

Anaphylactic reaction after the ingestion of chamomile tea: A study of cross-reactivity with other composite pollens

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We report a case of an 8-year-old atopic boy in whom ingestion of a chamomile-tea infusion precipitated a severe anaphylactic reaction. The patient suffers from hay fever and bronchial asthma caused by a variety of pollens (grass, olive, and mugwort). This severe reaction was developed after his first ingestion of chamomile tea. Studies revealed the presence of immediate skin test reactivity and a positive passive transfer test to chamomile-tea extract. Moreover, both specific antichamomile-tea extract and anti-Matricaria chamomilla-pollen extract IgE antibodies were detected by an ELISA technique. Cross-reactivity among chamomile-tea extract and the pollens of Matricaria chamomilla, Ambrosia trifida (giant ragweed), and Artemisia vulgaris (mugwort), was demonstrated by an ELISA-inhibition study. These findings suggest a type I IgE-mediated immunologic mechanism as being responsible for the patient's anaphylactic symptoms and also suggest that the patient cross-reacted the pollens of Matricaria chamomilla contained in the chamomile tea because he was previously sensitized to Artemisia pollen. (J ALLERGY CLIN IMMUNOL 1989;84:353-8.)

The Asteraceae (Compositae) are one of the largest families of flowering plants, comprising about 25,000 species. The real offenders of this family are the wind-pollinated plants that include members of the subtribe Ambrosiinae (*Ambrosia*, *Dicoria*, *Hymenoclea*, *Iva*, *Xanthium*, *Parthenice*, some *Baccharis*, and *Artemisia*). In North America, the species of *Ambrosia* are by far the most important cause of pollinosis, with *A. artemisiifolia* and *A. trifida* alone accounting for more hay fever than all other plants together.¹ Most Compositae pollen is potentially allergenic, particularly pollen that are most closely allied to ragweed and other Ambrosiinae pollen, since the possibility of cross-reaction with these pollens is likely to be high.² The plant *Matricaria chamomilla* also belongs

Abbreviations used

PBS: Phosphate-buffered saline
BSA: Bovine serum albumin

to the Compositae family, but, unlike the other previously mentioned members of this family, its pollination is entomophilous.¹ Although the infusion made from its flowers is a common beverage all over the world because of, in part, the numerous therapeutic properties attributed to it,³ very few cases of anaphylaxis after its ingestion have been described.^{4,5}

This article deals with a young patient who was initially observed with a severe anaphylactic reaction after ingesting for the first time a chamomile infusion. The results of the investigations carried out suggest that prior sensitization to *Artemisia* pollen resulted in a cross-reaction with the pollen of *Matricaria* contained in the infusion.

Case report

The patient, an 8-year-old boy, experienced hay fever and seasonal asthma caused by a variety of pollen for the last 3 years. Throughout the last 2 years, the patient was managed by immunotherapy with a mix of grass- and olive-

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TABLE I. IgE activity against chamomile tea and Compositae-pollen extracts in patient's serum detected by ELISA

ELISA wells coated with	Patient's serum		Control sera	
	Unheated	Heated*	Healthy†	Hay fever‡
None	0.04	ND	ND	ND
Chamomile tea	1.75	0.13	0.14 ± 0.05	0.11 ± 0.10
Pollen				
<i>Matricaria</i>	1.88	0.05	0.13 ± 0.03	0.15 ± 0.08
<i>Artemisia</i>	1.35	0.11	0.06 ± 0.07	0.17 ± 0.07
<i>Ambrosia</i>	1.44	0.12	0.15 ± 0.07	0.13 ± 0.05

ND, Not done.

Results are expressed in optical densities at 492 nm (mean ± SD, except patient's data that correspond to the mean of duplicates).

*Four hours at 56° C.

†From 22 nonatopic, control subjects.

‡Sera from five patients with hay fever with serum IgE levels between 500 to 1000 IU/ml.

pollen extract. His mother has bronchial asthma caused by an allergy to house dust mite.

In May 1987, a month after he stopped immunotherapy, the patient experienced night episodes of coughing, slight dyspnea, and wheezing. The patient's mother tried helping him by giving him an infusion of chamomile tea, and several minutes later the patient's condition suddenly worsened, developing dyspnea, increased coughing, chest tightness and wheezing, abdominal pain, vomiting, and general itchiness of the skin without wheal formation.

On arrival at our center, the patient was pale and sweating. He eventually became so confused that he lost consciousness and collapsed. On examination, he demonstrated tachypnea, supraclavicular recession, very weak pulse, heart rate of 120, and blood pressure so low that it could not be measured. Chest auscultation revealed disseminated rhonchi. Emergency treatment included subcutaneous injection of aqueous epinephrine, intravenous fluids, methylprednisolone, and chlorpheniramine. A significant improvement was observed after a few minutes. The patient regained consciousness, and 90 minutes later, the blood pressure recording revealed 100/60 mm Hg. The boy remained under observation in an emergency room for the following 24 hours.

MATERIAL AND METHODS

Preparation of allergen extracts

Two grams of the patient's chamomile-tea dust were defatted with acetone and extracted in 20 ml of 0.01 mol/L of phosphate and 0.15 mol/L of NaCl, pH 7.4 (PBS). The mixture was stirred for 24 hours at 4° C and then paper filtered (Whatman Ltd., Maidstone, England) and centrifuged (1500 g for 20 minutes). The supernatant was recovered and sterilized by 0.22 µm filtration (Millipore, Milshiem, France), having a final concentration of 1:10 wt/vol. Protein concentration was determined by use of Bio-Rad protein assay (Bio-Rad Laboratories, Richmond, Calif.).

The same procedure was used to extract the antigens from the following pure pollen samples: *M. chamomilla* (Allergon AB, Engelholm, Sweden), *Artemisia vulgaris*, and *Ambrosia trifida* (Miles Martin, Spokane, Wash.).

Skin tests

Skin prick tests were performed 2 weeks after the severe reaction occurred, beginning with a 1:100,000 wt/vol concentration of chamomile-tea extract, *M. chamomilla*-pollen extract, and *Artemisia*-pollen extract, and were progressively increased by tenfold until a positive reaction was obtained.

A battery of commercially available common allergens that included *Dermatophagoides pteronyssinus*, *Phleum pratense* (timothy), *Olea europaea* (olive), molds, and danders (Hollister-Stier Laboratories, Spokane, Wash.) were also skin prick tested.

Ten patients with hay fever and 10 normal individuals were tested with all the above-mentioned extracts as a control. Histamine dihydrochloride (1 mg/ml) was used as a positive control, and 50% glycerol was used as a negative control. All skin test sites were read after 15 minutes, and a wheal of at least 3 mm by 3 mm was considered as positive.

Passive transfer tests

Heated (56° C for 2 hours) and unheated samples (50 µl) of the patient's serum, previously screened for hepatitis B surface antigen, were injected intradermally into one non-allergic volunteer. Twenty-four hours later a prick test with 1:10 wt/vol of chamomile-tea extract was done in the pretreated skin sites and in a different skin area as control.

ELISA

The wells of a polystyrene 96-well microplate (Nunc, Roskilde, Denmark) were coated with chamomile, *Matricaria*, *Artemisia*, or *Ambrosia* extracts, at a protein concentration of 5 µg/ml in PBS. After an overnight incubation



FIG. 1. Chamomile-flour dust containing *M. chamomilla* pollens (small arrow). An anther full of this pollens (arrow). (Original magnification $\times 100$.)

at 4° C, the plates were washed with PBS containing 0.1% Tween 20 (washing buffer), and the wells were neutralized with 1% of BSA (Sigma Chemical Co., St. Louis, Mo.) in PBS for 1 hour at room temperature. After plates were washed, 100 μ l of undiluted serum was added per well, and the plates were incubated in a moist chamber for 4 hours at room temperature. At the end of the incubation period, the plates were washed, and the wells were filled with 100 μ l of 1:4000 dilution (PBS-BSA) of affinity-isolated goat F(ab')₂ antibodies to human ϵ -chain fragments and conjugated with peroxidase (Tago Inc., Burlingame, Calif.). These labeled antibodies were chosen for their lack of cross-reactivity with human IgG in the assay conditions used. After an overnight incubation at 4° C and a final washing step, 100 μ l of substrate solution (0.05% H₂O₂, 0.02 mol/L of o-phenylenediamine, and 0.1 mol/L of citrate buffer, pH 5.5) was added. The reaction was stopped with 100 μ l of 2 N HCl and read at 492 nm.

Inhibition assays

Cross-allergenic studies were performed according to the method of Gleich et al.⁶ but with ELISA. Briefly, 100 μ l of a 1:2 dilution in PBS of the patient's serum was mixed with the same volume of a number of serial dilutions of each extract sample, previously adjusted to 250 μ g/ml in protein. *D. pteronyssinus* extract (α -base, Dome-Hollister-Stier, Bridgend, U.K.) was used in each series of inhibitions to determine the amount of inhibition by an unrelated antigen extract. After overnight incubation at 4° C, all samples were tested for specific IgE, as above, without further dilution. Results were expressed as the inhibition percentage of the initial activity (nonabsorbed).

As control of specificity, 10 sera containing IgE to *D. pteronyssinus* were incubated in the same conditions with

the above extracts or PBS. In these cases, ELISA was performed with *D. pteronyssinus*-coated wells (3M Diagnostic Systems, Inc., Santa Clara, Calif.) following the same procedure described before.

RESULTS

Skin test

Testing with 1:100 wt/vol of chamomile-tea extract was enough to elicit in the patient a local reaction of 4 by 6 mm wheal. Positive immediate reactions were also observed after 1:1000 wt/vol *M. chamomilla* pollen and *Artemisia* pollen extracts. Skin tests with *Olea*- and *Phleum*-pollen extracts were also positive. Control, nonatopic subjects did not react to 1:10 wt/vol of all the above-mentioned extracts. All control, atopic subjects reacted to the grass-pollen extracts, but none of the subjects reacted to chamomile-tea extract, *Matricaria*-pollen, *Artemisia*-pollen, or *Ambrosia*-pollen extracts.

Prausnitz-Küstner test

The passive transfer recipient was negative to skin testing with chamomile-tea extract at the untreated and heat-treated serum sites. In contrast, testing with this extract at the unheated serum site was positive.

Specific IgE measurement

To confirm the presence in this patient of IgE antibodies to antigens contained in chamomile-tea extract, we tested the patient's serum for specific IgE by ELISA. We also tested pollen extracts from *Matricaria* and from other Compositae (*Ambrosia* and

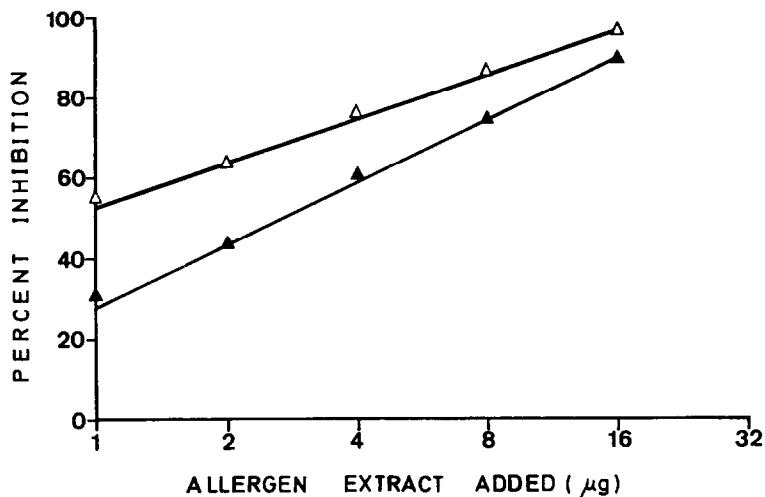


FIG. 2. Chamomile tea ELISA-inhibition assay; percent of inhibition of patient's serum by increasing amounts of chamomile tea (▲) and *M. chamomilla* pollen (Δ).

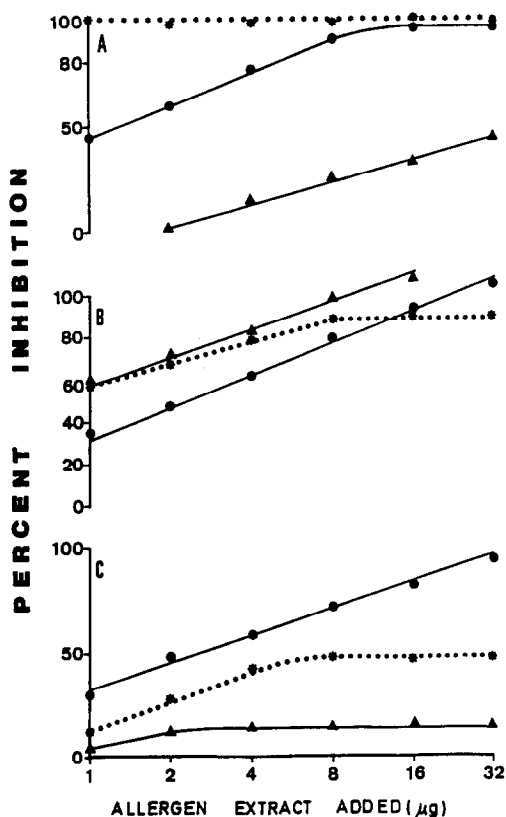


FIG. 3. ELISA-inhibition assays to composite pollens. A, *M. chamomilla*, B, *Ambrosia trifida*, C, *Artemisia vulgaris* with *Matricaria*-pollen inhibitor *...*, *Ambrosia*-pollen inhibitor Δ...Δ, and *Artemisia*-pollen inhibitor ●...●.

Artemisia). As presented in Table I, there was IgE activity not only to chamomile tea but also to the three pollens tested.

This activity was not observed if uncoated wells

were used, decreasing to background levels when patient's serum was first heated (Table I), as expected by the nature of the antibodies detected. In contrast, IgE activity to these extracts was not detectable in serum samples from 22 healthy individuals or from five patients with hay fever (Table I) containing high levels of serum IgE (total IgE in our patients' serum was 649 UI/ml).

Inhibition studies

Because of the above data, we were interested in knowing if *Matricaria* pollen, which was a conceivable contaminator of chamomile tea, could account for the allergenicity of this extract. First, we searched for the presence of pollen grains in the chamomile-flour dust by microscopy. Abundant pollen of *M. chamomilla*, but not other contaminating pollens, were found in the sample obtained from our patient (Fig. 1) and also in every chamomile-flour dust tested (not presented). Next, we performed inhibition assays with both chamomile and *Matricaria* extracts, as described in Material and Methods. That chamomile tea, as well as *Matricaria*-pollen extracts, was able to absorb all the serum IgE activity against chamomile tea is illustrated in Fig. 2. This activity was, however, unmodified when an unrelated control extract (*D. pteronyssinus*) was used (not presented).

Because a direct sensitization to *Matricaria* pollen was unlikely in our patient and given the above results, we considered the possibility of cross-reactivity with other Compositae pollens. This appeared to be the case, since all the patient's IgE activity to *Matricaria* (Fig. 3, A) and *Ambrosia* (Fig. 3, B) pollens could be absorbed completely by the *Artemisia* extract. In contrast, IgE activity to *Artemisia* was only partially



FIG. 4. *M. chamomilla* pollen.

absorbed with *Matricaria* (50%) or *Ambrosia* (18%)-pollen extracts (Fig. 3, C).

The specificity of the inhibitions with the above extracts was monitored by testing, at the higher concentrations, in a nonrelated ELISA system. The results (not presented) demonstrated their inability to inhibit the IgE activity to *D. pteronyssinus* of the 10 appropriate control sera, indicating that the above inhibitions were not a nonspecific phenomenon.

DISCUSSION

The clinical findings and the results of the investigations carried out in our patient suggest that the anaphylactic reaction was induced by the ingestion of chamomile tea and that the underlying mechanism was probably an IgE-mediated immunologic reaction. These conclusions are supported by the presence of an immediate response in both prick tests and the passive transference test, the absence of a skin response in the Prausnitz-Küstner test with preheated serum, and the presence of specific IgE to the *Matricaria*-flower extract. The negative results obtained in the control subjects support the specificity of these findings.

The microscopic examination of patient's chamomile-flour dust revealed the presence of large quantities of *M. chamomilla* pollens. Conversely, all IgE activity detected in vitro against the *Matricaria*-flower extract was absorbed by the *Matricaria* pollen. This fact would indicate that this component of the infusion was the allergen responsible for the clinical feature presented by our patient. The question to be answered concerned the mechanism of sensitization to this pollen (Fig. 4), since the patient (8 years of age) had never before ingested this type of infusion. The cross-reactivity observed in the ELISA inhibition

between *Matricaria* and *Artemisia* pollens would help to explain a mechanism of indirect sensitization. This cross-reactivity is not surprising because both *Matricaria* and *Artemisia* plants have a close taxonomic relation. These two plants belong to the same Compositae family and to the same tribe, Anthemideae.¹ The pollination of *Matricaria* plants is entomophilous, whereas the *Artemisia* plants demonstrate anemophilous pollination,¹ and a significant concentration of this pollen is found in the atmosphere around Madrid in August and September.⁷ Our results strongly suggest that IgE activity to *Matricaria* in our patient's serum was actually caused by its cross-reactivity with *Artemisia* pollen, which appeared as the sensitizing agent. Likewise, cross-reactivity could also account for the reactivity of the patient to the pollen of *Ambrosia trifida*, since this pollen is not found in Europe⁸ and the patient had never travelled abroad.

Even though *Ambrosia* pollen is the most important cause of hay fever in North America and the infusion of *M. chamomilla* is a common beverage, it is remarkable that so few cases of allergy to the latter have been described. Benner and Lee⁴ described an anaphylactic reaction after the ingestion of chamomile tea; their patient presented positive scratch tests to both chamomile tea and ragweed, which suggested to these authors the possibility of a cross-reaction between these two allergens. Casterline⁵ also described an anaphylactic reaction after the ingestion of chamomile tea in a woman who, as in the previous case, was also allergic to ragweed. Our results demonstrate for the first time the existence of cross-reactivity between *Matricaria*, *Ambrosia*, and *Artemisia* pollens, thus confirming the suspicions first raised by the above-mentioned authors.^{4,5} It has been reported that the ingestion of other Compositae pollens can cause

anaphylaxis,⁹ for example, *Helianthus annuus* (common sunflower), which is found as a contaminant in some, but not all, types of honey,¹⁰⁻¹² also *Taraxacum officinale* (dandelion), which may be found in a health food known as "bee honey,"¹³ and the pollen of *Prosopis* (mesquite), which, although it does not belong to the Compositae family, may also be found in "bee pollen."¹⁴ Finally, cases of contact dermatitis caused by *M. chamomilla* and other Compositae pollens have been described.¹⁵⁻¹⁷

The findings presented in this article might indicate that patients with hay fever caused by sensitization to Compositae pollens (ragweed or mugwort) should also be investigated to rule out sensitization to *M. chamomilla* because of the potential hazard of its infusions to these patients.

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