

Skin-Prick Testing as a Diagnostic Aid for Childhood Asthma

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Summary. Diagnosing asthma is problematic when based solely on reported symptoms. The purpose of this study was to evaluate skin-prick testing as a diagnostic aid for asthma in children. Skin-prick testing (SPT) was undertaken in children aged 2–10 years with either no history of wheeze ($n = 149$) or recent doctor-observed wheeze which responded to treatment with a bronchodilator, the “gold standard” ($n = 164$). Children with moderate or severe asthma were excluded. SPT positivity increased sharply at age 5 years in wheezers. Data were therefore divided into two age groups: 2–<5 years (57 controls, 97 wheezers) and 5–10 years (92 controls, 67 wheezers). The sensitivity, specificity, and likelihood ratios of SPT positivity for wheeze were 32%, 89%, and 2.9, respectively, in the younger children, and 82%, 85%, and 5.5, respectively, in the older children. For a prevalence of 30% for asthma, the positive predictive values of a positive SPT were 55% and 70% for the younger and older age groups, respectively. The test characteristics of SPT for helping diagnose asthma in schoolchildren are good. The prevalence of wheeze in preschool children is high, and so SPT should be helpful even in this group. We suggest that clinicians consider skin-prick testing as a diagnostic aid for asthma. *Pediatr Pulmonol.* 2005; 39:558–562. © 2005 Wiley-Liss, Inc.

Key words: atopy; skin prick test; diagnosis of asthma; children.

INTRODUCTION

There is no consensus about the definition of asthma and no simple diagnostic test for the disease.¹ One undisputed feature is the presence of airflow variability.² A diagnosis of asthma is straightforward when a child is observed to wheeze and responds to treatment with a bronchodilator, but it is often problematic when based solely on reported symptoms.³ Another marker of asthma is atopy. Sensitization to aeroallergens in groups of children with and without asthma showed that asthmatic children are more likely to be sensitized, but even in groups of similar age, the prevalence of sensitization is very variable, ranging from 32–77%.^{4–8} Sensitization in wheezy preschool children to aeroallergens is less frequent than in schoolchildren. The wheezing phenotypes in the preschool age group fall into two broad groups: nonatopic viral wheezers who are likely to stop at school age, and atopic wheezers who are likely to continue into school age.² Compared with studies evaluating clinical management of diseases, formal studies of test characteristics (sensitivity, specificity, likelihood ratios, and predictive values) of investigations for diseases are infrequent.⁹ It is our impression that skin-prick testing (SPT) is rarely used as a diagnostic aid for childhood asthma, although SPT is easy and feasible in general practice.¹⁰

The purpose of this study is to formally evaluate SPT positivity in children 2–10 years old as a diagnostic aid for the presence of mild, intermittent asthma. For the purposes

of this study, the terms “wheeze” and “asthma” are interchangeable.

SUBJECTS

Children between 2–10 years old of primarily Afro-Caribbean, Bangladeshi, and white British ethnicities, born and living in the east London districts of Tower Hamlets and City and Hackney, an inner city community, were divided into two groups: controls and wheezers. In the control or “nonwheezers” group, the children had no personal history of wheeze, difficulty breathing, or asthma; those with isolated cough were not excluded. Controls were recruited by questionnaire at local schools, hospital outpatient clinics, and inpatient wards where

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they had been admitted for nonrespiratory complaints. "Wheezers" were recruited from the Accident and Emergency Department and Ambulatory Unit at the Royal London Hospital, where they had presented in the previous 4–6 weeks and were documented as having wheeze by a pediatrician. These children's illnesses could have been labeled viral-induced wheeze or asthma. Children with known moderate or severe asthma, i.e., at step 2 or above (i.e., requiring continuous prophylactic treatment) in the British guidelines on the management of asthma,¹¹ were excluded. A positive clinical response to bronchodilator treatment, i.e., improvement in wheeze and difficulty breathing, was also documented. Children with other atopic disorders such as eczema were not excluded from either group. Children known to have chronic lung disease of infancy, cystic fibrosis, bronchiectasis, or structural lung diseases such as bronchomalacia were excluded.

METHODS

SPT was undertaken using either the lancet (Alk-Abello, Denmark) or Multitest II (Lincoln Diagnostics) methods. These methods are known to be highly reproducible.^{8,12,13} We changed to the Multitest II multiple head applicator during the study because application of allergens was both quicker and more acceptable to subjects. Results of tests are 98% concordant.¹⁴ Five aeroallergens (cat hair, dog dander, grass pollen, *Aspergillus fumigatus*, and *Dermatophagoides pteronyssinus*), histamine (positive control), and saline (negative control) (Alk-Abello, Denmark) were applied to the volar surface of each subject's forearm. Skin reaction was assessed 15 min after application. A positive response was defined as a wheal size equal to or greater than 3 mm above the negative control.¹⁵ Any child with such a response to one or more allergens was recorded as SPT-positive.

The study was approved by the local Ethics Committee. Signed consent was obtained from parents and older children.

Data Analysis

The relationship of SPT positivity to age between 2–<10 years was assessed using a moving average of 20 sample points (Nanowin Statistics Package). A plot of SPT positivity against age showed that in the wheezers, there was a sharp increase in the proportion of SPT positivity at about 5 years of age (Fig. 1). Accordingly, data were divided into two groups according to subject age (2–<5 years and 5–<10 years) to describe the test characteristics of SPT for diagnosing wheeze.

RESULTS

The numbers of subjects who underwent SPT are shown in Table 1. In the younger age group, the sensitivity and

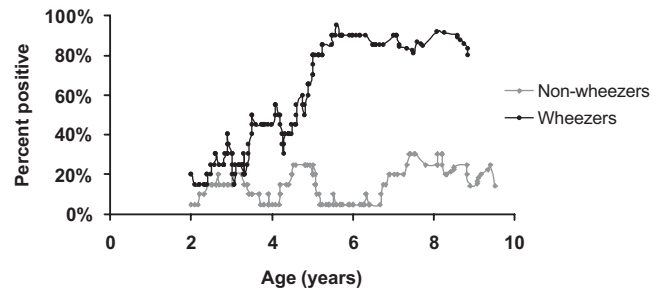


Fig. 1. Proportion of subjects by age with positive SPT to at least one common aeroallergen.

specificity of SPT positivity in distinguishing wheezers from nonwheezers were 32% (95% confidence interval (CI), 25–40%) and 89% (95% CI, 83–93%), respectively, i.e., 32% of wheezers were SPT-positive, as were 11% of nonwheezers. In the 5–10-year age group, SPT was 82% (95% CI, 71–89%) sensitive and 85% (95% CI, 80–89%) specific for wheeze, i.e., 82% of wheezers were SPT-positive, compared to 15% of nonwheezers.

The prevalence of asthma is likely to differ quite widely in different circumstances. Accordingly, the positive and negative predictive values⁹ for the SPT results for the two age groups for differing asthma prevalences were calculated and are shown in Table 2. The initial odds in favor of wheeze are the ratio prevalence/1-prevalence. These are increased by the likelihood ratio of a positive SPT, expressed as sensitivity/1-specificity for wheeze. The likelihood ratios for preschool and school children are 2.9 and 5.5 respectively. Similarly, a negative test multiplies the initial odds against wheeze by a factor of 1.3 for preschool children and 4.7 for the older children (likelihood ratios of a negative test result (i.e., $(1 - \text{sensitivity})/\text{specificity}$) = 0.76 and 0.21, respectively).

DISCUSSION

This is the first study reporting the prevalence of SPT positivity across the age range 2–10 years for children who were observed to wheeze and children from the same population with no history of wheeze or asthma. It is also the first study to formally evaluate SPT as a diagnostic test for asthma. Children with moderate or severe asthma were excluded, as the purpose of the study was to describe a test that could be useful in children with a history that might suggest asthma but where wheeze may never have been observed. It is this group which can be a diagnostic problem.

This study satisfies many of the criteria for the proper evaluation of a diagnostic test.¹⁶ Firstly, the children who have features of the "gold standard" for the disease were clearly defined. They had been observed to wheeze and were documented to have responded to treatment with a bronchodilator. All had mild intermittent asthma and were

TABLE 1—Numbers and Ages of Subjects in Whom SPT Was Undertaken

	Nonwheezers		Wheezers	
	Under 5 years n = 57	5–10 years n = 92	Under 5 years n = 97	5–10 years n = 67
Age (median and range)	3.5 (2.0–4.9)	6.4 (5.0–10.0)	3.4 (2.0–4.9)	6.2 (5.0–9.9)
M:F	27:30	46:46	65:32	46:21
Ethnicities, C:B:A:O	21:23:11:2	38:47:7:0	37:37:19:4	16:42:9:0

C, Caucasian; B, Bangladeshi/Asian; A, Afro-Caribbean; O, others.

at step 1 of our asthma guidelines.¹¹ SPT was not undertaken blind to the knowledge of the group the subject would fall into (i.e., wheezers vs. nonwheezers), as those tested in hospital would have been recruited after they had presented to the Emergency Department. It would have been difficult to design the study otherwise, but we believe, since the responses were measured, that bias would have been unlikely. Children without the disease were those with no history of reported or observed wheeze but who could have cough. The subjects in this group were clearly defined as “nonwheezers” rather than “healthy” controls. It is reasonable to include children with persistent isolated cough in the control group, as they had no history of wheeze or difficulty breathing. We did not exclude children who had histories of other atopic diseases, as the model for observed wheezers compared to nonwheezers should also apply to these children. Secondly, the wheezers would be comparable to the group in the population for whom diagnostic testing could be useful, i.e., those who had been reported to wheeze or have difficulty breathing but who had never been observed to wheeze. Thirdly, by including confidence intervals, we reported the numerical precision for the test indices, clearly described when results would be considered negative or indeterminate, and referenced test repeatability. SPT for aeroallergens is highly reproducible; within-occasion repeatability for SPT in children is good, with only 1.3% discordance for individual wheal response.¹³ Sensitization to common aeroallergens also appears to have good long-term stability.¹⁷ The main limitation of our study is that the results apply only to patients in a UK inner city area. It is known that children who live in rural

areas are less likely to be sensitized,¹⁸ but it is not clear whether this applies equally to healthy children and to children with a history of wheeze. The prevalence of SPT positivity in a study of asthma and atopy in Ashford, Kent, was 16.7%, similar to that reported in this study.¹⁹ In practical terms, if the diagnosis of asthma is considered in a child who has never been heard to wheeze, SPT positivity to one or more aeroallergens has over 80% sensitivity for wheeze in school-age children. Sensitivity is much poorer for the preschool child. For preschool children in whom the diagnosis of asthma is being considered on reported symptoms and who are SPT-negative, little objective testing is practical outside a specialist laboratory. Nevertheless, the prevalence of wheezing is high in this group, resulting in an increased positive predictive value of SPT. In addition, knowledge of SPT positivity is helpful in advising about prognosis⁵ and guiding treatment.²⁰ Positive and negative likelihood ratios of over 5 and under 0.2, respectively, for a test are considered strongly diagnostic.²¹ In schoolchildren who are SPT-negative and are truly wheezing, an alternative diagnosis to asthma, such as obliterative bronchiolitis or wheezing related to obesity, should be considered. This is particularly important where asthma treatment does not appear to be beneficial.²²

A longitudinal study of a selected group of children of atopic parents reported that 90% of those who were wheezy between 5–10 years were SPT-positive.²³ Our study differs from epidemiological studies relating wheeze and atopy in that our subjects were *observed* to wheeze. Most population studies reported the prevalence of atopy in healthy children compared to those with

TABLE 2—Positive and Negative Predictive Values of SPT for Different Prevalence Rates of Asthma

Prevalence of asthma	2–<5 years old		5–10 years old	
	Positive predictive value (%)	Negative predictive value (%)	Positive predictive value (%)	Negative predicted value (%)
10%	24	92	38	98
20%	42	84	58	95
30%	55	75	70	92
40%	66	66	78	88
50%	74	57	85	83

reported wheeze (Table 3), and this could explain some of the differences in atopic status between subjects of these studies and ours. There are some reservations about the validity of reported wheeze.³ The word “wheeze” is open to misinterpretation and is not translatable in some languages, and the reporting of wheeze can change with time.^{3,24} This may partly explain the wide variation in SPT positivity from 21%⁸ to 77%²⁵ reported in “asthmatics.”

Other factors may account for this wide variation in prevalence of sensitization among “asthmatics” and healthy controls.^{4,5,7,8,25} Rural and urban populations differ in prevalence of atopy. There are genetic differences between populations in atopic status.²⁶ Methods of skin-prick testing, definitions of positivity, and choice of allergen may also explain some of the differences. The results presented here apply to a contemporary UK urban population of mixed ethnic groups. Although atopy differs from place to place, it has been gradually increasing during the last two decades.^{27–29} This emphasizes the importance of having local contemporary data for reference purposes and the need for standardization in both the method of application and the panel of allergens used in SPT.

Although special expertise is required to apply and read these tests in children, SPT is much easier with the multiple head applicator device. The results are available within minutes. SPT is feasible in a primary-care setting.¹⁰ Although this report is concerned mainly with the diagnostic profile of SPT in the context of asthma, it is also in the patient's interest to understand the implications for allergen avoidance when tests are positive. As the prevalence of asthma in the community is uncertain because of the inaccuracy of the reporting of symptoms, our data can only be summarized by the fact that the odds of having wheeze in older children is multiplied by a factor of 5.5 by a positive SPT. Bearing in mind that a child who presents with respiratory symptoms to a general practitioner (GP) is more likely to have had wheeze than the general population, the prevalence of wheeze in the GP's population will be higher, and even higher in the group referred from general practice for a specialist opinion. This is the reason we calculated positive and negative predicted values for prevalences of up to 50%.

The noticeable error rates, particularly in preschool children where the test is poorly sensitive, suggest that SPT cannot be considered a stand-alone diagnostic test in this age group. Nevertheless, the prevalence of wheezing is high in children under age 5 years,² and with a prevalence of, say, 40%, the positive predictive value of a positive SPT is 66%, so that such a result could be an aid to diagnosis even in this age group.

The methodology of diagnostic research has been given less attention than research into the value of treatments.³⁰ A recent analysis of the evidence base for tests used in diagnosing and monitoring disease in respiratory medi-

TABLE 3—Population-Based Studies Investigating Prevalence of SPT Positivity Among Doctor Diagnosed Asthmatics and Healthy Controls

	Age (years)	Definition of asthma	Allergens tested	Definition of positivity	Asthmatic		Controls	
					N	% positivity	N	% positivity
Brooke et al. (1995), ⁴ Leicester, UK	4–7	Reported symptoms	Cat, dog, HDM ¹ , mixed grass, pollen	Assessed after 5–15 min 2 mm $\geq$ negative control	94	43.6%	105	23.8%
Schwartz (1995), ⁷ Boston, MA	6–12	Reported symptoms and doctor-diagnosed asthma	Cat, dog, HDM, and six other local grass allergens	Assessed after 20 min (length + width of flare) – (length + width of flare of negative control) $\geq$ 21 mm	127	32.0%	975	16.0%
Martinez et al. (1995), ⁵ Tucson, AZ	6	Reported symptoms (including persistent wheezers and late onset wheezers)	HDM and six other local grass/plant allergens	Wheal $\geq$ 2 mm	187	56.0%	317	33.8%
Remes (1996), ²⁵ Stockholm, Sweden	7–12	Doctor-diagnosed asthma and clinical examination	Cow, horse, cat, dog, cladosporium, and nine, local grass/tree allergens	Wheal $\geq$ 3 mm, no reaction of negative control	43	77.0%	204	46.0%
Penny et al. (2001), ⁸ Lima, Peru	5.7–11.3	Reported symptoms (using ISAAC) and symptomatic in last 12 months	HDM ¹ , cockroach, and penicillium	3 mm $\geq$ negative control	181	21.5%		

¹HDM, house dust mite.

cine suggested that the value of a large proportion of clinical tests, including lung function tests, is not supported by high-level evidence.³¹ Airflow variability measured by peak-flow variability during the day was criticized because measurements are unreliable.³² Other methods for lung-function testing are not generally used by the GP or general pediatrician. A change of 9% in forced expiratory volumes in 1 sec before and after bronchodilator in schoolchildren was 50% sensitive and 86% specific for previous wheeze, giving a likelihood ratio for previous wheeze of 3.5,³³ a diagnostic profile less robust for this age group than the SPT profile.

We have presented an evaluation of SPT in the diagnosis of childhood asthma, defined as reversible wheeze that has been observed. SPT is easy, especially with a multiple head applicator device.¹⁴ We recommend SPT to GPs and pediatricians when a diagnosis of asthma is considered on the basis of reported symptoms only, or is otherwise in doubt.

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