CASE REPORT

Prawns, Barnacles, and Nonsteroidal Anti-Inflammatory Drugs: Effect Modifiers or Interaction?

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Abstract

A 42-year-old woman with no history of atopy reported several episodes of generalized urticaria and shortness of breath after eating shellfish (prawns and barnacles) but with good tolerance of the same foods between episodes. Skin prick tests (SPTs), serum enzyme allergosorbent tests (EAST) for specific immunoglobulin (Ig) E, Western blot and inhibition assays, and oral challenge tests with prawns, barnacles, nonsteroidal anti-inflammatory drugs (NSAIDs), and alcohol as potential effect modifiers were performed.
Specific IgE to both barnacle and prawn were detected by SPTs and EAST. Results from a Western blot of raw prawn revealed an IgE binding band of 37 kDa and IgE binding bands of 143, 83, 38, 32, and 20 kDa appeared in the raw barnacle assay. Oral challenge tests were positive with prawns and prawn extract only if preceded by NSAIDs. Oral challenges with NSAIDs alone, prawns alone, barnacles with or without NSAIDs and alcohol led to no reaction.
A synergistic effect of NSAIDs in inducing anaphylaxis after prawn intake was confirmed. No similar effect was achieved with barnacles despite the presence of specific IgE. Additional factors needed to elicit a clinical reaction in food allergy may not be obvious and several oral challenge protocols are mandatory in such cases.

Key words: Barnacle. Nonsteroidal anti-inflammatory drugs. Prawn. Cross-reaction. Food allergy.

Resumen

Se presenta el caso de una mujer no atópica de 42 años de edad que había presentado varios episodios de urticaria generalizada y disnea tras comer marisco, langostinos y percebes, concretamente. La misma paciente había tolerado la ingesta de estos mismos alimentos en múltiples ocasiones entre los distintos episodios de anafilaxia. El estudio alergológico incluyó la realización de pruebas cutáneas en prick, análisis de la inmunoglobulina (Ig) E específica en suero así como estudios de inmunoblotting con ensayos de inhibición y pruebas de provocación oral con langostinos, percebes, antiinflamatorios noesteroides (AINEs) y alcohol como posibles agentes potenciadores de la reacción.
Se detectó IgE específica frente a langostino y percebe tanto en prueba cutánea como en suero. Los resultados del western blot con langostino crudo revelaron una banda de 37 kDa mientras que el ensayo con percebe crudo detectó bandas fijadoras de IgE de 143, 83, 38, 32 y 20 kDa. Las pruebas de provocación oral fueron positivas con langostinos y extracto de langostinos pero sólo si la prueba se precedía de la administración de AINEs. Las provocaciones aisladas con AINEs y langostinos resultaron negativas. Las provocaciones orales con percebes, acompañadas o no de alcohol y/o AINEs fueron bien toleradas por la paciente.
En *conclusión*, el estudio ha permitido demostrar un efecto sinérgico entre los AINEs y los langostinos, provocando una reacción anafiláctica lo que no se pudo comprobar en el caso de los percebes.

Palabras clave: Percebe. AINEs. Langostino. Reactividad cruzada. Alergia a alimentos.

Introduction

Most advances in the understanding of food hypersensitivity disorders are based on childhood food allergy and cannot explain food-related symptoms in adulthood [1,2]. The prevalence of adult food allergy has been estimated to be approximately 3% to 4% in several countries [1,3,4]. Diet and culture can influence food allergy development, explaining the different patterns of sensitization from one place to another, especially among adults [5]. Shellfish is an important cause of food hypersensitivity in Spain [6,7], as well as in the United States of America [8].

It is accepted that food allergy cannot be assumed simply based on the patient's or doctor's impression: the double-blind, placebo-controlled food challenge is the gold standard for diagnosis [9]. Nonetheless, there are many case reports dealing with "true allergic reactions" supposedly well-diagnosed simply based on the presence of biologically active, specific immunoglobulin (Ig) E. In fact, the presence of IgE suggests an IgE mechanism but, if food challenges are avoided because the reaction was severe, the allergic nature of the reaction cannot be confirmed. On the other hand, there have been cases in which well-controlled challenge tests failed and the ingestion of permitted foods resulted in severe reactions afterwards [10]. In such circumstances, the presence of factors unrelated to food might be required to provoke a clinically relevant reaction. We report a case of anaphylaxis due to crustacean allergy in which effect modifiers other than the allergen itself were needed to induce a clinical reaction.

Case Description

A 42-year-old woman, with no family or personal medical history of allergy had been diagnosed 7 years earlier with food allergy to crustaceans. The diagnosis was based on a clinical history of urticaria and angioedema shortly after eating prawns and a positive skin prick test (SPT) against this crustacean. Despite this, the patient had frequently tolerated all kinds of crustaceans for the last 7 years. She had noticed that the reaction only appeared when crustacean intake had been preceded by intake of a nonsteroidal anti-inflammatory drug (NSAID), such as aspirin or ibuprofen, which she usually took to treat headache. In December 2004, 2 hours after having eaten barnacles, the patient experienced an episode of generalized pruritus followed by throat itching, dysphonia and dyspnea, lip and palpebral angioedema with generalized urticaria, and dizziness. She was treated with subcutaneous epinephrine with total recovery 2 hours later. She had drunk a glass of white wine, which was thought to be the most likely cause of the reaction since she reported having taken no NSAIDs and she had previously tolerated barnacles with no problems. One week later, the patient had a second episode of anaphylaxis. She had eaten 500 g of barnacles with champagne an hour earlier. She was taken to the emergency department, where a general physical examination revealed cutaneous signs with tachycardia. Blood pressure upon examination was not noted in the record, but after treatment with subcutaneous epinephrine and intravenous diphenhydramine and hydrocortisone, blood pressure was within normal limits (110/70 mm Hg). The reaction resolved and the patient was referred to the allergy service of Hospital de Conxo in Santiago de Compostela, Spain, in stable condition for evaluation a month later.

The patient had no other relevant past medical or surgical history. Her menstrual period showed a monthly pattern unrelated to the anaphylactic episodes. She never reported symptoms consistent with eczema, asthma, or seasonal or perennial rhinitis. She led a sedentary life as a pharmacist and did not exercise. She did not smoke, drank alcohol rarely (only at special events), and reported no illicit drug use.

Testing Procedures

Extracts from raw and boiled fresh barnacles (*Pollicipes cornucopiae*) and prawns (*Pandalus borealis*) were prepared. Animal specimens were ground into small pieces, defatted and extracted by magnetic stirring in agitation in 50 mM phosphate-buffered saline at pH 7.5 for 4 hours at room temperature. The sample was centrifuged at 5 600g for 30 minutes, the supernatant dialyzed against water, and the extract filtered through a 0.22 µm-pore diameter membrane and freeze-dried. Extract protein content calculated weight per weight using the Bradford method [11] were as follows: raw prawn, 83%; raw barnacle, 70%; boiled prawn, 60%, and boiled barnacle, 74%. Tropomyosin from barnacle and prawn was purified as described by Smillie [12]. Barnacle and prawn extracts were used for in vitro analysis and prick and challenge tests.

A battery of commercially available common inhalant allergens, including house dust and storage mites, pollens, animal dander, and molds (ALK-Abelló Laboratories, Madrid, Spain) were used to investigate atopy. Prick–prick tests with boiled shrimp, lobster, small crab, spider crab, prawn, cockle, mussel, clam, scallop, razor shell clam, and raw and boiled barnacle were performed. SPTs with extracts of boiled (11 mg/mL) and raw barnacles (16 mg/mL), and boiled prawn (12 mg/mL) were performed on the patient and on 10 control subjects as well. All SPT reactions were read after 15 minutes, and a wheal diameter greater than 3 mm was considered positive.

Specific IgE to barnacle and prawn extracts, and prawn and barnacle tropomyosin were measured using the enzyme allergosorbent test (EAST). For that purpose, the solid phase was obtained by coupling the extract solution (10 mg/mL) to the 6-mm diameter cyanogen-bromide–activated paper discs, as described by Ceska and Lundkvist [13]. Results were expressed in accordance with the manufacturer's instructions for the specific IgE enzyme immunoassay kit (HYTEC HYCOR, Biomedical Ltd, Penicuit, UK), and values equal to or higher than 0.35 kU/L were considered positive. To determine the degree of cross-reaction between the tropomyosins from the 2 species (prawn and barnacle), an EAST-inhibition assay was performed following the method reported by Yman et al [14]. A pool of sera from non-allergic subjects was used as the negative control.

Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) was carried out according to the method of Laemmli [15]. Samples were dissolved in 0.125 M hydrogen

Summary of Test Results

Allergen	Method				
	SPT	EAST	OCT	OCT + ASA	OCT + Alcohol
Boiled barnacle extract (11 mg/mL)	20 × 11 mm	6.0 kU/L	Negative†	Negative	ND
Raw barnacle extract (18 mg/mL)	16 × 18 mm	3.2 kU/L	Negative†	ND	ND
Boiled prawn extract (12 mg/mL)	16 × 10 mm	1.4 kU/L	Negative†	Positive‡	ND
Barnacle tropomyosin	ND	7.6 kU/L	ND	ND	ND
Prawn tropomyosin	ND	7.5 kU/L	ND	ND	ND
Boiled barnacle	24× 13 mm§	ND	Negative	Negative	Negative
Raw barnacle	20 × 10 mm§	ND	ND	ND	ND
Boiled prawn	21 × 14 mm§	ND	Negative	Positive ‖	ND
ASA (cumulative dose, 965 mg)	ND	ND	Negative	ND	ND
Ibuprofen (cumulative dose, 700 mg)	ND	ND	Negative	ND	ND

* SPT indicates skin prick test; EAST, enzyme allergosorbent tests; OCT, oral challenge test; ASA, acetylsalicylic acid; ND, not done because it was not indicated or for specific clinical reasons.
† Spit–swallow challenge test
‡ Oral pruritus and hives after boiled prawn extract (54 mg) with 500 mg ASA. Three control subjects showed oral pruritus after the spit phase of challenge with boiled prawn extract without ASA
§ Prick–prick test
‖ Palpebral angioedema with hives over trunk and arms after a cumulative dose of 8 prawns with 500 mg ASA

chloride-Tris, pH 6.8, and were dissociated with 0.1% SDS at 100°C for 5 minutes. Separated protein bands were electrophoretically transferred to polyvinylene difluoride, essentially as described by Towbin et al [16]. After blocking, membranes were incubated overnight at 4°C with patient serum, incubated with antihuman IgE-horseradish peroxidase conjugate, and detected using the chemiluminescence method recommended by the manufacturer (ECL-Plus, Amersham Pharmacia Biotech, Little Chalfont, Buckinghamshire, UK).

To determine whether all the IgE binding proteins revealed in the raw barnacle blotting assay cross-react with prawn proteins, a Western blot and inhibition assay was performed. Patient serum was preincubated with the inhibitor phases overnight at 4°C; then raw barnacle membranes were incubated with the patient serum samples and immunodetection was performed as described above.

For oral challenge tests, informed written consent was obtained and fresh barnacles and prawns were purchased at the same market used by the patient 18 to 24 hours before each challenge test. Barnacles and prawns were boiled fresh on each test day. Challenge tests were performed on separate days using the following extracts: raw and boiled barnacles, boiled prawns, boiled barnacles, NSAIDs, and alcohol, according to the following protocols:

– *Boiled prawns*. Increasing amounts of boiled prawns (1, 2, 5, 10, and 20) were given at 2-hour intervals (cumulative dose of 38 prawns).

– *Boiled barnacles*. Boiled barnacles were given at increasing doses (2-hour intervals) beginning with 1 barnacle up to a total of 500 g of barnacles (the amount of barnacles similar to that eaten the day of the reaction).

– *Extracts of prawns and barnacles.* Extracts of boiled prawns and raw and boiled barnacles were freeze dried and stored until use. The 2-step spit-and-swallow procedure (local mucosal challenge) described by Ballmer-Weber et al [17] was used. Increasing doses at 30-minute intervals were given up to an equivalent of 18 boiled barnacles (1, 2, 5, and 10), 10 raw barnacles (1, 2, 3, and 5), and 10 boiled prawns (1, 2, 3, and 5) on 3 different days. Five control subjects (3, allergic to crustaceans, and 2, nonallergic) were tested with the boiled prawn extract, as well.

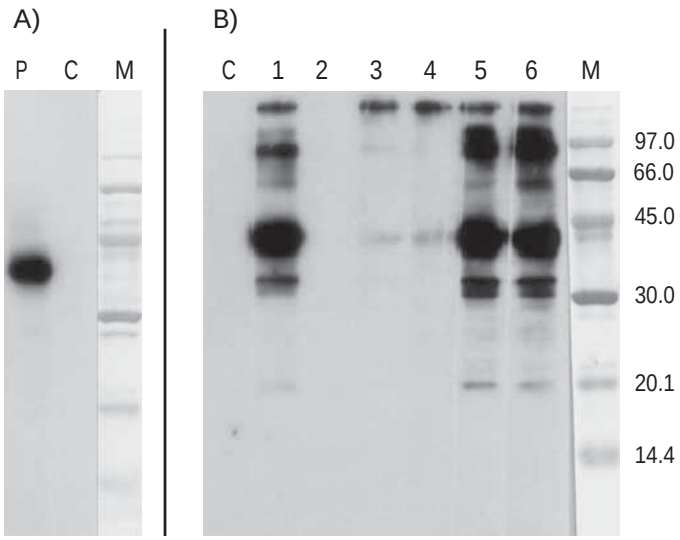
– *NSAIDs*. Acetylsalicylic acid (ASA) and ibuprofen were administered on 2 different days. For the ASA challenge, the patient began with a placebo followed shortly by a 30-mg dose of ASA, and then advanced to 60-mg, 125-mg, 250-mg, and 500-mg doses at 2-hour intervals (cumulative dose of 965 mg). One week later, increasing doses of ibuprofen from 100 mg to 400 mg were administered at 2-hour intervals up to a cumulative dose of 700 mg.

– *Boiled prawns and ASA*. An oral challenge with a single dose of 500 mg of ASA followed 1 hour later by increasing amounts of boiled prawns from 1 to 20 (cumulative dose of 38).

– *Extract of boiled prawns and ASA*. A single dose of 500 mg of ASA followed 1 hour later by the extract of boiled prawns (equivalent dose of 10 boiled prawns) administered by the 2-step spit-and-swallow procedure described above.

– *Boiled barnacles and ASA*. A single dose of 500 mg of ASA followed 1 hour later by increasing amounts of boiled barnacles from 1 to 16 (cumulative dose of 31 barnacles) at 2-hour intervals, and followed by as many barnacles as the patient wanted up to a total amount of 500 g.

– *Boiled barnacles and alcohol.* The patient was invited to eat as many boiled barnacles as she wanted while drinking 330 mL of white wine and finally 125 mL of champagne, under medical supervision.



A) Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) immunoglobulin E immunoblotting results for raw prawn extract. Lane P, patient serum; lane C, control serum (pool of sera from nonatopic subjects); lane M, molecular mass marker.
B) SDS-PAGE immunoblotting inhibition results for raw barnacle extract. Lane C, control serum (pool of sera from nonatopic subjects); lane 1, patient serum; lane 2, patient serum previously incubated with raw barnacle extract (0.6 mg/mL); lane 3, patient serum previously incubated with raw prawn extract (0.6 mg/mL); lane 4, patient serum previously incubated with prawn tropomyosin (60 µ/mL); lane 5, patient serum previously incubated with bovine serum albumin (60 µ/mL); lane 6, patient serum previously incubated with lamb extract (60 mg/mL); lane M, molecular mass marker.

Test Results

SPTs with common inhalants and prick–prick tests with small crab, cockle, mussel, clam, scallop, and razor shell clams were negative. SPTs with boiled and raw barnacle extracts and with boiled prawn were positive. The prick–prick with boiled shrimp, lobster, spider crab, prawn, and raw and boiled barnacle were positive (table).

In EAST and EAST–inhibition tests, positive results were obtained against raw and boiled barnacle, raw prawn, and both tropomyosins. Inhibition of IgE binding to raw barnacle extract was greater with barnacle tropomyosin (61%) than with prawn tropomyosin (52%) at a 25 µg/mL concentration. A summary of the results of the diagnostic tests is given in the table. Results from a Western blot of raw prawn revealed an IgE binding band at 37 kDa; IgE binding bands of 143, 83, 38, 32, and 20 kDa appeared in the raw barnacle assay (Figure 1A). All IgE-binding bands except the 143-kDa band disappeared when both raw prawn extract and large prawn tropomyosin were used as inhibitors (Figure 1B).

In oral challenge testing no reaction occurred after the first 4 tests or the last 2 tests. In the third test, 3 positive-control subjects (prawn-allergic patients) showed oral pruritus after the spit phase of the challenge while 2 negative-control subjects experienced no reaction. In the fifth test, 60 minutes after eating 8 prawns, preceded by a 500-mg dose of ASA 30 minutes earlier, the patient exhibited palpebral edema with hives over her trunk and arms. The patient was treated with 0.3 mL of intramuscular epinephrine 1/1000, and 50 mg of oral hydroxyzine orally with total recovery 2 hours later. In the sixth test, after 15 minutes of an equivalent dose of 3 prawns (54 mg of the extract) preceded by ASA, the patient complained of oral pruritus followed shortly by hives around her lips.

Discussion

Based on clinical history, the first impression was that the patient might react to prawns whenever they were eaten with NSAIDs but barnacles themselves seemed to be enough to induce symptoms if a sufficient amount were eaten. Our literature search located only 1 article dealing with barnacle hypersensitivity but oral challenges were not performed in those patients [18]. The detection of serum specific IgE against both barnacle and prawn tropomyosins, the main allergen among crustaceans [19,20], did not explain why the patient reacted so different to each food. Besides, no respiratory arthropod sensitization could explain the presence of specific IgE against tropomyosin in this patient [19,21]. The barnacle blotting assay showed a specific 143-kDa IgE binding protein not present in prawn and with no cross-reaction with prawn proteins. This protein became a candidate to explain the specific allergy to barnacle but the negative response to barnacles after oral challenge led us to reject that hypothesis.

In an elegant hypothetical approach, Larramendi [22] proposed a formula in which an allergic reaction might or might not be elicited, depending on the relative amount of some limiting factors and the relevant allergen to which the subject is sensitized. The same author suggested a classification of food allergy based not only on the ability of the food to induce an IgE response, but also on the susceptibility of the subject to react in the presence of limiting factors [23]. Factors that can modify the clinical response after the ingestion of some foods include the concomitant use of NSAIDs [24,25], exercise [26,27], a combination of both [28], alcohol [29], viruses [30], other foods [31], and perhaps some other unknown factors or combinations of factors still not described. Some of these factors may act by changing the allergenic potential of the food before ingestion, but others may interact after intake [22], increasing, for instance, intestinal absorption [24,25,28]. Moreover, the possibility of hidden allergens is always present [32].

From the results obtained in the oral challenge tests, NSAIDs, particularly ASA, can definitively be considered an associated factor required in combination with prawns to elicit the reaction in this patient. Despite the detailed study, however, the possible associated factor involved in the reactions with barnacles remains unknown.

The effect of the dose of allergen needed to provoke a

positive reaction, the threshold, was also taken into account [33]. However, the patient ate 500 g of boiled barnacles with no problems, and no changes in this result were obtained despite the use of ASA or alcohol. Exercise was also ruled out as a factor.

Some questions remain to be answered, leaving the problem of what recommendations patients should be given. We still do not have a definitive answer as to whether or not it is safe to eat a food when a specific IgE against it is detected and the clinical record shows that it is always present during the reaction, independently of the possible tolerance of the food between episodes. It can be argued that because additional factors may not be obvious to patients, careful history-taking is mandatory and a different protocol in each case may be necessary even though a solid conclusion may not be achievable in some cases. Perhaps, as has been suggested [22], the main question we should ask our patients is whether or not consumption of the candidate food precedes every reaction, rather than whether the reaction appears every time they consume the candidate food.

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