

Clinical aspects of allergic disease

Mite-contaminated foods as a cause of anaphylaxis

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Background: Although insect and arthropod contamination of certain foods has been recognized for many years, allergic manifestations caused by ingestion of mite allergens have only rarely been reported.

Objective: The purpose of this study is to present clinical observations in patients who experienced acute anaphylaxis after eating mite-contaminated foods.

Methods: Thirty atopic subjects who were first seen with systemic anaphylaxis precipitated by the ingestion of wheat-containing foods underwent skin prick tests with inhalant and food extracts, as well as with uncontaminated and mite-contaminated wheat flour. Flour samples were examined microscopically for identification and counting of mites. Der p 1 and Der f 1 levels were quantitated by using immunochemical methods.

Results: The most common symptoms were breathlessness, angioedema, wheezing, and rhinorrhea, which started between 10 and 240 minutes after eating. Abundant mites were present in the flour obtained from 28 patients; *Suidasia* spp. mites were found in grated bread from the other two patients. Positive prick test responses to *Dermatophagoides farinae*- and mite-contaminated flour and negative skin test responses to wheat extract, other food extracts, and uncontaminated wheat flour were found in all patients. Skin test responses were positive in volunteers with mite allergy even after heating the mite-contaminated flour at 100° C. Screening of 35 unselected flour samples demonstrated the presence of mites in 13 of them (37.1%).

Conclusions: Systemic anaphylaxis can occur after the ingestion of heated or unheated mite-contaminated foods. This problem may be more prevalent in tropical and subtropical countries than previously recognized. (J Allergy Clin Immunol 1997;99:738-43.)

Key words: Anaphylaxis, mites, *Dermatophagoides farinae*, wheat flour, food allergy

Allergy to food contaminants is being increasingly recognized,¹ but there are few reports in the literature on the possible occurrence of allergic manifestations

Abbreviations used

NSAID: Nonsteroidal antiinflammatory drug

SPT: Skin prick test

WF: Wheat flour

after ingestion of allergens regularly classified as inhalants. The recent description of two patients who experienced anaphylaxis after the ingestion of food contaminated with *Dermatophagoides farinae*^{2,3} prompted the report of our observations. Meanwhile, two other reports from Europe and Japan^{4,5} have shown that mite-contaminated food can indeed induce systemic anaphylaxis. These studies demonstrated systemic anaphylaxis after the ingestion of wheat flour (WF) contaminated with *Dermatophagoides* spp.⁴ in 12 patients and *Tyrophagus putrescentiae* in two cases.⁵ These studies confirm that systemic anaphylaxis can be induced by different mite species, including storage mites. Different mite species have also been implicated as aeroallergens in occupational and allergic asthma.⁶

We describe a series of 30 patients who were first seen with immediate hypersensitivity after eating foods prepared with WF containing high concentrations of mites belonging to several species in Venezuela. Such cases could be more common in North and South America, than previously thought, especially in regions with subtropical and tropical climates.

METHODS

Patient population

Between October 1982 and January 1996, 30 patients were evaluated because of unexplained anaphylaxis. All of them had symptoms promptly after ingestion of WF-containing foods. Clinical data were gathered by a questionnaire given to the patient and by physician interview. Items included age, sex, symptoms, date of the event, time course, previous allergic diseases, foods that provoke symptoms, and treatment. After informed consent was obtained, patients were included in the study. The protocol was approved by the Institutional Review Board of Centro Médico-Docente "La Trinidad."

Mite screening

The patients brought the packages containing the WF used to prepare the foods ingested before the anaphylactic episode to the physician's office. These WF samples were then used for mite identification and, after extraction, for skin testing. Flour

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Presented in part at the Fifty-first Annual Meeting of the American Academy of Allergy and Immunology in New York, February 1995.

Received for publication June 25, 1996; revised Nov. 13, 1996; accepted for publication Dec. 9, 1996.

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0091-6749/97 \$5.00 + 0 1/179718

TABLE I. Clinical data

Patient No.	Sex	Age (yr)	Reaction time (min)	History	Precipitating food(s)
1	M	20	60	Asthma, rhinitis	Pancakes
2	M	18	NA	Rhinitis	Pancakes
3	M	26	30	Asthma, rhinitis	Pancakes
4	M	24	10	Rhinitis, conjunctivitis	Pancakes, pizza
5	M	16	20	Asthma, rhinitis	Cake
6	F	21	NA	Asthma, rhinitis	Cake, pasta
7	M	24	30	Asthma, rhinitis	Cake
8	F	18	NA	Asthma, rhinitis	Cake
9	F	24	NA	Asthma, rhinitis	Pasta
10	F	25	20	Rhinitis	Pancakes
11	F	19	30	Rhinitis	Pancakes
12	F	15	15	Rhinitis	Pancakes
13	F	13	60	Rhinitis, atopic dermatitis	Pancakes
14	M	15	NA	Asthma, rhinitis	Pancakes
15	M	14	30	Asthma, rhinitis	Pancakes
16	M	19	30	Rhinitis	Pizza
17	F	27	30	Asthma, rhinitis, atopic dermatitis	Pancakes
18	M	15	60	Asthma, rhinitis	Pancakes
19	M	31	30	Rhinitis	Cornmeal cake
20	M	20	240	Rhinitis	Bread
21	F	39	30	Rhinitis	Pancakes
22	F	39	30	Rhinitis	Wheat/cheese appetizer
23	M	16	30	Rhinitis	Parmigiana steak
24	F	16	90	Asthma, rhinitis	Wheat sweet (alfajor)
25	F	37	30	Asthma, rhinitis	Parmigiana steak
26	F	27	30	Asthma, rhinitis	Pancakes
27	F	24	60	Asthma	Pancakes
28	F	45	NA	Rhinitis	Cake
29	F	25	15	Asthma, rhinitis	Béchamel sauce
30	M	15	30	Rhinitis	Pancakes

NA, Not available.

samples were examined under light microscopy for the presence or absence of mites. This part of the investigation was done at the physician's office. The prevalence of mite contamination in flour samples in Caracas was studied in 35 unselected WF samples from the four brands marketed. They were collected in houses and supermarkets from 25 different locations. Flour donors were questioned about brand, storage conditions, and date of purchase. Special attention was given to information about the date when the flour package was opened. Mite identification and counting of these samples was performed at the University of South Florida College of Medicine, Division of Allergy and Immunology, by one of the investigators (E. F. C.); also included were five samples from the patients who experienced anaphylaxis. WF samples from Venezuela's largest WF factory, taken every 2 weeks during an 8-month period, before and after impact sterilator treatment, were also investigated for the presence of mites.

Skin tests

Skin prick tests (SPTs) were performed on the forearm, and the results were read after 15 minutes. Commercial inhalant and food extracts diluted 1:10 (wt/vol) (Center Laboratories, Port Washington, N.Y.) and uncontaminated and mite-infested WF diluted 1:5 (wt/vol) in normal saline solution were used for skin testing. Histamine phosphate (1 mg/ml) and glycerosaline solution served as positive and negative controls, respectively. A

wheel greater than the glycerosaline control by 3 mm or more was considered a positive response.

To assess the thermal sensitivity of mite antigens present in the flour, duplicate mite-contaminated samples were heated for 1 hour at 100° C by autoclaving. Heated flour was then tested for allergenic activity in SPTs in 13 volunteers sensitive to mites; an unheated control sample was tested simultaneously.

Quantitation of mite allergens

Der p 1 and Der f 1 content was quantified by ELISA by using previously described methods.⁷ A total of 38 flour samples, including three from patients who experienced anaphylaxis, were analyzed.

Statistical analysis

Comparison of the difference between SPT responses with mite-contaminated WF before and after heating was performed with Student's *t* test, with a 0.05 significance level.

RESULTS

Clinical data

We have identified 30 individuals (16 women and 14 men) who were first seen with anaphylaxis immediately after ingestion of mite-contaminated foods. The clinical characteristics of these subjects are summarized in Table

TABLE II. Clinical manifestations

Symptoms	No. of patients (%)
Breathlessness	27 (90.0)
Angioedema	15 (50.0)
Wheezing	12 (40.0)
Rhinorrhea	9 (30.0)
Cough	8 (26.6)
Stridor	6 (20.0)
Dysphagia	6 (20.0)
Urticaria	6 (20.0)
Abdominal cramps	4 (13.3)
Conjunctivitis	3 (10.0)
Skin rash	2 (6.6)
Dysphonia	2 (6.6)
Sneezing	1 (3.3)
Vomiting 1 (3.3)	
Cyanosis	1 (3.3)
Pruritus	1 (3.3)
Tachycardia	1 (3.3)

I. The mean age of the subjects was 23.1 ± 8.4 years (range, 13 to 45 years).

All patients were atopic, as demonstrated by positive skin test responses to a panel of aeroallergens that included house dust, *D. farinae*, molds, weed, grass and tree pollen mixtures, dog allergens, cat allergens, and feathers. All showed strong SPT reactions to *D. farinae*; 14 subjects had rhinitis and asthma previously; 12 had rhinitis exclusively; one had rhinitis combined with asthma and atopic dermatitis; one had rhinitis and atopic eczema; one had rhinitis and conjunctivitis; and one had asthma exclusively.

The foods responsible for induction of the anaphylactic episodes are also shown in Table I. Homemade pancakes were the most frequently incriminated food (in 16 patients). As shown in Table I, patients 4 and 6 reacted to more than one wheat-containing food. Patients 11 and 28, in addition to having anaphylaxis triggered by the oral route, also complained of difficulty in breathing, rhinorrhea, conjunctivitis, and eyelid edema after the inhalation of mite-contaminated flour while preparing pancakes (patient 11) or a cake (patient 28). Patient 19 had life-threatening symptoms, including cyanosis, induced by the ingestion of cornmeal cake prepared with a mite-containing commercial mixture of corn and wheat flours.

Symptoms began between 10 and 240 minutes after ingestion in 24 patients and earlier than 60 minutes after ingestion in 22 and included the following (in order of frequency): breathlessness, facial angioedema, wheezing, rhinorrhea, cough, stridor, dysphagia, urticaria, conjunctivitis, abdominal cramps, dysphonia, sneezing, tachycardia, vomiting, cyanosis, pruritus, and morbilliform rash (Table II). Two patients in this series were treated in the intensive care unit because of acute respiratory failure. Twenty patients (66.6%) had a history of sensitivity to nonsteroidal antiinflammatory drugs (NSAIDs), as manifested by urticaria or angio-

edema. A history of reactions to aspirin was present in 18 patients; to pyrazolone in 11; to acetaminophen in four; to diclofenac in three; to ibuprofen in three; and to naproxen, glafenin, octafenin, tiaprofenic acid, ketoprofen, flurbiprofen, and salsalate in one. Sensitivity to more than one NSAID was present in most patients.

All 30 patients have been followed up for 3 months to 14 years (mean, 19.1 ± 23.1 months) and no repeat episodes of anaphylaxis have occurred, even though they continue to eat WF-containing foods. However, they have been cautioned to avoid any WF that appears to be old, wet, or dark. Patients 4 and 10 had recurrent anaphylaxis provoked by mite-containing pancakes (two times for patient 4 and three times for patient 10) before diagnosis was made and adequate preventive measures were instituted.

Skin tests

SPT responses were positive with *D. farinae* and mite-contaminated flour in all 30 patients. However, skin test responses were negative with commercial wheat, other foods, and uncontaminated WF. The sizes of wheal diameters were compared in 13 individuals allergic to mites by using mite-containing WF before and after heating. There was a significant reduction in the mean sizes of the wheals after heat treatment of the flour. Mean wheal size before heating was 9.0 mm, and after heating, it was 7.07 mm ($p = 0.05$). However, in all cases positive reactions (wheal >3 mm) were observed with both heated and unheated flours. These results suggest the presence of heat-labile and heat-stable allergens in the mite-contaminated flour.

Mite identification

The WF from 28 patients contained abundant *D. farinae* mites in different stages of development, as well as other mite species (*Suidasia*, *Aleuroglyphus*, *D. pteronyssinus*). Amounts as high as 5000 mites per gram of flour were counted at the University of South Florida College of Medicine in five of these samples. One WF sample contained 100 μg of Der f 1 allergen and 0.54 μg of Der p 1 per gram of flour. In patients 23 and 25, the reactions were induced by the ingestion of steaks covered with grated bread; microscopic observation of the grated bread used for cooking demonstrated high levels of *Suidasia* spp.

Thirty-five additional unselected WF samples from 25 different locations in Caracas were screened for mites. Twenty-nine packages had been preopened for periods ranging from several days to weeks; of these, 23 were stored at room temperature, and six were kept in the refrigerator. Six additional packages were opened immediately before examination (five were kept at room temperature and one was stored at 4°C). Mites from five different species were found in 13 samples (37.1%) (Table III). Four packages were opened just before screening and stored at room temperature; the other mite-positive WF packages had been opened earlier. In

this group, seven packages were kept at room temperature and two at 4° C (Table III). No measurable quantities of Der p 1 or Der f 1 allergens were detected in these 35 samples.

These findings suggest that mite contamination could be occurring in the factory before the flour is packed or at home before or after the package is opened. To clarify this point, we studied WF samples from the largest factory in Venezuela, collected every 2 weeks for 8 months, before and after impact sterilator treatment. No live mites were observed. A follow-up study of these flour samples, stored at room temperature for up to 11 months, did not reveal the presence of any mites.

DISCUSSION

House dust mites, mainly pyroglyphids from the genus *Dermatophagoides*, are the most important source of inhalant indoor allergens worldwide⁸⁻¹⁰ (including Venezuela).^{11, 12} Mites are known to infest stored foods¹³ and to produce rhinitis or asthma as food-related inhalant allergies, generally occurring as occupational diseases.¹⁴ All these ailments occur despite modern control measures against biologic contamination. In fact, the food industry and the government accept that, for practical purposes, food cannot be made completely insect-free, and a level of up to 75 insect "fragments" per 50 grams of grain sample is permitted.¹⁴

Although anaphylaxis caused by hidden food allergens is being increasingly recognized,¹ there are very few reports dealing with allergy from the ingestion of antigens of insect or arthropod origin, and mites are not regarded as sources of ingestant allergens. The review article by Phillips and Burkholder concluded that "additional case histories linking arthropods to food-illness and injuries are also needed."¹⁴

The recent descriptions by Erben et al.² and Spiegel et al.³ of two patients who had systemic anaphylaxis after eating beignets prepared with a *D. farinae*-containing ready-made beignet mix encouraged us to report our observations with a number of similar cases over a 14-year period. We have observed generalized allergic reactions occurring rapidly after ingestion of foods prepared with WF heavily infested with mites in 30 atopic subjects who were sensitive to mites. It must be noticed that skin test reactivity to *Dermatophagoides* spp. in our general population is 14.5%,¹⁵ whereas in nonanaphylactic individuals with atopy, it varies between 7.3% and 54%.¹⁶ Clinical manifestations; the time course of the events; and the response to the usual emergency treatment with epinephrine, intravenous corticosteroids, oxygen, fluid replacement, and antihistamines are strongly suggestive of an immediate-type hypersensitivity reaction. It must be mentioned that in this group of patients, no cause was determined in the emergency department. Most of the patients were released with the diagnosis of "unexplained anaphylaxis," "bronchial asthma," "laryngeal edema," or even "urticaria" or "angioedema." In only a few of the patients, the misdiagnosis of wheat

TABLE III. Mite species in 35 flour samples

Species	No. of positive samples*	Mites/gm	
		Mean	Range
<i>Suidasia</i> spp.	5	1300	100-2500
<i>D. pteronyssinus</i>	4	50	20-100
<i>Aleuroglyphus ovatus</i>	2	2550	100-5000
<i>Lepidoglyphus destructor</i>	2	90	80-100
<i>Blomia tropicalis</i>	1	50	

*A total of 13 samples (37.1%) analyzed contained mites. One sample contained two mite species.

allergy was entertained. We believe that this syndrome may be occurring in tropical environments more often than recognized, but only some patients are appropriately referred to the allergist for further diagnostic study and treatment. In this regard, we must mention that recently Klein and Yocum¹⁷ observed that in about 50% of the cases of unexplained anaphylaxis, patients are not referred to the allergist for study and follow-up.

For ethical reasons, we did not perform oral challenges with mite-contaminated flour in these patients, and it could therefore be argued that we have not demonstrated a cause-effect relationship between allergy to mites and the observed clinical picture. Nevertheless, two of our patients experienced repeated episodes of acute, life-threatening anaphylaxis induced by the ingestion of mite-infested foods.

House dust mites are the most important source of allergens for a considerable portion of the population in Caracas, and because of geographic and climatic conditions, allergies tend to be perennial. Local temperatures and high relative humidity are in the range considered to be most favorable for mite growth.¹⁸⁻²⁰ We believe that a low degree of mite infestation in the flour could evolve into mite proliferation when flour packages are left at room temperature for days to weeks. Therefore tropical and subtropical climates would bear a higher risk for mite contamination of flour.

Our results also suggest that mite contamination may occur at home or at the factory because we observed mites in four packages opened immediately before screening. Although flour is submitted to impact treatment at the sterilator in order to destroy any live insects or arthropods and their eggs, a low degree of infestation, perhaps resisting adverse conditions by means of transformation into a desiccation-resistant, prolonged, quiescent, protonymphal stage that survives dry conditions, would result in a substantial mite population later when climate conditions become optimal for reproduction.^{21, 22} An improperly sealed container would also allow the entry of mites and therefore permit colonization during transfer or storage.

The results of skin tests performed with mite-contaminated WF before and after heating suggest the presence of heat-resistant allergens, which is in agreement with the induction of anaphylaxis by cooked and extensively heated WF, and of heat-sensitive allergens because,

after heating the flour, there was a decrease in the size of the wheal in about half of the individuals tested. We postulate that, because of its heat-resistance, the responsible allergen or allergens would probably belong to group 2 allergens (Der 2), present in higher concentrations in mite bodies. It has been demonstrated that group I allergens (Der p 1 and Der f 1), highly concentrated in the feces, are heat-labile²³ and therefore more likely to be denatured during heating.

In some of our patients' WF samples, we found up to 5000 *D. farinae* and *Aleuroglyphus ovatus* mites per gram of flour. *Suidasia* spp. were also detected in large numbers. The latter species is in the same family (Acaridae) as *Tyrophagus putrescentiae*, also incriminated in two case of anaphylactic shock in Japan.⁵ We confirmed that about 33 gm of flour is used to make one pancake, which means that the patient would ingest about 165,000 mites per pancake. We calculated that some of these patients may have ingested as much as 3300 µg (3.3 mg) of group I allergen per pancake, an extremely high amount that could provoke systemic anaphylaxis in the mite-sensitive subject. It has been suggested that the mean ratio between Der p 1 and Der p 2 in house dust is approximately 2.5:1.²⁴ Therefore the Der p 2 concentration in these samples could have been approximately 1320 µg per pancake (1.32 mg). We therefore postulate that the ingestion of more than 1 mg of Der p 2 or Der p 1 could be a risk factor for anaphylaxis in individuals allergic to mites. The ingestion of approximately 5000 mites per gram of food also seems to be a risk factor.

Another observation that deserves further study is the presence of an increased prevalence of sensitivity to NSAIDs in our study group. This finding was rather unexpected considering that allergy to mites is an IgE-mediated condition, whereas sensitivity to NSAIDs is generally regarded as being non immunologically mediated or anaphylactoid. It has been reported that the prevalence of sensitivity to aspirin varies between 21% and 30% in patients with chronic urticaria.²⁵ In a previous study, we found that sensitivity to aspirin was more frequent in atopic subjects than in nonatopic subjects with chronic urticaria or angioedema.²⁶ We investigated the prevalence of a history of sensitivity to NSAIDs in nonselected atopic patients (with asthma, rhinosinusitis, conjunctivitis, and eczema), and we found that 23% of adults had such a history. Our findings of increased prevalence of a history of sensitivity to NSAIDs in atopic individuals who experience systemic anaphylaxis after ingestion of mite-contaminated foods have recently been reproduced by Blanco et al.⁴ in the Canary Islands, Spain.

In conclusion, we have observed a number of cases of severe anaphylaxis precipitated by ingestion of mite-contaminated foods. These observations have two other important implications. (1) There is the risk of sensitization for the general population through long-term regular ingestion of low quantities of inhalant allergens, mainly mites, "hidden" in the food. (2) There is the possibility of an aggravation of symptoms

of preexisting allergic diseases (urticaria, asthma, rhinitis, or atopic dermatitis) by ingestion of mite-contaminated foods.

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