.0378

Key words: Shrimp. Tropomyosin. IgE. Oral food challenges. Cross-reactivity.

Palabras clave: Gamba. Tropomiosina. IgE. Provocación oral con alimentos. Reactividad cruzada.

Immunological cross-reactivity between shrimp, mites, cockroach, and *Ascaris lumbricoides* is thought to be due to IgE responses to shared allergens, particularly tropomyosin. IgE-binding homologous epitopes have been identified in invertebrate tropomyosins, thus indicating a structural basis for cross-reactivity between allergenic tropomyosins [1]. However, their clinical relevance is unpredictable. Tuano and Davis [2] described 4 mite-allergic patients with rhinitis with and without asthma, who developed oral allergy syndrome upon ingestion of shrimp, although their reaction did not progress to anaphylaxis during oral food challenges (OFC) [2].

We report the results of supervised OFC with shrimp in 3 patients with perennial rhinitis and controlled moderate to severe asthma who presented strong positive skin prick test (SPT) and IgE results to shrimp, but denied ever having eaten shrimp, other crustaceans, or mollusks. Patients also had positive SPT results and high IgE levels to mites and cockroach. IgE and IgG4 levels and the outcomes of OFC are shown in the Table. IgE immunoblots were performed with shrimp extract and tropomyosins (Supplementary Figure). Double-blind, placebo-controlled food challenge (DBPCFC) was performed with 10 mg, 100 mg, 1 g, and 4 g of shrimp (Supplementary Material), with a 20-minute interval between first and second dose and subsequently at 30-minute intervals (cumulative dose, 5.11 g; 1 g of shrimp protein). Negative DBPCFCs were followed by an open challenge after 1 week,

with 4 g of shrimp, followed by 16 g of shrimp 30 minutes after the first dose (cumulative dose, 20 g; 3.8 g of shrimp protein). The study was approved by the local ethics committee, and patients signed the informed consent document.

Patient 1 was a 42-year-old man with high IgE to shrimp and tropomyosins and positive results for IgE to shrimp arginine kinase and sarcoplasmic calcium-binding protein. The result of the DBPCFC was negative, although the patient experienced transient mild labial edema and oral pruritus after 4 g in the open challenge. No medication was necessary, and no symptoms were observed after 16 g.

Patient 2 was a 51-year-old man with high IgE to shrimp and tropomyosins and moderate levels of IgE to arginine kinase. He had no symptoms in the DBPCFC, but presented erythema, pruritus, urticaria, and mouth tingling, 5 minutes after receiving 16 g of shrimp in the open challenge. The symptoms resolved within 30 minutes of treatment with intravenous antihistamine and corticosteroid.

Patient 3 was a 58-year-old woman with high IgE to shrimp and tropomyosins. The result of the DBPCFC was negative, although 10 minutes after eating 16 g of shrimp in the open challenge, she presented with generalized erythema and itching, followed by urticaria, progressively severe dyspnea with wheezing upon pulmonary auscultation, abdominal pain, nausea, and vomiting. She received 2 doses of intramuscular epinephrine, intravenous antihistamine, intravenous high-dose hydrocortisone, and inhaled albuterol, although she progressed rapidly to respiratory failure requiring endotracheal intubation and admission to the intensive care unit. Her symptoms improved gradually, and she was extubated after 48 hours. She was discharged without symptoms 5 days later. Prior to the challenges, the patient's asthma was well controlled with daily budesonide 400 µg/formoterol 12 µg bid. During the previous 18 months, she denied asthma symptoms and acute exacerbations, albuterol use, and impairment of daily activities.

Table. Component-Resolved Diagnosis and Clinical Parameters in Asthmatic Patients Who Underwent Oral Food Challenges With Shrimp

Parameter	Patient 1[a]	Patient 2[a]	Patient 3[a]
Skin tests to shrimp, wheal diameters[b]	8×10 mm	9×11 mm	7×9 mm
Total IgE, kU/L[c]	200	583	89.6
IgE to *Dermatophagoides pteronyssinus*, kU/L[c]	25.7	57.1	36.7
IgE to *Blattella germanica*, kU/L[c]	29.2	59.8	46.2
IgE to *Periplaneta americana*, kU/L[c]	14.8	25.6	18.1
IgE to shrimp, kU/L[c]	56.2	81.5	40.8
IgE to shrimp tropomyosin Pen a 1, kU/L[c]	44.2	64.7	31.7
IgE to shrimp tropomyosin Pen m 1, ISU-E[d]	70	64	38
IgE to shrimp arginine kinase Pen m 2, ISU-E[d]	16	3.7	<0.3
IgE to shrimp calcium binding protein Pen m 4, ISU-E[d]	0.4	<0.3	<0.3
IgE to *D pteronyssinus* tropomyosin Der p 10, ISU-E[d]	75	74	52
IgE to *B germanica* tropomyosin Bla g 7, ISU-E[d]	65	77	39
IgE to *Anisakis simplex* tropomyosin Ani s 3, ISU-E[d,e]	60	59	30
IgE to shrimp tropomyosin by ELISA, IU/mL	56.3	43.9	28.6
IgE to cockroach tropomyosin by ELISA, IU/mL	164.1	130.7	56.8
IgG4 to shrimp tropomyosin Pen m1, kU/L[c]	0.22	0.01	0.10
Outcomes of oral food challenges with shrimp[f]	Transient lip swelling and throat itching	Mouth tingling, urticaria and cutaneous pruritus	Severe anaphylaxis requiring intubation and ICU admission

[a]All patients presented IgE to additional allergens not related to tropomyosins in ImmunoCAP-ISAC: patient 1 had low levels of IgE to pollen allergens Cyn d 1 (0.4 ISU-E) and Phl p 4 (0.7 ISU-E) and to cross-reactive carbohydrate determinants (0.3 ISU-E); patient 2 had positive results to Der p 2 (4.4 ISU-E) and Der f 2 (5.7 ISU-E); and patient 3 had positive results to Der p 1 (6.2 ISU-E), Der p 2 (4.4 ISU-E), Der f 1 (10 ISU-E), Der f 2 (7.2 ISU-E), and Fel d 1 (0.4 ISU-E)

[b]Skin tests were performed using commercial Greer 1:20 wt/vol glycerinated shrimp extract, produced from raw (uncooked) shrimp of the species *Litopenaeus setiferus* (white shrimp), *Farfantepenaeus aztecus* (brown shrimp), and *Farfantepenaeus duorarum* (pink shrimp). Wheals were accompanied by erythema in all 3 patients.

[c]Measured by ImmunoCAP. Levels >3.5 kU/L of specific IgE are considered high according to the manufacturer.

[d]Measured by ImmunoCAP-ISAC. Levels ≥15 ISU-E are considered very high according to the manufacturer.

[e]Parasite *Anisakis simplex* tropomyosin Ani s 3 presents 97% sequence identity to *Ascaris lumbricoides* tropomyosin Asc l 3.

[f]All 3 patients had negative DBPCFC with a cumulative dose of 5.11 g of shrimp, followed by reactions during the open challenge with up to 20 g of shrimp performed 1 week apart from the DBPCFC.

The IgE immunoblots showed that all 3 patients had strong reactivity to shrimp and cockroach tropomyosins and much lower reactivity to other protein bands; however, there were no differences in the intensity of staining, thus indicating a lack of correlation with the severity of the allergic reactions (Supplementary Figure). While we would like to extend our observations to a larger number of patients, we stopped the shrimp challenges owing to the risk of severe reactions.

IgE antibodies to shrimp have been detected in mite and cockroach-allergic orthodox Jews who have never eaten shrimp and are attributed to IgE cross-reactivity to tropomyosin [3]. IgE to tropomyosin added value to the diagnosis of shrimp allergy, as compared with SPT or IgE to shrimp, predicting more often a positive OFC with shrimp [4]. Among inner city children with asthma, high exposure to cockroach in the home was significantly correlated with higher IgE levels to cockroach and shrimp, suggesting that exposure to cockroach could drive the immune response towards production of IgE to shrimp [5]. Allergic reactions upon ingestion of shrimp in the cases we report (asthma patients who had never eaten shrimp) suggest that IgE sensitization to mites and cockroach, primarily through the respiratory tract, and perhaps via parasite infections, could induce cross-sensitization to shrimp in a way that ingestion of shrimp could potentially lead to life-threatening systemic allergic reactions.

None of the patients in the present report reacted in the DBPCFC, most likely because of the low dose [6]. Higher doses may be required to trigger symptoms in patients whose primary sensitization occurred via inhalation, owing to the affinity of the antibodies. Low levels of IgG4 to shrimp tropomyosin, which indicate limited exposure, make it unlikely that IgG4 antibodies could function as blocking antibodies protecting against clinical reactions at lower doses of allergen [7].

Our experience with shrimp challenge taught us that allergic reactions in shrimp-sensitized patients upon ingestion of shrimp are largely unpredictable, thus underscoring the inability of current tests to predict true life-threatening shrimp allergy. House dust mite–induced asthma and elevated IgE to shrimp and mite tropomyosins were strongly associated with allergic reactions after ingestion of shrimp by shrimp-sensitized individuals [8]. Cut-off values of wheal diameter on skin testing for predicting true shrimp allergy have been proposed [8], although the allergen content of commercial crustacean extracts may be highly variable, thus reducing the clinical usefulness of this approach [9]. Component-resolved diagnosis indicates that IgE to tropomyosin, sarcoplasmic binding-protein, and myosin light chain may increase the predictive value for developing allergic reactions upon ingestion of shrimp [7]; however, levels of specific IgE have not been correlated with the severity of allergic reactions. Novel allergens including fructose biphosphate aldolase, which is associated with life-threatening anaphylaxis, may provide additional diagnostic specificity [7,10]. Despite the relevance of these observations, we still need a biomarker to predict clinical reactivity. Based on current knowledge, shrimp challenges would not be advisable in patients with house dust mite–induced asthma who present high levels of IgE to shrimp and to shrimp tropomyosin. Patients with these clinical and serological characteristics need to be cautioned about the risks of eating shrimp, other crustaceans, and mollusks. Strict avoidance should be recommended in these cases.

Funding

This study was supported by the Institute of Investigation in Immunology, National Institutes of Science and Technology, Brazilian National Council for Scientific and Technological Development (iii-INCT-CNPq), and a joint CNPq and São Paulo Research Foundation (FAPESP) grant (Research for the Unified Public Health System PPSUS).

Conflicts of Interest

TF Martins received a doctoral scholarship from São Paulo Research Foundation (FAPESP).

AS Moreno holds a fellowship for Coordination of Superior Level Staff Improvement (CAPES) and a FAPESP postdoctoral fellowship.

KS Santos received a Young Researcher Grant from FAPESP.

LK Arruda received a CNPq Research Productivity Grant.

The remaining authors declare that they have no conflicts of interest.

Previous Presentations

This study was presented as a poster at the European Academy of Allergy and Clinical Immunology EAACI Congress 2016 in Vienna, Austria.

References

1. Ayuso R, Lehrer SB, Reese G. Identification of continuous, allergenic regions of the major shrimp allergen Pen a 1 (tropomyosin). Int Arch Allergy Immunol. 2002;127(1):27-37.
2. Tuano KTS, Davis CM. Oral allergy syndrome in shrimp and house dust mite allergies. J Allergy Clin Immunol Pract. 2018;6(6):2163-4.
3. Fernandes J, Reshef A, Patton L, Ayuso R, Reese G, Lehrer SB. Immunoglobulin E antibody reactivity to the major shrimp allergen, tropomyosin, in unexposed Orthodox Jews. Clin Exp Allergy. 2003;33(7):956-61.
4. Yang AC, Arruda LK, Santos AB, Barbosa MC, Chapman MD, Galvão CE, et al. Measurement of IgE antibodies to shrimp tropomyosin is superior to skin prick testing with commercial extract and measurement of IgE to shrimp for predicting clinically relevant allergic reactions after shrimp ingestion. J Allergy Clin Immunol. 2010;125(4):872-8.
5. Wang J, Calatroni A, Visness CM, Sampson HA. Correlation of specific IgE to shrimp with cockroach and dust mite exposure and sensitization in an inner-city population. J Allergy Clin Immunol. 2011;128(4):834-7.
6. Ballmer-Weber BK, Fernandez-Rivas M, Beyer K, Defernez M, Sperrin M, Mackie AR, et al. How much is too much? Threshold dose distributions for 5 food allergens. J Allergy Clin Immunol. 2015;135(4):964-71.
7. Pascal M, Grishina G, Yang AC, Sánchez-García S, Lin J, Towle D, et al. Molecular diagnosis of shrimp allergy: efficiency of

several allergens to predict clinical reactivity. J Allergy Clin Immunol Pract. 2015;3(4):521-9
8. Farioli L, Losappio LM, Giuffrida MG, Pravettoni V, Micarelli G, Nichelatti M, et al. Mite-induced asthma and IgE levels to shrimp, mite, tropomyosin, arginine kinase, and Der p 10 are the most relevant risk factors for challenge-proven shrimp allergy. Int Arch Allergy Immunol. 2017;174(3-4):133-43.
9. Asero R, Scala E, Villalta D, Pravettoni V, Arena A, Billeri L, et al. Shrimp allergy: analysis of commercially available extracts for in vivo diagnosis. J Investig Allergol Clin Immunol. 2017;27(3):175-82.
10. Gamboa PM, Bartolomé B, García Lirio E, Cuesta-Herranz J, Pastor-Vargas C. Aldolase: A new Crustacea allergen. Ann Allergy Asthma Immunol. 2018;121(2):246-7.

Manuscript received September 25, 2018; accepted for publication January 22, 2019.

L Karla Arruda
Ribeirão Preto Medical School
Av. Bandeirantes, 3900
Ribeirão Preto
SP 14049-900, Brazil
E-mail: karla@fmrp.usp.br