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Skin prick test response to enzyme enolase of the baker's yeast (Saccharomyces cerevisiae) in diagnosis of respiratory allergy

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SUMMARY

Background: *The aim of the study is to prove that Saccharomyces cerevisiae enolase, the major allergen of the baker's yeast, induces allergic immediate response in patients with inhalant allergy sensitized to Candida albicans extract.*
Material and methods: *The study was performed in three groups of patients: I. 20 atopic patients with respiratory allergy sensitized to Candida albicans and inhalant allergens (mite, feather, pollens) II. 30 patients with respiratory allergy, positive skin tests to inhalant allergens but negative skin tests to Candida albicans and other fungi; III. 20 nonatopic, healthy individuals. Skin prick test of purified enolase from Saccharomyces cerevisiae (bakers yeast) at concentration 1 and 10 mg/ml was performed in all groups. The results were documented planimetrically.*
Results: *95% of patients sensitized to Candida albicans extract showed positive skin reactions to Saccharomyces cerevisiae enolase, 10% of patients of group II and none of the patients of the control group had positive skin responses to enolase. The mean wheal size (mm^2) in skin prick test to Candida albicans, Saccharomyces cerevisiae enolase at concentration 10 mg/ml was $x=15.17\pm11.08$, 15.76 ± 19.67 and at concentration 1 mg/ml 10.02 ± 10.49, respectively.*
Conclusions: *1. Saccharomyces cereviasiae enolase induces an immediate allergic reaction in skin in subjects with respiratory allergy and positive skin prick test results to Candida albicans and other fungi. 2. Enolase can be an important allergenic component of the Candida albicans extract.*

BACKGROUND

Among numerous factors causing allergic disorders, fungi are considered to play an important role. Microfungi unquestionably are an important allergen source, and a principal cause of mould allergy. High concentration of spores in ambient air and their diameter allowing to penetrate distal airways facilitate fungal respiratory allergy.

Sensitization to some fungal species is more prevalent than to other species. The significance of fungi (Cladosporum herbarum, Alternaria alternata, Penicillum notatum, and Aspergillus fumigatus) in pathophysiology of bronchial asthma and allergic rhinitis is well recognized. Skin prick tests to their extracts are positive in 5–16% of the whole population, whereas the intracutaneous test, which is regarded to be less specific and more sensitive than prick test, is positive in as high a portion as 24% of the population [1]. At least 12% of allergic subjects are sensitized to Alternaria alternata, butt less than 7% may react to Cladosporum herbarum [1–3].

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Candida albicans coexists with man as a harmless commensal in the digestive system and vaginal tract and less frequently as an opportunistic pathogen but its role as allergen is disputed. Several publications have suggested that Candida albicans is allergenic [4–7].

Other fungal species such as Pityrosporum ovale and Saccharomyces cerevisiae do not induce respiratory allergy but are an important pathogenic factor in urticaria and atopic dermatitis [7,8].

It was also observed that fungal allergy usually coexisted with a sensitization to other extrinsic aeroallergens.

A number of studies have been carried out on fungal allergens until now. The significance of numerous allergens including proteins (enolase and acid protease) and polysaccharides (mannan) has been reported [8–10]. A cross-allergenicity between some fungal species has been also well documented. It seems that one of the antigens responsible for this phenomenon could be a glycolytic enzyme enolase [10,12]. This enzyme has been proved to be a major allergen of Saccharomyces cerevisiae and Candida albicans, and one of allergens in extracts of Cladosporium herbarum and Alternaria alternata.

The aim of our study was to assess if enzyme enolase, isolated from Saccharomyces cerevisiae, is able to induce an immediate allergic reaction in skin prick test in subjects with respiratory allergy/skin allergy and positive skin prick test results to Candida albicans, and whether it can be responsible for the cross-reactivity between the fungal species.

MATERIAL AND METHODS

Subjects

The patients who entered the study were divided into three groups. The group I consisted of 20 atopic subjects, 12 male and 8 female, age: 24.1±9.2 (mean±SD), suffering from allergic rhinitis and/or bronchial asthma. They had a positive skin prick test to crude extract of Candida albicans. They also had positive skin prick test responses to some of the common extrinsic allergens: Dermatophagoides pteronyssimus, Dermatophagoides farinae, feather, dog, cat, grasses. Additionally, they had been tested to three fungal species Alternaria alternata, Cladosporum herbarum, Penicillum notatum: 11/20 showed positive reaction to Alternaria alternata, 9/20 to Cladosporum herbarum and 6/20 to Penicillum notatum. Group II consisted of 30 patients, 14 male and 16 female, age: 32.2±10.3, with symptoms of respiratory allergy confirmed by positive skin prick test to inhaled allergen extracts and negative skin tests to extracts of tested fungi. All of the patients were free of chest infections, had stable bronchial asthma and received no antihistamine or systemic corticosteroids medication during the time of the study. Group III (control) consisted of 20 subjects, 8 male and 12 female, age: 20.9±3.1, without any symptoms of respiratory allergy, and with negative skin prick test to inhaled allergens and fungal extracts. Before skin testing, a full explanation of the procedure had been given to all the participants and their consent was obtained.

Study design

Skin tests

In all groups skin prick tests to panel inhalant allergens, moulds, Candida albicans and enolase in concentrations 1 mg/ml and 10 mg/ml (Sigma cat. no. E 6126) were carried out according to Nordic recommendations [11]. The patients' skin was wiped with 70 percent ethanol and allowed to dry, after which the sites for testing were marked with a pen. Extracts for testing were supplied as 1:10 glycerinated solutions. One drop of each test extract was applied in duplicate on the healthy skin using a rubber bulb dropper, after which the skin was punctured through the drop with a sterile skin test lancet. To help avoid carryover of allergen from one test site to another, a separate needle was employed for each test extract. The needle punctures were deep enough to penetrate the epidermis but not to draw blood. After the puncture was made, the drop of allergen was wiped away after the time of two minutes. The results were measured after 20 minutes with a weal diameter exceeding 3 mm and more than 50% histamine test results regarded as positive. The positive test results were patterned on a transparent film to obtain a planimetric evaluation. The weal areas were compared and the final results were expressed in sq. mm.

Solution of histamine dihydrochloride 1 mg/ml was used as a positive control and saline-glycerol solution as a negative control. Positive and negative control tests were placed whenever a patient underwent skin testing. The negative control test

may aid in identifying patients who reacted non-specifically or exhibited dermographism to the minor skin trauma associated with testing. The positive control was done to prove if the skin reactivity was not diminished, for example by medications such as antihistamine preparations or psychotropic drugs.

All skin prick tests were performed on the volar aspect of the forearm with a distance of 5 cm between points.

All the allergens were fresh and used for the study only. Inhaled allergen extracts were manufactured by Allergopharma (Allergopharma Hamburg Germany).

RESULTS

All the study patients had negative results of the negative control test and positive results with histamine.

Out of the 20 atopic patients with respiratory allergy, whose skin tests showed positive responses to C. albicans and C. herbarum or/and A. alternata, 75% (15/20) had positive skin responses to enolase Saccharomyces cerevisiae at concentration of 1 mg/ml and 95% (19/20) positive reaction for enolase at concentration of 10 mg/ml. The mean weal areas of skin test with C. albicans was 15.17 ± 11.08 mm^2 while the mean weal area of skin test with enolase at concentration of 10 mg/ml was 15.76 ± 19.67 mm^2. Attention should be paid to the fact that skin prick areas to Candida albicans and Saccharomyces cerevisiae enolase have been very similar.

Among patients from group II with signs of atopy but without fungal sensitization (all skin tests with fungal allergens were negative) we have found highly positive skin prick test to enolase in three cases i.e. in 10% (3/30). In these patients the mean wheal area of skin test with enolase was 12.3 ± 10.09 mm^2.

We have not observed any positive skin tests to enolase in control group subjects at either concentration.

DISCUSSION

In the study group of atopic patients suffering from respiratory diseases and sensitive to Candida albicans, we have shown that 95% of the individuals manifested positive skin test results with baker's yeast enolase. Moreover, the results were very similar to the ones obtained in skin test with Candida albicans. Positive skin test to Saccharomyces cerevisiae enolase does not necessarily indicate a sensitization to this yeast, but may be a sign of an allergy to Candida albicans or even a different fungal species, which probably results from cross-reactivity among different fungal species.

Saccharomyces cerevisiae, the baker's yeast, is commonly used in foods. It may be also responsible for symptoms of chronic urticaria as well as atopic dermatitis. Positive skin prick tests to Saccharomyces cerevisiae and/or Pityrosporum ovale and /or Candida albicans are seen in as high a portion as 70-94% of patients with atopic dermatitis [8]. Some of the subjects with severe recurrent type of this disease synthesize also specific IgE antibodies against these yeasts [8,9]. Saccharomyces cerevisiae, contrary to other species, is not responsible for respiratory allergy apart from its possible role in the pathophysiology of baker's asthma. Hence a likelihood of its allergic impact in the study group of patients suffering from allergic respiratory diseases is very low.

Studies on the allergenic compounds of yeasts have shown that one of the major yeast allergens seems to be 51kD protein – enzyme enolase [12]. As it was proved by Baldo and Backer, among 47 subjects with positive skin prick test to baker's yeast, 23 reacted positively to enolase at concentration 10 mg/ml. Specific IgE against Saccharomyces cereviasiae enolase was detected in 22 patients among 32 with specific IgE against yeast extract [9]. The other important Saccharomyces cerevisiae allergens are: mannan – a compound of the cellular wall and enzyme alcohol dehydrogenase. These allergens are also detected in extracts of other fungi i.e. Candida albicans, Alternaria alternata and Cladosporum herbarum and may be responsible for cross-reactivity among various yeasts species. In spite of some structural similarity (homologous aminoacid sequence) between different types of enolase, antigenic determinants are not necessarily identical. Various enolases may have, besides common, their own epitopes for IgE antibodies. It could explain the fact, described by Sovolainen, that Saccharomyces cerevisiae enolase was able only in part to block binding Candida albicans enolase in immunoblotting reaction [6].

Positive skin test results with Saccharomyces cerevisiae in atopic individuals suffering from atopic

respiratory diseases but having negative skin test results with Candida albicans, Alternaria alternata, Cladosporum herbarum, and Penicillum notatum can be also accounted for by the phenomenon of cross-reactivity among fungal species. The fact can be explained in twofold manner: the studied individuals are either sensitive to baker's yeast, which however is not supported by clinical observation, or they are sensitive to a fungal species cross-reactive with baker's yeast enolase, not included in the present study.

These patterns of cross-reactivity are considered as important factors in pollen allergy and food allergy. Cross reactivity is also significant in fungal allergy. If fungal allergy is to be properly diagnosed and managed, the limits and extent of these patterns must be determined.

The importance of enolase in immunopathophysiology of respiratory allergy has not been entirely clarified yet. Further clinical investigations will be required to evaluate the role of this enzyme in the cross-reactivity with other yeast species.

The study suggests diagnostic usefulness of a screening test with Saccharomyces cerevisiae enolase in the diagnosis of individuals suspected of fungal allergy.

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