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Phadiatop™ compared to skin-prick test as a tool for diagnosing atopy in epidemiological studies in schoolchildren

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The validity of the Phadiatop™ test as compared to the skin-prick test (SPT) for diagnosing atopy in the epidemiological field has not been studied in schoolchildren. The aim of the present study was to evaluate its validity for classifying schoolchildren 9–12 yr old into atopics and non-atopics. A total of 621 children whose parents authorized both a SPT and a blood extraction from all children participating in the phase II of the International Study of Allergies in Children (ISAAC) in Cartagena (Spain) were included in the analysis. A positive SPT was that with at least a wheal having a maximum diameter of 3 mm, once the negative value had been subtracted. Phadiatop™ was performed according to the manufacturer instructions. Diagnostic tests using SPT as the gold standard were calculated for the whole group of children and also for those with asthma or rhinoconjunctivitis and for children without any of them. The results of the tests were: sensitivity 85.0% (95% CI 82.2–87.8%), specificity 85.5% (95%CI 82.7–88.3%), positive predictive value 72.7% (95%CI 69.0–76.1%), negative predictive value 92.7% (95%CI 90.6–94.7%) and accuracy 85.3% (95%CI 82.3–88.0%). The results improved among the symptomatic groups. Phadiatop™ can be used as a valid alternative to SPT in the epidemiological setting to diagnose atopy.

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The most usual tool for diagnosing atopy is skin-prick test (SPT), which is a cheap, quick and reliable way of detecting specific immunoglobulin (Ig) E against a large number of allergens. Furthermore, SPT has been the most frequent test used for defining atopy in epidemiological studies, both in adults and children. For example, a very large epidemiological study in children (phase II of the International Study of Asthma and Allergies in Childhood, ISAAC) includes a SPT module in order to define atopy in a large and diverse population of schoolchildren (1). However, in the school setting, SPT can be time-consuming and more difficult to perform than venous puncture, which is faster and easier to carry out. In certain situations, authorization from ethic committees and from parents can be easier to obtain for a venous puncture than for a SPT.

Phadiatop™ is a different way of diagnosing atopy. The main disadvantages of this test are its high price and that it is not designed to show the exact allergen(s) to which an individual is sensitized to, but demonstrates a specific reaction to at least one of the allergens of the mixture, whichever the reaction(s) may be. However, storing a minimal amount of serum offers the possibility of a more thorough investigation of the specific IgE afterwards, if necessary and when enough funds are available. There are several studies that have compared Phadiatop™ with other methods of measuring IgE in serum from children (2–5), mainly in the clinical setting. Other studies have compared Phadiatop™ with SPT in children suffering from asthma, rhinitis or conjuntivitis (6, 7); in children submitted to an allergy clinic (8, 9) or to a primary care centre (4); or who have a

family history of atopy (10). Phadiatop™ has also been used for diagnosing atopy as a risk factor for later asthma in infants hospitalized for wheezing (11) and in a cohort of newborns (12).

However, to the best of our knowledge, only one study – performed in adults – has evaluated the validity of Phadiatop™ for diagnosing atopy as compared with SPT in the general population (13). The aim of the present study is to evaluate if Phadiatop™ is also comparable with SPT in a cohort of schoolchildren 9–12 yr old.

Methods

Study population

As a part of the ISAAC II study in Spain, the centre of Cartagena surveyed 1471 children 9–12 yr old. The details of sampling and participation rate have been described elsewhere (14). From this sample of 1471 children, 1012 authorizations for performing a SPT and 720 authorizations for extracting a blood sample were obtained. A total of 621 children had both tests done, and were included in the present analysis.

Skin-prick test

SPT was performed according to the ISAAC phase II protocol (1) which includes the following allergens (ALK-Abello, Denmark): *Dermatophagoides pteronysinus*, *Dermatophagoides farinae*, cat, *Alternaria*, mixed trees (*Betula*, *Alnus* and *Corylus*) and mixed grasses (*Dactylis*, *Lolium*, *Festuca*, *Poa*, *Phelum* and *Avena*). Olive and *Parietaria* (ALK-Abello) were added as prevalent allergens of the area. The number of children sensitized only to dog is very low in our area, so this allergen was not included. A doctor and a nurse performed all SPTs. They were trained prior to the start of the study by performing three series of 16 pricks with 10 mg/ml of histamine on the volar surface of the arm of a volunteer. The coefficient of variation was less than 20% in the last series. The contours of each wheal were outlined and transferred to an adhesive transparent tape for later reading. SPT-positive subjects were defined as those who had at least one positive reaction (wheal maximum diameter measuring 3 mm or more after subtraction of the negative value).

Phadiatop™ test

The Phadiatop™ assay was carried out according to the manufacturer's instructions (Pharmacia Diagnostics, Uppsala, Sweden) using the UniCAP automated system. According to the information supplied by the Spanish branch, Phadiatop™ includes the following allergens: Mites (*D. pteronyssinus* and *D. fariane*), pets (cat and dog), mixed moulds (*Penicillium*, *Cladosporium*, *Aspergillus* and *Alternaria*), mixed grasses (*Parietaria*, *Lolium*, *Phleum* and *Cynodon*), *Artemisia* and mixed trees (*Acer*, *Betula*, *Ulmus*, *Quercus*, *Olea*, *Salix*, *Pinus*, *Eucalyptus*, *Acacia* and *Malaleuca*). The test gives a qualitative result – either positive or negative – according to the amount of fluorescence relative to a reference value. In the present study, this value corresponded to a concentration of 0.35 kU/l of specific IgE. Although the results can be interpreted quantitatively, the present analysis was directed to reach a diagnosis of atopy; so this test was only interpreted in a qualitative fashion, positive or negative.

Disease definitions

Asthma was defined as a positive answer to the question: 'Has your child had wheezing or whistling in the chest during the last 12 months?' Similarly, rhinoconjunctivitis was defined as a positive answer to both the following questions: 'In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu?', and 'In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?'

Statistical analysis

Diagnostic tests, including sensitivity specificity, positive and negative predictive values together with accuracy and positive and negative likelihood ratios (LR), were calculated using the SPT as the gold standard. The LR is the ratio of the probability of the specific test results in people who do have the disease to the probability in people who do not. For tests with only two outcomes (positive or negative), LR can be calculated directly from sensitivity and specificity as follows (15):

$$+\mathrm{LR} = \mathrm{sensitivity}/(1 - \mathrm{specificity})$$

$$-\mathrm{LR} = (1 - \mathrm{sensitivity})/\mathrm{specificity}$$

The diagnostic odds ratio, a new indicator of the overall test performance, was calculated according to Glas et al. (16). This approach uses the odds ratio as a single indicator of diagnostic performance and can be calculated as $+\mathrm{LR}/-\mathrm{LR}$. It has the advantage of being based on a

well-known epidemiological tool and of the strength of the association between having a positive test (Phadiatop^{TM} positive) and suffering the condition (being atopic according to the SPT test) being expressed in only one number. An additional advantage is that this test is independent of the prevalence of the disease (here, the prevalence of atopy).

All calculations were carried out for the whole population and were repeated for the children with asthma and for those with rhinoconjunctivitis. The odds ratios of suffering from asthma or rhinoconjunctivitis being either prick-positive and/or Phadiatop^{TM}-positive were also calculated. All calculations were performed by means of the Stata v7 software (College Station, TX, USA).

Ethical approval

The ISAAC phase II study was approved by the Ethics Committee of the 'Doce de Octubre' hospital for all Spanish centres that were involved, including that of Cartagena.

Results

The number of children in each group was: whole population, 621; asthmatics, 79; children with rhinoconjunctivitis, 102; and children with neither of the two diseases, 474. The percentage of children with a positive SPT or Phadiatop^{TM} test was 30.0% and 36.4%, respectively, among the whole population. Among those children with asthma the figures were 61.2% and 70.9%, and among those with rhinoconjunctivitis the respective percentages were 60.6% and 67.6%. Children having neither asthma nor rhinoconjunctivitis had less frequent positive tests: 22.3% for SPT and 27.2% for Phadiatop^{TM}.

The classification differences of children in each group (whole population, asthmatics, children with rhinoconjunctivitis and healthy children) were: 10.0%, 8.8%, 11.0% and 9.7% false positives (negative SPT but positive Phadiatop^{TM}), and 4.7%, 1.2%, 2% and 5.5% false negatives (positive SPT but negative Phadiatop^{TM}).

The results of the diagnostic tests in the whole population and also in the different groups of children with or without the disease are shown in Table 1. Sensitivity was higher among those children either with asthma or with rhinoconjunctivitis as compared to the total population and to those children without either disease. Conversely, specificity was higher in the group of healthy children and in the whole population. The positive predictive value was only moderate in the whole population and low in the children without any disease. However, the negative predictive value was high in all four groups. The positive LR are to be considered only moderate (none of them reaches 10); while the negative LR was very good in the two groups of diseased children (less than 0.1).

The overall diagnostic performance, as expressed by the diagnostic odds ratio, was best among the asthmatic children and was half among the children with rhinoconjunctivitis. Compared with those groups, this performance was much lower in the whole population and in the group of healthy children.

The odds ratios for suffering from asthma or rhinoconjunctivitis in children SPT-positive or Phadiatop^{TM}-positive are illustrated in Fig. 1.

Discussion

The validity of Phadiatop^{TM} as compared to SPT for diagnosing atopy among schoolchildren seems to be quite acceptable in the whole population, although the positive predictive value is less than that could be desirable. Phadiatop^{TM} seems to diagnose 'in excess' as compared to SPT (the rate of false positive is around 10% in all groups). False negatives vary

Table 1. Results of the diagnostics tests for Phadiatop^{TM} using skin-prick test as the gold standard in different groups of children

	Whole population (n = 621)	Asthmatic children (n = 79)	Children with rhino-conjunctivitis (n = 102)	Children without any respiratory symptom (n = 474)
Sensitivity (%)	85.0 (82.2–87.8)	98.0 (94.9–100)	96.7 (93.2–100)	76.1 (72.3–80.0)
Specificity (%)	85.5 (82.7–88.3)	75.9 (66.4–85.3)	73.8 (65.3–82.3)	87.4 (84.4–90.4)
+PV (%)	72.7 (69.0–76.1)	87.5 (80.2–94.8)	84.0 (77.0–91.2)	64.3 (60.0–68.6)
−PV (%)	92.7 (90.6–94.7)	95.6 (91.2–100)	93.9 (89.3–98.6)	92.4 (90.1–94.8)
Accuracy (%)	85.3 (82.3–88.0)	89.9 (81.0–95.5)	87.2 (79.2–93.0)	84.8 (81.2–87.9)
+LR	5.87 (4.62–7.44)	4.06 (2.13–7.75)	3.69 (2.00–4.80)	6.04 (4.52–8.07)
−LR	0.17 (0.12–0.25)	0.03 (0.04–0.19)	0.04 (0.01–0.2)	0.27 (0.19–0.38)
Diagnostic OR	33.4 (20.7–53.8)	154.0 (17.8–1328.4)	81.7 (17.0–392.2)	22.1 (12.9–37.9)

PV, predictive values; LR, likelihood ratio; OR, odds ratio, 95% confidence interval in brackets.

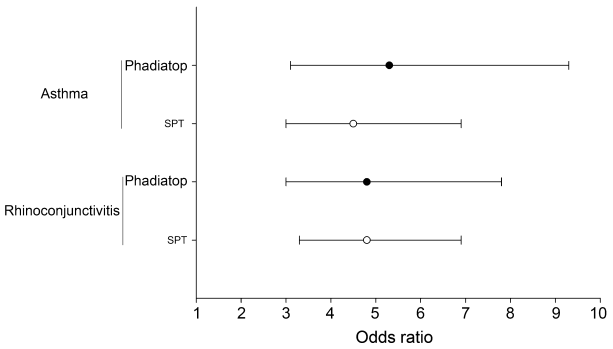

Fig. 1. Odds ratios for suffering from asthma or rhinoconjunctivitis when atopy is defined by Phadiatop^{TM} or by skin-prick test.

according to the group of children: the rate is lower in the group with either disease and much lower than the false positives in each group. These findings together with the results of the LR point at variations of Phadiatop^{TM} validity depending on the prevalence of atopy in a given environment: the lower the prevalence the higher rate of false positives and the poorer values of negative LR. Taking the results of the diagnostic tests together, it could be interpreted that Phadiatop^{TM} is better for ruling in atopy in children with allergic disease than for ruling it out in healthy children.

Using the diagnostic odds ratio, which has certain advantages referred to previously; it is quite clear that the validity of Phadiatop^{TM} is greatest among the asthmatic children and lowest among the healthy ones. Although it is said that the test is independent of the prevalence of the disease (atopy in this case), it is quite clear that it varies according to the prevalence of its clinical expression, as it is asthma. It cannot be ruled out that the cut-off point for considering a Phadiatop^{TM} test positive is responsible for a part of the findings: a higher intensity of atopy in children with asthma or rhinoconjunctivitis could be expected. Choosing a lower cut-off point would probably balance the negative LR among the healthy.

In the only population-based study (adults), Vidal et al. (13) compared Phadiatop^{TM} with SPT to diagnose atopy. The overall accuracy (85.6%) was quite comparable with that obtained in the present study. Furthermore, the positive predictive value was – as in the present results – substantially smaller (72.6%) than the negative predictive value (89.9%). The authors of that study also calculated the diagnostic tests in a subsample of adults with symptoms of asthma or rhinitis. As in the present study, the positive predictive value improved (to 83.5%); and sensitivity grew as well (from 70.8% to 79.2%) while specificity and the negative predictive value remained quite constant. The panel of allergens used in the aforementioned study was fairly similar to the one used in the present one.

If we consider SPT as the gold standard, then some misclassification bias is expected from measuring atopy by Phadiatop^{TM} in the general population. Usually, but not always, non-differential misclassification causes bias of odds ratio towards the null (17). This is a contingency that can be overcome by increasing the number of the sample. However, in the present case, misclassification seems to be differential (to the false positive), which normally leads to bias away from the null. However, it seems that this bias is not very important. As shown in Fig. 1, the odds ratios for suffering from asthma or from rhicoconjunctivitis are very similar when atopy is defined by SPT or Phadiatop^{TM}. On the other hand, the fact that SPT could depend on the allergens included in the test makes it quite variable in itself, thus not being a very reliable gold standard. It is also probable that by increasing the number of allergens tested, more children would be considered atopics, allowing Phadiatop^{TM} to increase its diagnostic validiy.

There are certain limitations in this study. The most important one is considering SPT as the gold standard when several factors can affect its own validity, independently of the number of allergens included. The variability dependent on the different fieldworkers was relatively controlled. However, certain variability cannot be totally ruled out. Another limitation of the present study is the fact that the allergens included in the SPT were not exactly the same as those included by the manufacturer in the Phadiatop^{TM}. The validity of Phadiatop^{TM} in an environment such as the Mediterranean coast which is not specifically contemplated in the allergen mixture of this test (although includes the most relevant allergens) should be considered as an advantage. A further limitation of the present study is that we did not perform any analysis of specific IgE in the serum of children that were positive to Phadiatop^{TM} and negative to SPT. However, it does not seem to be absolutely necessary for the purpose of the present analysis.

Furthermore, the relatively low proportion of children included in the analysis from the total sample may warn of a selection bias. Although we could not perform the two tests in the whole population of children (actually there was a drop from 1012 to 621 children), the prevalence of atopy, in case it changed, does not affect many of

the diagnostic tests. However, it does change the pre-test probability, and thus, predictive values should be interpreted with caution.

In summary, although the diagnostic validity of Phadiatop™ was not perfect as compared with the SPT taken as the gold standard in this epidemiological study in schoolchildren, it could be used as an alternative to SPT in this setting, if it is considered more convenient. Some caution should be claimed owing to a possible differential misclassification that could bias odds ratios away from the null hypothesis, especially if the results show values that are near unity. However, from the practical point of view it does not seem that this differential misclassification has an important impact on the odds ratios found for asthma or for rhinoconjunctivitis in this population of schoolchildren.

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