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Clinical epidemiology of IgE-mediated cutaneous and oculo-conjunctival allergic diseases

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Abstract

Background: IgE-mediated allergic disease may clinically manifest itself with either a single symptom or a multisymptomatic disease involving different organs. In this work we investigated whether gender and age of the patients and reactivity to specific allergens are related to different clinical presentations of IgE-mediated allergic disease, considering in particular eye-conjunctival and cutaneous symptoms, alone or in combination.
Methods: Epidemiological and clinical data related to patients of the Local Health Unit of Torino and Alessandria were collected. Measuring of specific Immunoglobulin E (IgE) was carried out by using allergenic extracts and by the employment of the chemiluminescence method. Clinical outcomes were the presence of eye-conjunctival, cutaneous (with also other symptom), and only cutaneous symptoms. The covariates under study were the type of allergen (mite, epithelium, poaceae, food, trees and grasses), number and localisation of the allergic reactions, gender, age over 30 years. For each clinical outcome, a logistic regression analysis was performed. Statistical significance was set at $p < 0.05$.
Results: 844 patients with allergic problems (clinical manifestations of allergic disease) entered the study. We found that exposure to epithelium [OR=3,61; IC 95% (2,17; 6,00)], poaceae [OR=2,24; IC 95% (1,46; 3,42)], grasses [OR=2,06; IC 95% (1.35; 3,14)] and age over 30 years [OR=2,05; IC 95% (1,35; 3,13)] are risk factors for the development of eye-conjunctival symptoms. With regard to cutaneous allergic reactions, exposure to mite [OR=1,49; IC 95% (1,07; 2,08)], food [OR=4,16; IC 95% (3,01; 5,75)] and multidistrict symptoms [OR=3,63; IC 95% (2,54; 5,20)] should be risk factors. Instead, considering only cutaneous reactions, possible risk factor is the exposure to food [OR=3,58; IC 95% (2,54; 5,03)]. The exposure to trees is associated with a reduction of the likelihood to have cutaneous [OR=0,45; IC 95% (0,26; 0,76)] and only cutaneous reactions [OR=0,24; IC 95% (0,11; 0,53)]. For only cutaneous symptoms, a reduction in probability is present for the exposure to the grasses [OR=0,60; IC 95% (0,38; 0,94)] too.
Conclusions: The study highlighted significant associations between subgroups of allergens and specific symptoms. As a consequence, in the presence of cutaneous symptoms, IgE tests could be restricted to mite and food, and to epithelium, poaceae and grasses in the presence of oculo-conjunctival symptoms.

Key words: allergic oculo-conjunctivitis, specific IgEs, allergic dermatitis

Introduction

In vitro tests for specific IgEs are common routine in the laboratory diagnosis of IgE-mediated allergic disease. Since the first tests employing the Radioallergosorbent procedure (RAST [1,2]), the methodology has continuously evolved, both at the level of the technology [3-6] and of the spectrum of allergens tested [7,8], now reaching the hundreds. Therefore, a large panel of tests is currently available to propose a precise diagnosis of specific allergopathy. Unfortunately, the technological resources are not matched by

an equally detailed and standardized way of integrating the laboratory analysis within the clinical diagnostic process.

Various scientific and healthcare organizations, like the World Health Organization, recommend the search for specific IgEs be conducted only after a detailed clinical-anamnestic analysis and after in vivo tests such as the cutaneous stimulation ("prick") test that, by reproducing the pathogenetic process of IgE-mediated allergy, reaches a high sensitivity and ability to detect the presence of IgEs triggering histamine release. Following these criteria, the diagnosis and the consequent definition of the appropriate treatment should be reached in the vast majority of the cases, with the limited exception of non-IgE-mediated pathologies, such as cell-mediated reactions (detectable with the patch test[9]), food intolerance[10-12] or drug adverse effects[13]. The guidelines also recommend to limit in vitro tests for specific IgEs to the cases where the prick tests could harm the patient by inducing anaphylapsis (like in the case of hymenoptera venom[14,15]), or could not be executed e.g. for poor patient compliance, low cutaneous reactivity or concomitant anti-histaminic treatment. However, the guidelines are frequently not properly followed[16-18], and the correct interpretation of the tests is influenced by many factors. Among them, of particular importance is the well-documented cross-reactivity between allergenic extracts[19-21], which in many cases does not allow a precise definition of the allergologic situation. This issue can only in part be addressed using recombinant allergens[22]. Moreover, it is currently matter of discussion which threshold value should be assigned to each allergene for clinical predictivity, and, in particular, whether each allergen family should be given a different cut-off [23-28]. In this view, our previous work has shown that, when the clinical presentation is suggestive of allergic disease, even low IgE levels can be significantly correlated with the diagnosis[29]. As a consequence of the complexity of the field, physicians frequently request long lists of allergens to be tested, even without previous clinical and in vivo analysis, which leads to long lists of negative results.

The present study aims at defining epidemiological relationships between reactivity to commonly tested allergens, as well as gender and age of the patients, and two frequent manifestations of allergic disease, i.e. cutaneous[30,31] and oculo-conjunctival, the latter presenting in a wide range of clinical variants[32-36]. Eventually, the definition of associations between specific allergic symptoms and reactivity to subsets of allergens could provide a rationale for the selection of allergens to be tested based on the clinical presentation. More severe allergic pathologies, like asthma, are being extensively assessed in multicentric studies[37,38] and are not considered in this work.

Methods

Epidemiological and clinical data, related to patients of the Local Health Unit of Torino (ASL TO5: Carmagnola, Chieri, Moncalieri, Nichelino) and Alessandria (ASL AL: Acqui Terme, Novi Ligure, Ovada), were collected using an electronic sheet. The collected variables included: age, gender, symptoms, divided for type and localisation, and results to the specific IgE tests.

Measuring of specific Immunoglobulin E (IgE) was done using allergenic extracts and with chemiluminescence method. The used instruments were Advia Centaur e Immulite 2000 (respectively Bayer and DPC before 2007 and after both Siemens, NY, USA).

Serum derived from test tube Vacutainer (Becton Dickinson, NJ, USA).

For the study, according to the technical specific of all instructions given from industries, level of positive for IgE analysis, during the execution of the tests, was set at 0.35.

Clinical outcomes were the presence of eye-conjunctival, cutaneous (with also other symptoms), and only cutaneous symptoms. The covariates under study were the type of allergen (mite, epithelium, poaceae, food, trees and grasses), number and localisation of the allergic reactions (unisymptomatic (reference), district or multidistrict), gender and age over 30 years.

For each clinical outcome, a logistic regression analysis was performed.

Statistical significance was set at $p < 0.05$.

Statistical analysis was performed by using SPSS 12.0 for Windows.

Results

844 patients with allergic problems (clinical manifestations of allergic disease) entered the study (444 Males - 400 Females). The characteristics of the samples are shown in Table 1, according to distribution of age, gender, symptoms and results of IgE tests.

In Table 2 results of crude and adjusted analysis are shown. Exposure to epithelium [OR=3,61; IC 95% (2,17; 6,00)], poaceae [OR=2,24; IC 95% (1,46; 3,42)], grasses [OR=2,06; IC 95% (1.35; 3,14)] and age over 30 years [OR=2,05; IC 95% (1,35; 3,13)] are risk factors for the development

Table 1. Characteristics of the sample under study.

		Frequencies (%)	
Age over 30 years		46.6	
Gender	Male	52.6	
	Female	47.4	
Localisation	Unisymptomatic	60.9	
	District	13.3	
	Multidistrict	25.8	
		Negative to IgE test (%)	Positive to IgE test (%)
Mite		69.2	30.8
Epithelium		88.6	11.4
Food		64.1	35.9
Poaceae		72.9	27.1
Trees		88.7	11.3
Grasses		73.7	26.3
Eye-conjunctival		85.5	14.5
Cutaneous symptoms		62.4	37.6
Only cutaneous symptoms		76.8	23.2

Table 2. Results of Logistic regression.

	Eye-conjunctival		Cutaneous symptoms		Only cutaneous symptoms	
	OR crude *(IC95%)*	OR adj* *(IC95%)*	OR crude *(IC95%)*	OR adj^ *(IC95%)*	OR crude *(IC95%)*	OR adj° *(IC95%)*
Mite	1.50 *(1.01;2.23)*	1.30 *(0.84;2.02)*	1.31 *(0.97;1.76)*	1.49 *(1.07;2.08)*	0.96 *(0.68;1.36)*	1.23 *(0.85;1.79)*
Epithelium	4.11 *(2.56;6.61)*	3.61 *(2.17;6.00)*	1.22 *(0.79;1.87)*	0.91 *(0.55;1.50)*	0.63 *(0.36;1.11)*	0.71 *(0.39;1.30)*
Food	0.51 *(0.33;0.79)*		3.51 *(2.61;4.71)*	4.16 *(3.01;5.75)*	3.58 *(2.57;4.98)*	3.58 *(2.54;5.03)*
Poaceae	2.69 *(1.81;4.00)*	2.24 *(1.46.3.42)*	0.93 *(0.68;1.27)*	1.10 *(0.76;1.60)*	0.60 *(0.41;0.88)*	1.06 *(0.69;1.64)*
Trees	2.73 *(1.67;4.48)*	1.47 *(0.84;2.58)*	0.67 *(0.42;1.06)*	0.45 *(0.26;0.76)*	0.24 *(0.11;0.52)*	0.24 *(0.11;0.53)*
Grasses	2.73 *(1.84;4.06)*	2.06 *(1.35;3.14)*	0.66 *(0.48;0.92)*	0.70 *(0.49;1.02)*	0.41 *(0.27;0.63)*	0.60 *(0.38;0.94)*
Unisymptomatic			1 *(Reference)*	1 *(Reference)*		
District			1.40 *(0.92;2.15)*	1.47 *(0.93;2.33)*		
Multidistrict			2.92 *(2.10;4.04)*	3.63 *(2.54;5.20)*		
Male gender	0.63 *(0.42;0.92)*	0.68 *(0.45;1.02)*	0.73 *(0.55;0.96)*	0.92 *(0.68;1.26)*	0.87 *(0.63;1.20)*	1.00 *(0.71;1.41)*
Age over 30 years	*(1.37;3.00)*	*(1.35;3.13)*	*(0.50;0.87)*	*(0.67;1.29)*	*(0.36;0.70)*	

* adjusted for Mite, Epithelium, poaceae, Trees, Grasses, Male gender and Age over 30 years;
^ adjusted for Mite, Epithelium, Food, poaceae, Trees, Grasses, Localisation, Male gender and Age over 30 years;
° adjusted for Mite, Epithelium, Food, poaceae, Trees, Grasses and Male gender.

of eye-conjunctival symptoms.

Regard to cutaneous allergic reactions, exposure to mite [OR=1,49; IC 95% (1,07; 2,08)], food [OR=4,16; IC 95% (3,01; 5,75)] and multidistrict symptoms [OR=3,63; IC 95% (2,54; 5,20)] should be risk factors. At the end, considering only cutaneous reactions, possible risk factor is the exposure to food [OR=3,58; IC 95% (2,54; 5,03)].

Instead the exposure to trees is associated with a reduction of the likelihood to have cutaneous [OR=0,45; IC 95% (0,26; 0,76)] and only cutaneous reactions [OR=0,24; IC 95% (0,11; 0,53)]. For only cutaneous symptoms, a reduction of likelihood is present for the exposure to the grasses [OR=0,60; IC 95% (0,38; 0,94)] too.

Discussion

Our study highlighted significant correlations between exposure to specific allergens and

different clinical manifestations of allergic disease. In the analysis, we considered reactivity to the various allergens as an index of exposure to them, and the possible risk of developing specific symptoms. However, the results can also be considered from the opposing point of view, i.e., the presence of a given clinical presentation can be associated to a higher probability of positive reaction to specific subsets of allergens.

In particular, we found an increased risk of developing oculo-conjunctival symptoms in patients with positive response to epithelium, poaceae and grasses, and in patients more than 30 years old. In the case of cutaneous symptoms, which are more frequent in the first years of life[39], a strong association was found between reactivity to food and monosymptomatic cutaneous disease, while cutaneous symptoms within the context of multisymptomatic presentations are associated to mite and food.

The analysis also highlighted a surprising reduction of the risk of developing dermatitis for patients positive to trees, as dermatological symptoms alone or combined with other allergic manifestations. A similar risk reduction was observed for monosymptomatic cutaneous disease upon positivity to grasses. Epidemiologically speaking, these results indicate trees and grasses as "protective" factors towards cutaneous presentations of allergic disease. But what does "protective" mean, in this context? In our view, the selection of allergens to be tested should be guided by the clinical-anamnestic information, including geographic area of residence and age[40], and, when possible, in vivo tests. Our data add further information on which antigens should be tested in the presence of given allergic symptoms. Accordingly, when an allergen is "protective" towards a symptom, it is probably useless to test in the presence of that symptom because the result will be most likely negative. The information presented here is most useful when it is not possible to perform in vivo tests to guide the IgE search. In these cases, the presence of only cutaneous symptoms would direct the search on food, while mite and food should be tested for multisymptomatic presentation with cutaneous symptoms. Conversely, oculo-conjunctival symptoms would guide the search on epithelium, poaceae and grasses. Analysis of all the other allergens could be postponed, given their lower "risk" of positivity.

To consolidate the results presented here, wider studies should be conducted, involving large patient numbers and different geographical areas. Such studies require extensive exchanges of information between clinicians, laboratories and epidemiologists, which, in perspective, can greatly improve the diagnostic approach to allergic diseases. An optimal frame for such exchanges could be the recently established protocols for laboratory "networking", such as the LOINC protocols (http://loinc.org). In this perspective, appropriate forms should be defined to guide the clinicians in providing, together with the requests for allergological tests, the clinical information required for statistical association studies.

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