

Asthma caused by bromelain: an occupational allergy

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Summary

Bromelains consist of a group of proteolytic enzymes of Bromeliaceae. They are commonly used in pharmaceutical industries, food production and in diagnostic laboratories. Bromelains are known to cause IgE-mediated reactions of both the immediate type and the 'late phase reaction of immediate type reaction' with predominantly respiratory symptoms. We report four cases of occupational allergy to bromelain in workers of a blood grouping laboratory. These observations prompted us to investigate the sensitization rate to bromelain in all workers of the particular diagnostic laboratory who had contact with bromelain. These results were compared with those obtained from healthy, randomly selected individuals without evident bromelain exposure. Our findings indicate that (i) bromelain is a strong sensitizer, (ii) sensitization usually occurs due to inhalation and not to ingestion, (iii) bromelain allergy is occupationally acquired, and adequate precautions are necessary. We can further state that (iv) skin testing with relatively pure allergens such as isolated proteases like bromelain may induce systemic reactions, even at very high dilutions.

Introduction

Bromelains consist of a group of proteolytic enzymes of Bromeliaceae. The highest concentrations are found in the stock of ripe pineapple but bromelains are also present in the fruit pulp.

Bromelains are glycoproteins with one carbohydrate chain per protein molecule. The active site is represented by the reactive sulphhydryl group of cystein. The sequence of amino acids near the active site is similar to papain. A detailed physical, chemical, biochemical and pharmaceutical specification has been provided by Cooreman *et al.* [1].

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Bromelain has been variously applied in medicine: pineapple juice served as an antihelmintic agent in former decades. Due to anti-phlogistic, anti-oedematous and proteolytic properties bromelain was used in local therapy following trauma, surgery and heat injuries, as well as in the treatment of leg ulcers. It was also prescribed orally as a digestive aid.

Today bromelain is used in food production as a tenderizer for meat and as a clearing enzyme in beverage. In blood grouping laboratories bromelain is used as a reaction booster.

Occupational sensitization to proteolytic enzymes due to inhalative exposure has previously been reported [2-8]. Patients revealed IgE-mediated reactions with predominantly bronchial manifestation.

We observed four cases of bromelain-induced occupational bronchial asthma in workers of a diagnostic laboratory and performed a comparative investigation to determine the significance of occupational inhalative exposure for bromelain allergy.

Subjects and methods

Patients

Four female patients, employed in a blood grouping laboratory, had to weigh out powdery bromelain daily and prepare hydrous solutions of this substance for automatic blood grouping. In this way, frequent and intensive contact of the mucous membranes of the respiratory system with bromelain dust occurred. These patients were referred to our Department for allergological exploration due to inhalative symptoms suspicious of bromelain allergy. Patient data concerning age, duration of periodical exposure and symptoms due to bromelain allergy are included in Table 1. In patient 1, retirement was necessary because of a chronic-obstructive bronchopneumopathia.

There were no signs of atopy in any case.

Prick tests

Skin tests were performed by a single prick on the volar aspect of the forearms with various inhalation and food allergens (Bencard, Worthing, U.K.; Dome/Hollister Stier, Slough, U.K.). Bromelain and papain were tested as hydrous solutions 1:10 000 (0.0001 mg/ml) and 1:1000 (0.001 mg/ml). The negative control was a physiological solution of NaCl; the positive control was histamine 1:1000.

IgE determination

Total IgE was determined with Phadezym PRIST® (Pharmacia, Uppsala, Sweden), specific IgE (atopy screening) and IgE-antibodies to bromelain and papain with Phadezym RAST® (Pharmacia).

Comparative study

Seventeen female workers of the said diagnostic laboratory had evident contact to powdery bromelain in history. These 17 workers (group I) were compared with 15 randomly selected, healthy female individuals within the same age range (group II).

Total IgE, bromelain and papain-specific IgE antibodies were determined in each subject and the patients were asked about any allergic manifestation in history.

The results obtained were compared using the Chi-square test.

Table 1. Patient data

Patient no.	Age (years)	Duration of exposure (years)	Symptoms	Total IgE	Bromelain-specific IgE	Prick test with bromelain
1	56	4	Bronchial asthma, difficulties in swallowing, itching in the throat and wheeze after handling with bromelain; anaphylactic reactions due to consumption of fresh pineapples	< 100 kU/l	Class 4	++++ (test concentration: 0.0001 mg/ml) Systemic reaction
2	46	4	Bronchial asthma, wheeze, conjunctivitis and rhinitis after handling with bromelain; vomiting due to consumption of fresh pineapple	< 100 kU/l	Class 2	++++ (test concentration: 0.0001 mg/ml)
3	29	1	Wheeze, eye irritation and rhinitis after handling with bromelain	< 100 kU/l	Class 3	++++ (test concentration: 0.0001 mg/ml) Systemic reaction
4	33	2	Wheeze, eye irritation and rhinitis after handling with bromelain	< 100 kU/l	Class 3	n.d.

n.d. = Not done.

Results

Allergological exploration

None of the four patients showed any positive prick-test reaction to the various inhalation and food allergens tested nor to papain. Bromelain led to positive test reactions (weals and pseudopodia to the proximal upper arm) in a concentration of 0.0001 mg/ml in patients 1, 2 and 3 (Table 1). Thus, any higher concentration was not further tested. In all three patients the positive test reactions persisted for hours. In cases 1 and 3, severe asthmatic attacks occurred about 3 hr after testing.

Total IgE was within normal range in all four patients (< 100 kU/l). Antigen-specific IgE antibodies to cat epithelium, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and *Phleum pratense* (atopy screening) were not detectable.

Bromelain-specific IgE antibodies were detectable in all four cases (Table 1), whereas specific IgE to papain was entirely negative.

Comparative investigation

Total IgE. IgE levels < 100 kU/l (normal range) were found in 12/17 subjects of group I and in 10/15 of group II ($P > 0.05$). In five patients of group I and in five patients of group II, a slight increase of total IgE could be detected (100–300 kU/l) ($P > 0.05$).

Table 2. Bromelain allergy—comparative study results

	Group I* (n = 17)	Group II* (n = 15)	χ^2 test
IgE in normal range (< 100 kU/l)	12	10	
IgE slightly increased (100–300 kU/l)	5	5	
Bromelain-specific IgE	7	0	$P < 0.01$
Papain-specific IgE	0	0	
Symptoms due to bromelain allergy	4	0	$P < 0.05$
Patients with bromelain allergy and atopy	0	0	

* Group I: patients with previous bromelain exposure; group II: randomly selected patients.

Specific IgE. Seven patients of group I showed specific IgE antibodies to bromelain (1/7 class 4, 2/7 class 3, 2/7 class 2, 2/7 class 1)—all subjects of the control group remained negative ($P < 0.01$).

Papain-specific IgE antibodies could not be detected in any patient.

Symptoms due to bromelain allergy occurred in four patients of group I (23.5%) but in none of group II ($P < 0.05$) (Table 2). All four patients with symptoms showed bromelain-specific IgE antibodies (but normal total IgE levels). Of seven subjects with specific antibodies, four (57.1%) revealed clinical symptoms.

Prick tests with bromelain and papain were performed only in three patients with specific IgE antibodies and allergic reactions to the proteases. Two of three probands tested revealed systemic anaphylactic reactions due to the prick test (bromelain 0.0001 mg/ml) necessitating intensive treatment. Thus, further skin tests were avoided.

Discussion

Previously, bromelain-induced allergic reactions with predominantly bronchial manifestations were reported to take place in collaborators of pharmaceutical industries [2–6]. We observed bromelain allergy in patients employed in a blood grouping laboratory. Recent reports, as well as our findings, indicate that bromelain allergy is usually occupationally acquired. Obviously sensitization takes place via the respiratory system. Elicitation of allergic reactions may occur not only from respiratory but also from gastrointestinal exposure, as seen in two of our patients.

Clinical appearance, demonstration of specific IgE antibodies and positive prick tests clearly indicate that bromelain can cause immediate type reactions.

In three patients with bromelain allergy, prick tests with bromelain were performed. It is remarkable that a very low concentration (0.0001 mg bromelain/ml) led to strongly positive prick-test reactions on the forearm (erythema, weals) and to pseudopodia to the proximal upper arm in all patients tested. These reactions persisted for hours and were refractory to antihistamine and steroid treatment. Two patients tested developed a severe asthmatic attack requiring intensive therapy. In prick tests, these reactions are extremely unusual, but similar systemic reactions due to the testing of proteases have recently been reported [7]. This report, as well as our observations, indicate that testing proteases in general should be done with utmost caution. The

probands tested have to be watched for some hours because of possible 'delayed reactions'.

The asthmatic attack in two cases, occurring about 3 hr after testing, may be interpreted as the 'delayed type of immediate type reaction'. Recently, special emphasis has been paid to this particular reaction type because it has been discussed as the main pathogenetic pathway of asthma in many patients [9,10].

As shown in our comparative study, we can state that bromelain allergy is not dependent on atopic constitution. No patient with bromelain allergy showed increased total IgE (atopy marker) and none of the patients with increased total IgE had developed bromelain allergy. This is remarkable because most types of inhalative allergy commonly depend on atopic constitution.

Cross-reactivity between bromelain and papain [2,3] could not be confirmed in our study. In all patients with proven bromelain allergy, prick tests and specific IgE to papain were entirely negative. There was also no history of papain intolerance in any proband.

It is worth mentioning that patient 1 was retired because of a chronic-obstructive bronchopneumopathia. The connection of this disease with the occupationally acquired bromelain allergy remains to be determined. As there is no apparent allergen exposure at present, the symptoms might be triggered by non-specific mechanisms, but the possibility of unconscious bromelain exposure via food must also be kept in mind.

Bromelain and papain proteases are used as tenderizers for meat and as clearing enzymes in beverages [8]. However, none of our patients showed symptoms of bromelain allergy after consumption of any food or beverage, except two patients with manifest bromelain allergy when eating pineapple. Because of the small number of patients tested in our study, and the few reports concerning the problem of allergy to food-added proteases, the role of bromelain and papain as possible sensitizers via the gastrointestinal system remains to be determined.

We conclude that bromelain is a strong sensitizer causing IgE-mediated reactions, and that inhalation is the usual way of sensitization. The diagnosis can be confirmed by prick test and RAST. However, prick tests with bromelain are rather dangerous and have to be performed with utmost care. As bromelain is an important occupational allergen, adequate precautions are required when working with proteases. Handling bromelain and other proteolytic enzymes in an unbound form like a powder or a spray should be avoided.

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