Allergol Immunopathol (Madr). 2012;40(5):295–300

Allergologia et immunopathologia

www.elsevier.es/ai

ORIGINAL ARTICLE

Respiratory allergy to fungi in Barcelona, Spain: Clinical aspects, diagnosis and specific treatment in a general allergy unit

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Received 4 April 2011; accepted 21 September 2011
Available online 1 December 2011

KEYWORDS
Fungal allergy;
Alternaria;
Rhinitis;
Asthma;
Diagnosis

Abstract
Background: The importance of hypersensitivity to fungal allergens is a relatively unknown and somewhat controversial subject.
Methods: An open prospective study was carried out in just one centre to determine the clinical and epidemiological characteristics as well as the diagnostic usefulness of skin prick and conjunctiva provocation tests, associated with total and specific IgE determination in two groups of patients, one of which was monosensitised to fungi and the other of which had multiple sensitisations, including fungi.
Results: Rhinitis, exclusive or associated with asthma, was the main consultation cause (88% in monosensitised patients). Severe asthma was rarely found. In the polysensitised group, 64% were simultaneously allergic to moulds and mites.

Alternaria alternata was the most common sensitising fungus, although a considerable number of cases were associated with other species such as *Cladosporium*, *Penicillium* and/or *Aspergillus*. The skin prick test gave the highest sensitivity and specificity. In 67% of the cases, the specific IgE was found between classes 3 and 4. The conjunctival provocation test was an innocuous and highly useful method for verifying the diagnosis and determining the degree of clinical sensitisation. A large number of patients exclusively allergic to fungi received specific immunotherapy, and it was generally well tolerated.
Conclusions: This protocolised study shows the importance of *Alternaria* and other fungi sensitisations in rhinitis alone or associated with asthma. Combined diagnosis of prick test, specific IgE and conjunctiva provocation test is very useful for deciding specific immunotherapy.

Introduction

There is growing interest in understanding the role that airborne fungi play in respiratory allergies. Numerous publications refer to the increasing severity of diseases caused by hypersensitisation to moulds such as severe asthma,[1,2] allergic bronchopulmonary aspergillosis[3] and hypersensi-

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doi:10.1016/j.aller.2011.09.003

tivity pneumonitis,[4] which are all fortunately infrequent clinical manifestations. Less severe ailments such as rhinitis or mild, intermittent asthma are largely the reasons for consultations in allergological services.

Due to their biological characteristics, fungi can develop outdoors, principally on decaying vegetal material, but they also grow and disperse their allergenic spores inside buildings.[5,6] Climatological conditions, temperature, humidity, wind, as well as the availability of organic substrates on which they can develop are the factors that determine the presence of fungal species in the atmosphere outdoors, and this can vary depending on the geographical region studied. Thus, variable levels of fungal sensitisation have been described. Cold zones have low levels,[7] while warm or hot areas have high levels.[8,9] In Mediterranean geographical zones, there are high levels of sensitivity to fungi, as shown in several published studies.[8,10]

Study methodology, with few exceptions, has not been standardised, and the criteria for defining and evaluating fungal allergy are quite diverse. Furthermore, in many publications the number of subjects studied is too low to draw definitive conclusions.

The fact that most patients are also sensitised to other pneumoallergens makes it difficult to clearly understand the importance of fungal allergy. In order to determine if there are differences between polysensitised patients who also are allergic to fungi, and those patients only sensitised to fungi, it is important to have a large enough pool of similarly studied patients.

This open prospective study was performed using standardised methodology, carried out by the same group of professionals, in patients from a single clinical centre, thus allowing for a detailed analysis of different aspects of clinical manifestations, the relationship between sensitisation to fungi and other allergens, as well as routine diagnostic procedures, and to consider some aspects of therapeutic procedures.

Patients and methods

(1) Between September 2005 and September 2010, a total of 12,000 patients were seen for the first time, 73% of which were for respiratory manifestations. Approximately 30% of them were not allergic, the remainder showed positive test for dust mites and for different type of pollen or epithelia. We excluded patients with negative test to fungi.

(2) After a detailed medical record and a spirometry were carried out, diagnostic tests for pneumoallergens were performed.

The first test was the skin prick test, based on the GA^{2}LEN[11] proposals, expanded to include four moulds.

All persons whose tests presented a wheal $\geq$3 mm ($\geq$9 mm^2) with adequate positive and negative controls, to one or more fungal allergens were included in a questionnaire regarding age, where they lived, the clinical manifestations and degree of severity as well as seasonality of their symptoms.

The other systematic routine diagnostic tests were carried out and the results were recorded on the same questionnaire.

(3) Diagnostic tests:

Standard skin prick test: 36 glycerinated extracts from plant and tree pollens prevalent in the zone, cat and dog epithelia, feathers, house dust mites, as well as four moulds (*Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus* and *Penicillium crhysogenum*) were used. A reduced battery of 16 allergens was used for children under 7 years of age. Fungal extracts were provided by Bial-Aristegui Laboratories (Bilbao, Spain); a positive control was used (histamine 10 mg/mL) as well as a negative control (glycerinated saline solution). When deemed appropriate, skin prick test against other fungi were also performed (*Candida albicans*, *Fusarium* sp., *Mucor* sp., *Helminthosporium* sp., *Botrytis* sp., *Stemphylium* sp., *Ustilago* sp.).

Tests were read 20 min after the puncture, and the diameter of the wheal was recorded on a special form.

Analytical determinations: A count of blood eosinophils and total serum IgE was performed in all cases. Specific IgE level was determined using the ImmunoCap test (Phadia AB, Uppsala, Sweden) for all allergens which induced clinically significant skin prick test results.

Conjunctival provocation test: Depending on the analytical results, and considering the clinical data, a provocation test was performed. One drop of aqueous extract of the corresponding allergen (Bial Aristegui Laboratories) was placed into the conjunctival sac, beginning with the smallest concentration, (1/10 which corresponds to 3.027 BEU*/ml) (*BEU = Biological Equivalent Units, that is: activity units from the allergen manufacturer used in the study), and the concentration was increased to 25%, 50% or 100% (63,280 BEU), until redness, itching and in some cases, epiphora, sneezing and nasal secretions were produced. At this point the reaction was stopped using saline eye washes, and if necessary, using eye drops with azelastine 0.5 mg/ml or dexamethasone 1 mg/ml. This semiquantitative test is positive considering the lowest extract dilution which provokes the reaction.

As needed, other diagnostic tests were performed (study of food or drug allergies). If deemed necessary, X-rays of the thorax or sinus scans were requested.

Once the study of each patient was complete, the specialist indicates the specific immunotherapy to the implicated fungus, and recorded this treatment on the questionnaire form.

(4) Statistical evaluation.

A descriptive analysis of the samples was performed using demographic variables and the medical history of the patients. The average, *SD* and range were determined for the quantitative variables, and a frequency analysis was performed on the qualitative variables.

Afterwards, an analysis was performed to establish the comparability between monosensitised and polysensitised patients. The non-parametric Mann–Whitney test was used for continuous quantitative variables and chi-square analysis was used for the qualitative variables.

The data were analysed using the PASW Statistics v18.0 statistical package (SPSS Inc, Chicago, Illinois).