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The Role of the Atopy Patch Test in the Diagnosis of Allergy

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Abstract

The diagnosis of allergy is mainly based on the combination of clinical history data and results of skin prick tests (SPT) or in vitro IgE tests, including specific IgE measurement, and, as third level testing, challenges with the suspected allergens. The atopy patch test (APT) that assesses the type 4, delayed hypersensitivity, is insufficiently used. We review the data obtained in recent studies on the diagnostic utility of the APT in patients with AR, especially when house dust mites are the cause of allergy.

Keywords: Allergic rhinitis; Allergens; Sensitization; Diagnostic tests; Atopy patch test

Introduction

The elements that usually concur to the diagnosis of allergic diseases are clinical history, skin prick tests (SPT) with allergen extracts, in vitro measurement of allergen-specific IgE antibodies and challenge tests with the probably involved allergens [1-4]. Clinical history is aimed at providing the data to suspect allergy, that will be confirmed if SPTs are positive to allergens that are in agreement with the history [5]. Also SPT are unable to yield directly the diagnosis of allergy, because a positive result indicates sensitization but not necessarily clinical allergy [6]. In doubtful cases, challenge tests may be performed, even though recently introduced in vitro techniques, such as component resolved diagnosis, that detects specific IgE to single allergen molecular components [7], and the basophil activation test, that reveals the reactivity of basophils in blood from allergic patients to the suspected allergens [8], may achieve the final diagnosis and thus avoid to perform the challenges. However, all these tests assess the type 1, IgE-mediated hypersensitivity, but there is increasing awareness that also the type 4, T-cell-mediated mechanism may be often responsible of allergy.

Indeed, the atopy patch test (APT), that was introduced in 1989 to evaluate the role of aeroallergens in atopic dermatitis [9] has the ability to reproduce the pathophysiology of T-cell-mediated hypersensitivity, as demonstrated by skin biopsies showing that 24 hours after the application of the APT with house dust mites a Th2 oriented cytokine pattern was detected, but after 48 hours a shift to a Th1 pattern was found, as occurs in the typical skin lesions of atopic dermatitis patients [10]. Moreover, APT application to the skin of these patients elicited an influx of inflammatory dendritic epidermal cells [11]. In the ensuing years an important role for the APT in the diagnosis of atopic dermatitis was highlighted [12,13] and some studies began to observe a possible role of the APT also in the diagnosis of respiratory allergy.

The Demonstration of the Utility of the APT in Respiratory Allergy

Guler et al. reported in 2006 that in 25% of children with rhinitis or asthma and positive results to SPT with Dermatophagoides pteronyssinus, also APT was positive, this leading the authors to conclude that positive APT results may imply that delayed hypersensitivity reactions play a role in children with asthma and rhinitis due to allergy to mites [14]. Actually, subsequent studies confirmed and expanded this observation. In a study on 297 children, the patients were divided into 3 groups: current atopic dermatitis alone, current atopic dermatitis and respiratory symptoms, and past atopic dermatitis with respiratory symptoms. The APT, with dominant importance for Dermatophagoides, was significantly more frequently positive in patients with atopic dermatitis, and multivariate analysis showed high odds ratios (OR) concerning the likelihood to have atopic dermatitis in patients with positive APT (OR, 21.9) and to have a positive APT result in patients with atopic dermatitis (OR, 17.4). The risk was even higher in patients with current dermatitis and respiratory disease (OR, 21.9) and in patients with past dermatitis and respiratory disease (OR, 22.8) [15]. A further study on 399 patients included the in vitro measurement of specific IgE, using the same division in subgroups as in the previous study, with a control group of patients with respiratory allergy but no history of atopic dermatitis. The APT was significantly more frequently positive in the groups with current or past dermatitis than in the control group, while SPT and specific IgE in serum were significantly more frequently positive in the control group [16]. These observations stimulated a reappraisal of the role of APT in the diagnosis of rhinitis and asthma, especially in patients with a positive history (past or current) for atopic dermatitis [17,18].

Zhao et al. recently confirmed this association by evaluating the frequency of positive APT to Dermatophagoides in a self-selected population in Beijing (healthy university student volunteers). Of 201 students studied, 25.9% had positive results to APT. In subjects with negative history for atopic dermatitis, rhinitis, or asthma, the positivity rate of APT was 13.6% but it was much higher in subjects with rhinitis or asthma (56.1%, $P<0.05$) [19]. These findings confirmed that a positive APT to Dermatophagoides is significantly related not only to atopic dermatitis but also to respiratory allergy, revealing the importance of the delayed, T cell-mediated mechanism in such patients.

Considering that the dust mites are the most important source of respiratory allergy worldwide [20], these findings should support the use of APT in epidemiological studies on allergy, that thus far was disregarded. A very recent survey investigated the positive response to APT in an unselected pediatric population in Italy [21]. The study was

based on a specific questionnaire, containing the three core ISAAC (International Study on Asthma and Allergy in Children) modules asking about the diagnosis of atopic dermatitis, allergic rhinitis, wheezing, and asthma [22], and on SPT and APT, applied on the entire scholastic population attending a Primary school and a Junior Secondary school in the rural town of San Marco in Lamis, 12.000 inhabitants (Puglia, Italy). Of the 456 questionnaires returned, 61.2% were negative for any sign or symptom, while 38.8% were positive for symptoms of atopic dermatitis, rhinitis, or asthma/wheezing. Among these subjects, 17.1% had a positive SPT and 12.5% had a positive ATP. In particular, 13.4% of subjects were positive only to SPT and 8.8% were positive only to APT, dust mites being the allergen most frequently positive, while for pollen positive results concerned almost exclusively the SPT. The finding of a prevalence of positive results to APT not so distant from the positive results to SPT, and in particular the observation that in 8.8% of subjects the APT was the only positive test, suggest that the APT should be added as a tool in future epidemiological studies, to avoid to overlook the not negligible portion of patients with T-cell-mediated allergy.

Conclusion

The recent literature makes apparent that the APT should be included in the panel of tests to be commonly used in the diagnosis of respiratory allergy. In fact, a positive result of APT, that is related to the type 4, delayed hypersensitivity, ranged, as assessed by the data from the available studies, from to 25% to 56%, and in approximately 10% of cases the APT was the only positive test. The element suggesting such mechanism is the presence of a positive history for past or current atopic dermatitis. The allergen sources most frequently involved in this kind of sensitization are the dust mites. The combination of the impaired skin barrier function in atopic dermatitis, that allows proteins to enter into the viable epidermis, and the ability of mite allergens, especially the cysteine and serine proteases, to disrupt epithelial tight junctions and to penetrate into the epidermis thus activating the keratinocytes, may account for such dominant role [18]. The fact that the APT may be the only positive test in patients with respiratory allergy underlines the importance of including this test in the diagnostic work-up of allergy. Otherwise, patients with negative results to SPT or in vitro IgE tests may be mistakenly classified as non-allergic and thus inappropriately managed.

A rate of a positive result exclusively to APT comparable to that observed in clinical studies -8.8%- was reported in the only epidemiological survey thus far available that tested the APT in an unselected population [21]. Epidemiology is a powerful tool in investigating the importance of allergic diseases, and the recent data show a steadily increase in the prevalence of allergic diseases [22], but using only SPT or in vitro IgE tests, as generally done, and not also APT, allows only the estimation of the IgE-mediated hypersensitivity and misses the detection of T-cell-mediated allergy.

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