Original Article

Evaluation of the Phadiatop™ test in the diagnosis of allergic sensitization in a general adult population

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Summary. *Background:* Phadiatop™ is a commercially available qualitative serological test employed for screening of allergic sensitization in patients with suspected allergic diseases. *Aim:* The study evaluated the diagnostic accuracy of Phadiatop™ for the diagnosis of allergic sensitization in a general adult population. *Methods*: A total of 469 subjects from the population of A-Estrada (Spain) were selected by age-stratified random sampling (age range, 18-92 years). Phadiatop™ test (Uni-CAP method) was performed in serum samples from 465 of these subjects. Skin prick tests to a panel of 13 relevant aeroallergens in the studied area (including mites, pollens, moulds, and animal dander) were employed as the reference diagnostic procedure. Subjects with at least a positive skin prick test (≥4 mm, n= 120) were considered to have allergic sensitization. *Results:* Phadiatop™ sensitivity was 70.8% (95% CI 61.7-78.6%), specificity 90.7% (95% CI 87.0-93.5%), positive predictive value 72.6% (95% CI 63.5-80.3%), negative predictive value 89.9% (95% CI 86.2-92.8%), global accuracy 85.6% (95% CI 82.0-88.6%), negative likelihood ratio 0.3 (95% CI 0.2-0.4), and positive likelihood ratio 7.6 (95% CI 5.4-10.8). A high proportion of false-positive Phadiatop™ cases showed (a) increased total serum IgE levels, (b) significant alcohol consumption, and (c) small-sized (below the diagnostic cut-off) wheal reactions on SPT. A high proportion of false-negative Phadiatop™ cases showed exclusive storage mite sensitization. Sensitivity and positive predictive value of Phadiatop™ were somewhat higher among individuals with a history of nasal or bronchial symptoms. *Conclusions:* Phadiatop™ is a valuable tool for the diagnosis of allergic sensitization in a general adult population. However, limitations of the test should be taken into account in similar surveys.

Key Words: Atopy, allergic sensitization, prick-tests, specific IgE, Phadiatop, sensitivity, specificity.

Introduction

The presence of specific IgE against common environmental aeroallergens represents the classical definition of atopy [1]. Recent consensus, however, prefers to designate this situation as allergic sensitization, and to reserve the term atopy for patients who also have an allergic disease (asthma, rhinoconjunctivitis, or eczema) [2]. In clinical practice, evidence of allergic sensitization can be elucidated by two methods, namely skin prick tests (SPT) and specific serum IgE assays [2]. Skin prick tests are the most useful single modality for demonstrating an IgE-mediated underlying mechanism in suspected allergic diseases [3]. Skin prick tests are reliable, cheap, easy to perform, and they offer a prompt result [3]. The presence of positive SPT to relevant airborne allergens is also the standard for the definition of allergic sensitization and atopy in large epidemiological studies [1,3]. However, SPT may be subjected to a number of problems such as choice and storage of allergens, prick test technique and individual interpretation. Advantages of serum specific IgE assays are convenience for the patient, lack of risks and the possibility of testing subjects unable to stop medications that could alter the results of SPT [4]. A major disadvantage of serum specific IgE assays is their

high cost, especially in case of assays for multiple allergens. Phadiatop™ is a commercially available variant of serum specific IgE assay test that was introduced for the screening of allergic sensitization in 1987 [5]. The test has developed successive variants, but all of them have as common principle the simultaneous testing for serum specific IgE to a mixture of relevant allergens causing common inhalant allergies. The test is qualitative, a positive result being suggestive of allergic sensitization although the test does not inform to which specific allergens the patient is sensitized [5]. Multiple studies have shown the high value of Phadiatop™ for diagnosis of allergy in patients with rhinitis or bronchial asthma using SPT or multiple serum specific IgE assays as standard references [6-16]. In these settings, however, the prevalence of allergy is high thus favouring accuracy of the test, particularly increasing positive predictive values [17,18]. Diagnostic accuracy of Phadiatop™ may vary not only with the prevalence of allergic sensitization in the studied population, but also with the aeroallergen profile of a given area. In this sense, it should be noted that the aeroallergen composition of Phadiatop™ is fixed and not stated by the manufacturer.

An evaluation of the diagnostic accuracy of Phadiatop™ in population-based studies could be of interest in order to use it as a tool for classification of subjects or as a screening test. Phadiatop™ seemed to provide a valuable and reproducible method to detect overall sensitization to inhalant allergens in a selected population of young Italian military students [19-21]. To our knowledge, there is no study that evaluates the diagnostic accuracy of Phadiatop™ for detecting allergic sensitization in a general population. The present study was aimed to investigate the accuracy of Phadiatop™ in the diagnosis of allergic sensitization in a general adult population from an area where mites are the predominant aeroallergens, using SPT results as the reference standard.

Subjects and Methods

Study design and setting

This evaluation of a diagnostic test formed part of the cross-sectional A-Estrada Allergy Study. The study profile is represented in Figure 1. Detailed descriptions of setting, sampling, and participants have been published elsewhere [22,23]. An age-stratified random sample of adult (18 years and older) individuals from the municipality of A-Estrada (NW of Spain, 42º40'N/ 8º30'W) was drawn from the National Health System Registry, which covers more than 95% of the population. Subjects unable to give informed consent were considered ineligible. Subjects were invited to participate in the study by a personal letter. A total of 469 subjects (67.2% of eligible) participated in the study. Median age of the participants was 54 years (range, 18-92 years). Two hundred and six (43.9%) were males. Most participants lived in a rural environment (352 cases, 75.0%), and the remainder lived in the A-Estrada village. There were no significant differences in age, gender, and residence (rural or urban) between subjects who participated in the study and those who did not. From February to December 2000, all subjects were successively convened to the Primary Care Centre for evaluation.

Diagnostic work-up

An interviewer-administered questionnaire (see below) was performed in all subjects. Skin prick tests to a panel of relevant aeroallergens in the studied area (see below) represented the reference standard for allergic sensitization and were performed in all cases. UniCAP-Phadiatop™ assay (see below) represented the trial test and was performed in serum samples of 465 out of the 469 individuals (99.1%). Serum samples were unavailable in the remaining four cases because of technical reasons. Blood samples for Phadiatop™ assay were taken the same day of SPT in all cases and were stored frozen at –20ºC until tested. An expert specialist who was unaware of SPT results performed Phadiatop™ assays.

Questionnaire

The history of upper respiratory symptoms was investigated by means of the following questions: (a) "have you ever had a problem with sneezing, or a runny or blocked nose when you did not have a cold or the flu?", and (b) "have you ever had wheezing or whistling in the chest at any time in the past?", exploring the presence of nasal and bronchial symptoms, respectively. Subjects were classified as symptomatic when answering "yes" to any of these questions.

Skin prick tests (SPT)

The panel of SPT to aeroallergens included mites *(Dermatophagoides pteronyssinus, Lepidoglyphus destructor, Tyrophagus putrescentiae*), pollens (*Lolium perenne, Plantago lanceolata, Betula alba, Parietaria judaica*), moulds (*Alternaria alternata, Aspergillus spp., Penicillium notatum, Cladosporium herbarum*), and animal dander (dog and cat) (ALK-Abelló, Spain). Control SPT included 10 mg/ml histamine and saline solution. Standard procedures were followed [24]. Wheals ≥4 mm after 15 minutes were considered indicative of a positive reaction [3]. Mites, and particularly storage mites (*Tyrophagus putrescentiae* and *Lepidoglyphus destructor*) were the leading causes of

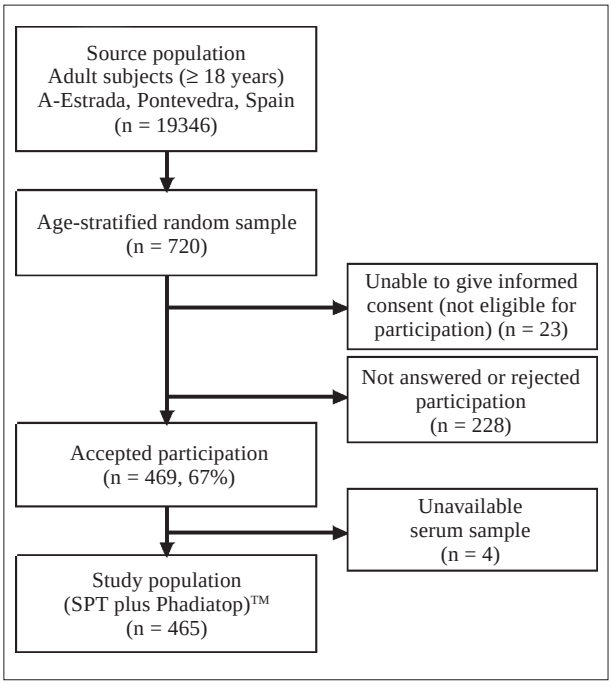

Figure 1. Study profile.

allergic sensitization throughout all ages. A detailed description of the sensitization profile in the studied population has been reported elsewhere [23]. Patients with at least one positive SPT were considered to have allergic sensitization [2].

Phadiatop™

UniCAP-Phadiatop™ assay (Pharmacia&Upjohn, Uppsala, Sweden) is based on the ImmunoCAP technology (Pharmacia&Upjohn, Uppsala, Sweden). It consists of a solid-phase immunoassay for serum specific IgE using a balanced mixture of relevant allergens causing common inhalant allergies coupled to ImmunoCAP. The manufacturer has not revealed the precise formulation of Phadiatop™. Procedure recommendations were strictly followed. Calculation of results was performed automatically according to the fluorescence response obtained for patient samples compared to the response obtained for the reference serum supplied. The test gives a qualitative result, either positive or negative depending on the fluorescence response. When a patient sample gives a fluorescence response higher than or equal to that of the reference serum, a positive test result is indicated. On the contrary, a patient sample with a lower fluorescence response indicates a negative test result.

Total serum IgE

Chemiluminiscent immunoassay (Immulite™, Diagnostic Products Corporation, LA, USA) was employed for total IgE assays in the same serum samples.

Statistical analysis

The sensitivity, specificity, positive predictive value, negative predictive value, accuracy, as well as positive and negative likelihood ratios [25] were calculated to characterize the Phadiatop™ test. The SPT result was the reference for the diagnosis of allergic sensitization. Diagnostic accuracy of Phadiatop™ was investigated (a) in the whole sample and (b) in symptomatic individuals.

Table 1. Crosstab of Phadiatop™ and SPT results in the whole population studied (includes symptomatic and asymptomatic patients).

	Allergic sensitization (SPT-positive) n = 120	**No allergic sensitization (SPT-negative)** n = 345
Phadiatop™ - positive n=117	True positive: n = 85	False positive: n = 32
Phadiatop™ - negative n=348	False negative: n = 35	True negative: n = 313

Ethical considerations.

The study conformed to the principles of the Helsinki's declaration, and was reviewed and approved by the local Research Committee.

Results

Data defining diagnostic accuracy of the Phadiatop™ test using the SPT results as reference standard in the whole studied population are represented in Table 1. Phadiatop™ sensitivity was 70.8% (95% CI 61.7-78.6%), and specificity was 90.7% (95% CI 87.0-93.5%). Phadiatop™ positive predictive value was 72.6% (95% CI 63.5-80.3%), and negative predictive value was 89.9% (95% CI 86.2-92.8%). Phadiatop™ correctly classified subjects as allergic-sensitized or non-allergic-sensitized in 398 out of 465 cases (overall accuracy 85.6%, 95% CI 82.0-88.6%). Phadiatop™ positive

Table 2. Variables associated with Phadiatop™ results in the whole population studied.

Factor	True negative (n = 313)	False positive (n = 32)	True positive (n = 85)	False negative (n = 31)
Age (years)	56 (18-92)	56 (29-85)	38 (18-83)	47 (19-83)
Sex (male)	134 (42.8%)	18 (56.3%)	40 (47.1%)	13 (37.1%)
Smoking habit	58 (18.5%)	7 (21.9%)	28 (33.0%)	7 (20.0%)
Alcohol intake (>140g/week)	67 (21.4%)	11 (34.4%)	18 (21.2%)	4 (11.4%)
Increased serum IgE (>100 IU/mL)	44 (14.1%)	19 (59.4%)	70 (82.4%)	17 (48.6%)
Positive SPT (≥4 mm)				
- Moulds	0 (0%)	0 (0%)	5 (5.9%)	6 (17.1%)
- Animal danders	0 (0%)	0 (0%)	5 (5.9%)	0 (0%)
- Pollens	0 (0%)	0 (0%)	35 (41.2%)	12 (34.3%)
- Mites	0 (0%)	0 (0%)	79 (92.9%)	31 (88.6%)
- Exclusively storage mites*	0 (0%)	0 (0%)	23 (27.0%)	16 (45.7%)
Sum of SPT diameters (mm)**	0 (0-4)	1 (0-3)	21 (4-87)	10 (4-36)

Figures are median and ranges (within parentheses), or absolute numbers and percentages (within parentheses).
* Positive SPT to *Lepidoglyphus destructor* and/or *Tyrophagus putrescentiae* together with negative SPT to all the remaining allergens tested.
** Summing up of maximum wheal diameters equal or larger than 1 mm on SPT to all 13 allergens tested.

likelihood ratio was 7.6 (95% CI 5.4-10.8), and negative likelihood ratio was 0.3 (95% CI 0.2-0.4).

False-positive result rate and false-negative result rate of Phadiatop™ test were 6.9% and 7.5%, respectively. Characteristics of false-positive and false-negative Phadiatop™ cases are represented in Table 2. False-negative cases showed a high proportion of exclusive storage mite sensitization (positive SPT to *Lepidoglyphus destructor* and/or *Tyrophagus putrescentiae* together with negative SPT to all the remaining allergens tested). False-positive cases showed a high proportion of (a) increased (higher than 100 IU/mL) total serum IgE levels, (b) significant (higher than 140 g/week) alcohol intake, and (c) small-sized (below the diagnostic cut-off, 4 mm) wheal reactions on SPT, present in 17 out of 32 cases (53%) (Table 2).

Data defining diagnostic accuracy of the Phadiatop™ test using the SPT results as reference standard in symptomatic subjects (individuals reporting a history of either nasal symptoms or wheezing, n=221) are represented in Table 3. Among these symptomatic patients, Phadiatop™ sensitivity was 79.2% (95% CI 68.2-87.3%), and specificity was 91.6% (95% CI 85.6-95.4%). Phadiatop™ positive predictive value was 83.5% (95% CI 72.6-90.8%), and negative predictive value was 89.1% (95% CI 82.8-93.5%). Phadiatop™ correctly classified subjects as allergic-sensitized or non-allergic-sensitized in 193 out of 221 cases (overall accuracy 87.3%, 95% CI 82.0-91.3%). Phadiatop™ positive likelihood ratio was 9.5 (95% CI 5.5-16.6), and negative likelihood ratio was 0.22 (95% CI 0.14-0.35) in this subgroup of symptomatic individuals.

Table 3. Crosstab of Phadiatop™ and SPT results in symptomatic subjects (individuals reporting a history of either nasal symptoms or wheezing).

	Allergic sensitization (SPT-positive) n = 77	No allergic sensitization (SPT-negative) n = 144
Phadiatop™ - positive n=73	True positive: n = 61	False positive: n = 12
Phadiatop™ - negative n=148	False negative: n = 16	True negative: n = 132

Discussion

The present study shows a satisfactory diagnostic accuracy of Phadiatop™ for the mass screening of allergic sensitization (defined as a positive SPT against a panel of relevant inhalants in the studied area) in a general adult population. Both sensitivity and specificity are above 70%. Moreover, the observed positive likelihood ratio of 7.6 suggests a good usefulness of the method [25]. The study was performed in an unselected sample of adults, and both the reference test (SPT) and the trial test (Phadiatop™) were performed simultaneously and in all cases, thus avoiding both verification (work-up) bias and review bias. To our knowledge, this is the first such study in a general adult

Table 4. Summary of studies reporting accuracy of the Phadiatop™ test for diagnosis of allergic disorders.

Authors	Setting and study population	Standard for diagnosis of allergic disorder	Number of subjects	Prevalence of allergic disorder	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Gustafsson & Danielsson, 1988 [6]	Children with asthma and/or rhinitis (Sweden)	Serum specific IgE	100	57%	95%	100%	100%	91%
Zimmerman and Forsyth, 1988 [7]	Children with asthma (Canada)	Total and specific serum IgE	109	41%	98%	98%	97%*	98%
Matricardi et al. 1989 [19]	Male adult (17-24 year) military students (Italy)	Skin prick tests	300	16%	100%	95%	81%	100%
Matricardi et al., 1990 [20]	Male adult (17-24 year) military students (Italy)	Skin prick tests and/or specific serum IgE plus clinical data	600	13%	98%	87%	53%	99%
Dekker et al., 1990 [8]	Adolescents and adults with asthma (Netherlands)	Serum specific IgE and Specialist diagnosis	249	57%	100%*	83%*	89%	95%
Eriksson, 1990 [9]	Adults with asthma and/or rhinitis (Sweden)	Skin prick tests	100	53%	92%	98%	98%	92%
Cantani et al., 1990 [10]	Children with asthma and/or rhinitis (Italy)	Clinical data, skin prick tests, total and specific serum IgE	98	56%	87%	100%	100%	86%
Wever et al., 1990 [11]	Adults with chronic airway obstruction (Netherlands)	Serum specific IgE	204	27%	94%*	98%*	96%	97%
Salkie, 1991 [12]	Children with suspected respiratory allergy (Canada)	Serum specific IgE	92	23%	90%*	95%*	86%*	97%*
Köhl & Debelic, 1991 [13]	Children and adults with asthma and/or rhinitis (Germany)	Skin prick tests and clinical data	300	50%	96%	92%	92%*	95%*
Matricardi et al., 1994 [21]	Male adult (17-24 year) military students (Italy)	Skin prick tests and clinical data	1815	14%	98%	77%	42%	99%
Bujia & Rasp, 1995 [27]	Adults with rhinitis (Germany)	Skin prick tests and clinical data	508	52%	98%	96%	96%	98%
Lilja et al., 1995 [14]	Children with family history of atopic disease (Sweden)	Skin prick tests	193	19%	86%	94%	78%*	96%*
Paganelli et al., 1998 [15]	Children and adults with asthma and/or rhinitis (six European countries)	Skin prick tests and clinical data	894	62%	93%	89%*	93%*	88%*
Williams et al., 2001 [16]	Children and adolescents with asthma and/or rhinitis (USA)	Skin prick tests	145	73%	98%	95%	98%*	94%*
Present study	General adult population (Spain)	Skin prick tests	465	26%**	70% (61-78%)	90% (87-93%)	72% (63-80%)	89% (86-92%)

Percentages are approximated to entire values. * Calculated from reported data. ** Unweighted value. Figures within parentheses are 95% confidence intervals.

population. In an elegant series of studies in a somewhat selected population of young (17-24 year-old) Italian air force military students, Matricardi et al. showed that Phadiatop™ is a valid test in mass-screening programmes, with a particularly high sensitivity and negative predictive value [19-21]. Tschopp et al. evaluated the diagnostic accuracy of Phadiatop™ for the diagnosis of clinically defined allergic asthma and rhinitis in 8329 Swiss adults [26]. With that purpose, the diagnostic efficiency of Phadiatop™ was somewhat lower than that of SPT [26]. However, the main purpose of Phadiatop™ test is not diagnosis of asthma or rhinitis, but diagnosis of allergic sensitization in patients with asthma or rhinitis. Such evaluation of diagnostic accuracy of Phadiatop™ for the diagnosis of allergic sensitization defined by SPT was not performed in the study of Tschopp et al. [26].

Previous studies evaluating the diagnostic accuracy of Phadiatop™ for the diagnosis of allergy in patients with asthma or rhinitis in a variety of clinical settings (summarized in Table 4) showed both higher sensitivity and higher positive predictive value than those observed in the present study in a general adult population [6-16,27]. It is known that estimates of accuracy of a given test are not always transferable [17,18]. Firstly, standard diagnostic criteria of allergic disorders may vary. Some studies investigated the accuracy of Phadiatop™ for the diagnosis of allergic sensitization (evaluated by means of either SPT or multi-serum specific IgE), while others investigated the accuracy of Phadiatop™ for the diagnosis of allergy (allergic sensitization plus clinical symptoms) (Table 3). Secondly, variation in the prevalence of these allergic disorders among populations can explain at least part of the differences in the diagnostic values of a test. Increasing prevalence of the studied phenomenon is followed by increasing sensitivity and, particularly, increasing positive predictive value of a given test [18]. The present study was performed in a general adult population, with a relatively low prevalence of allergic sensitization. Matricardi et al. reported a similarly low positive predictive value when using the Phadiatop™ test in mass screening programmes [19-21] (Table 3). In contrast, positive predictive value of Phadiatop™ is higher in clinics of asthma or rhinitis, where the prevalence of allergic sensitization is also high (Table 3). In fact, both sensitivity and positive predictive value of Phadiatop™ increased when symptomatic individuals of the present study were considered separately. A Bayesian approach [28] indicates that the positive predictive value of Phadiatop™ would further increase to 95% if the prevalence of allergic sensitization increased to 75%.

Additional peculiar characteristics of the studied population may also explain some discrepancies among studies of accuracy of the Phadiatop™ test. On the one hand, subjects from the studied population with false-negative Phadiatop™ results showed a high (nearly 50%) rate of exclusive sensitization to storage mites (*Tyrophagus putrescentiae* or *Lepidoglyphus destructor*) on SPT. These mites are the most common causes of allergic sensitization in the studied area [23,29]. It has been reported that Phadiatop™ may be less accurate in patients with mite allergy than in patients with pollen allergy [20]. Of note, the Phadiatop™ test includes mite, pollen, mould, and animal dander allergens, but the exact allergen composition is unknown, thus representing a limitation to interpretation of test results. It can be argued that storage mite allergens are not included in its composition, but this remains speculative. New variants of Phadiatop™ test have been developed in order to detect allergic sensitization in some professional environments [30]. On the other hand, subjects with false-positive Phadiatop™ results showed a high rate of increased total serum IgE, and a high rate of significant alcohol intake, which is a known cause of IgE increase [22,31]. This can suggest that unspecific total serum IgE increase could induce false-positive Phadiatop™ results in these cases. In fact, alcoholic patients show a high prevalence of false-positive Phadiatop™ results (unpublished observations). It is noteworthy, however, that more than half the subjects with false-positive Phadiatop™ results showed small (below the standard cut-off for positivity, 4 mm) wheal reactions on SPT. This could indicate that Phadiatop™ results in some of these cases may be not actually false positive, but could be true-positive depending on the cut-off standard of the reference test.

Summarising, Phadiatop™ assay offers a satisfactory accuracy for the diagnosis of allergic sensitization in a general adult population using SPT as the reference test. SPT are reliable, cheaper, and represent a standard method for investigating allergic sensitization in similar epidemiological studies [32]. In addition, SPT offers information about specific allergen sensitization. In this setting, Phadiatop™ may be an alternative when SPT are not feasible. However, limitations of the Phadiatop™ test in similar mass-screening programmes should be taken into account.

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