In search of childhood asthma: questionnaire, tests of bronchial hyperresponsiveness, and clinical evaluation

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Background: The definition or diagnosis of asthma is a challenge for both clinicians and epidemiologists. Symptom history is usually supplemented with tests of bronchial hyperresponsiveness (BHR) in spite of their uncertainty in improving diagnostic accuracy.

Methods: To assess the interrelationship between respiratory symptoms, BHR, and clinical diagnosis of asthma, the respiratory symptoms of 1633 schoolchildren were screened using a questionnaire (response rate 81.2%) and a clinical study was conducted in a subsample of 247 children. Data from a free running test and a methacholine inhalation challenge test were available in 218 children. The diagnosis of asthma was confirmed by a paediatric allergist.

Results: Despite their high specificity (>0.97), BHR tests did not significantly improve the diagnostic accuracy after the symptom history: area under the receiver operator characteristic (ROC) curve was 0.90 for a logistic regression model with four symptoms and 0.94 for the symptoms with free running test and methacholine inhalation challenge results. On the other hand, BHR tests had low sensitivity (0.35–0.47), whereas several symptoms had both high specificity (>0.97) and sensitivity (>0.7) in relation to clinical asthma, which makes them a better tool for asthma epidemiology than BHR.

Conclusions: Symptom history still forms the basis for defining asthma in both clinical and epidemiological settings. BHR tests only marginally increased the diagnostic accuracy after symptom history had been taken into account. The diagnosis of childhood asthma should not therefore be overlooked in symptomatic cases with no objective evidence of BHR. Moreover, BHR should not be required for defining asthma in epidemiological studies.

The definition or diagnosis of childhood asthma remains a challenge for both clinicians and epidemiologists.^{1–3} In both settings symptom history forms a basis for the definition, but objective evidence of variable airway obstruction is usually required, or at least regarded as beneficial.⁴ For a clinician, objective evidence gives support to the diagnosis of asthma and may help in determining the severity of the disease. For an epidemiologist, the tests of bronchial hyperresponsiveness (BHR) may help in formulating the case definition of asthma. These tests are less influenced by recognition or awareness of symptoms, and by linguistic or cultural differences, than the data based on symptom questionnaires alone.

There is an increasing demand for diagnosing asthma as early as possible. Recent studies suggest that the treatment of asthma should be initiated at an early phase of the disease before any lung function abnormalities have developed.⁵ At the same time, the increased prevalence of asthma has become a major public health issue, calling for standardised methodology in epidemiological studies.³ A validation of symptom questionnaires by the BHR tests has been suggested for these purposes. Some studies have been carried out in children to accomplish this goal, but studies comparing symptoms and BHR tests with the clinical diagnosis of asthma are few.^{6–8}

We evaluated the interrelationship between the questionnaire based symptom history, the results of a free running test and methacholine inhalation challenge, and the clinical diagnosis of asthma. The aim of our study was to assess how much BHR tests would increase the diagnostic accuracy of childhood asthma after the symptom history had been taken into account.

METHODS

Study design

The study had two phases: a screening phase and a clinical phase. In the screening phase⁹ a written symptom question-

naire was sent to a population based sample of children aged 7–12 years; 1633 (81%) questionnaires were returned. From these 1633 children, 229 with respiratory symptoms were enrolled in the Finnish part of the PEACE study⁹; this study was completed by 186 children. These 186 children and a further 128 randomly selected non-symptomatic controls were invited to participate in the clinical phase of the study; a total of 247 children (79% of those invited) agreed to take part (fig 1).^{10 11}

Approval for the screening phase of the study was given by the ethics committee of the National Public Health Institute, Helsinki, Finland, and for the clinical study by the ethics committee of the Kuopio University Hospital, Kuopio, Finland.

Grouping of children

Screening groups

The children were divided into the following screening groups based on the questionnaire responses⁹:

Asthma and/or wheeze

Reporting of doctor diagnosed asthma and/or any wheezing (wheezy chest apart from colds or attacks of shortness of breath with wheezing) during the past 12 months.

Dry cough at night

Reporting of dry cough at night, but not any type of wheezing, during the past 12 months.

Abbreviations: FVC, forced vital capacity; FEV₁, forced expiratory volume in one second; MMEF, maximal mid expiratory flow; ΔFEV₁ (%), percentage fall index for FEV₁; PD₂₀FEV₁, provocative dose of inhaled methacholine causing a 20% fall in FEV₁.

Figure 1 Flowchart of the study: sampling scheme and grouping of the children in the screening phase and after clinical assessment for asthma. *Number of participants from the 10% random sample. †In addition to subjects with incomplete data, six asthmatic children on inhaled steroids were excluded.

No respiratory symptoms

None of the above characteristics (that is, reporting of asthma diagnosis, wheeze, or cough).

Diagnostic groups

The clinical phase included an interview with the parents, clinical status assessment, and measurements of lung function and BHR. The children were classified on clinical grounds into three diagnostic groups by the paediatric allergist (KR) (for details see Remes *et al*¹⁰):

Clinical asthma

A symptom history consistent with asthma and at least one objective clinical, lung function or challenge test finding: acute symptoms with auscultatory wheezing disappearing after inhaled β_2 agonist associated with $>15\%$ increase in peak flow (PEF); in 4 week home PEF measurements $>20\%$ variability and $>15\%$ increase in PEF on at least three occasions after inhaled β_2 agonist; baseline obstruction with $>15\%$ improvement in PEF or FEV₁ after inhaled β_2 agonist; pathological free running test ($\geq 10\%$ fall in FEV₁) or methacholine inhalation challenge (provocative dose causing $\geq 20\%$ fall in FEV₁ of ≤ 400 μg) ($n=43$).

Possible asthma

A symptom history consistent with asthma but no objective findings ($n=34$).

Controls

No symptoms suggestive of asthma or other chronic or recurrent respiratory disorder ($n=170$).

Diagnostic tests

No short acting β_2 agonist, anticholinergic drugs, or cromones were administered for 12 hours before the tests, no long term β_2 agonist for 2 days, no theophylline or cough medication for 3 days, and most antihistamines were not given for 3 days before testing (except cetirizine and hydroxyzine (5 days) and astemizole (8 weeks)). Inhaled steroids were not withheld. Baseline FEV₁ had to be $\geq 70\%$ predicted. In cases of acute respiratory infection the tests were postponed for 2 weeks.

Baseline flow volume spirometric tests

Baseline spirometric tests were performed and the spirometric indices were selected according to the criteria of the European Respiratory Society⁴ as described earlier.⁹

Free running test

After baseline recordings with a pneumotachographic spirometer,⁹ the lung function measurements were repeated with a hand held turbine spirometer (Micro Plus, Micro Medical Ltd, Rochester, UK) which was used in the follow up free running test. The measurement technique and the selection of spirometric indices were similar to those in the pneumotachographic flow volume spirometric test except that the

Table 2 Agreement between the pathological responses in the free running test (FRT) and the methacholine inhalation challenge (MIC) in 212 children with complete data

MIC	FRT	
	Positive	Negative
Positive	10 (4.7%)	13 (6.1%)
Negative	9 (4.2%)	180 (84.9%)

Pathological responses (% of total): $\geq 10\%$ fall in FEV₁ in FRT and provocative dose ≤ 400 μ g causing a 20% fall in FEV₁ in MIC test. $\kappa=0.42$, $p<0.0001$.

were adjusted for the sampling scheme to avoid verification bias.¹⁵ In addition, the Youden's index was calculated for each screening method (symptoms, free running test, methacholine inhalation challenge) or their combination in order to serve as an overall indicator of validity.^{3 6}

RESULTS

Complete and valid lung function and challenge test data were available for 218 of a total of 247 participating children. As steroids effectively reduce BHR,¹⁶ six asthmatic children on inhaled steroids were excluded from the analyses (fig 1). The bronchodilation test was missing in three children, but otherwise they were included. The drop outs from the three screening groups were analysed separately. They did not significantly differ from the initial source population ($n=1633$) with respect to parental history of asthma, sex, or parent-reported allergies to pollens, animal danders, and house dust mites (data not shown).

Demographic data and baseline spirometric values

The screening and diagnostic groups did not differ from each other by age, but there were more boys and more atopic individuals among the asthmatic children. In the baseline spirometric tests only MMEF in the asthmatic children was, on average, lower than in the other children (table 1).

Free running test and bronchial lability index

The children who reported asthma and/or wheeze in the screening questionnaire had significantly larger Δ FEV₁(%) in the free running tests than the non-symptomatic children (table 1). In fact, the children who did not report asthma or any respiratory symptoms in the screening questionnaire did not have marked ($>15\%$) reductions in FEV₁. Interestingly, two children with cough as the only respiratory symptom had clear responses in the free running tests. Eleven (16.2%) children who reported asthma and/or wheeze, six (8.0%) with dry cough at night, and two (2.9%) of the children who did not report any respiratory symptoms in the screening questionnaire had pathological responses ($\geq 10\%$ fall) in the free running test ($p=0.023$).

Most children with clinical asthma had normal free running test results and only a few children had large responses. Twelve (35.3%) children with clinical asthma, three with possible asthma (9.7%), and four controls (2.7%) had a pathological response in the free running test ($p<0.001$). Using a 10% cut off point for the bronchial lability index (%), 12 children with clinical asthma (35.3%), three with possible asthma (9.7%), and seven controls (4.8%) had pathological responses ($p<0.001$).

Methacholine inhalation challenge

The methacholine inhalation challenge was pathological in 16 children who reported asthma and/or wheeze (23.5%), in five with dry cough at night (6.7%), and in two who did not report

Figure 2 Receiver operating characteristic (ROC) curves for the multivariate models relating clinical asthma to the questionnaire data (Q) or to both the questionnaire and BHR data (Q & C). The areas under the ROC curves were 0.895 (Q) and 0.936 (Q & C), respectively. Variables included in the models are given as footnotes in table 3; model Q, symptoms 1–4; model Q & C, symptoms 1–4 and BHR tests 5–6.

any respiratory symptoms (2.9%) in the screening questionnaire ($p<0.001$). Similar results were obtained when the methacholine challenge results were compared between the diagnostic groups; a pathological result was found in 16 children with clinical asthma (47.1%), in five with possible asthma (16.1%), and in two controls (1.4%) ($p<0.001$). In addition, mild to moderate reactions (PD_{20} FEV₁ 400–4900 μ g) were common in children with clinical asthma, so that only five of these 34 children (14.7%) did not reach the 20% fall in FEV₁ during the methacholine challenge—that is, their PD_{20} FEV₁ was >4900 μ g.

Association between free running test and methacholine challenge results

The results of the methacholine challenge (PD_{20} FEV₁) and of the free running test (Δ FEV₁(%)) correlated poorly although statistically significantly with each other (Spearman's $r=0.31$, $p<0.0001$). The correlation tended to be higher in the children with clinical asthma ($r=0.37$), intermediate in children with possible asthma ($r=0.25$), and lowest in control children ($r=0.12$). There was moderate agreement between the pathological results of the free running test and the methacholine challenge ($\kappa=0.42$, $p<0.0001$; table 2).

Added value of BHR tests in predicting clinical asthma

We were able to predict asthma almost as accurately by the symptom history alone—that is, the symptoms reported in the screening questionnaire—as if we supplemented the decision by the results of the BHR tests (fig 2). However, all of the selected variables significantly contributed to the model as assessed by the likelihood ratio test (data not shown).

Sensitivity and specificity analysis

Individual questions on shortness of breath, wheezy chest, and dry cough at night were highly specific but not very sensitive for the pathological free running test and methacholine challenge results, so the corresponding Youden's indices ranged between 0.16 and 0.46. In contrast, these questions had a relatively high sensitivity and specificity for clinical asthma with a Youden's index of 0.63–0.75 (table 3).

Both the free running test and the methacholine inhalation challenge were equally specific for clinical asthma, but the methacholine challenge had higher sensitivity. The sampling adjusted positive and negative predictive values of the free running test for clinical asthma were 0.28 and 0.98, respectively; the corresponding values for the methacholine challenge were 0.35 and 0.98. The combination of the free

Table 3 Sensitivity, specificity, and Youden's index of screening methods for bronchial hyperresponsiveness (BHR) and clinical asthma: (1) respiratory symptoms reported in the parental screening questionnaire, (2) tests of BHR, and (3) a combination of symptoms and BHR tests

Screening method	Free running test			Methacholine inhalation challenge			Clinical asthma		
	Sensitivity	Specificity	Youden's index	Sensitivity	Specificity	Youden's index	Sensitivity	Specificity	Youden's index
(1) Symptoms only									
Wheezy chest apart from colds, in the past 12 months ¹	0.25	0.96	0.21	0.30	0.97	0.27	0.78	0.97	0.75
Attacks of shortness of breath with wheezing in the past 12 months ²	0.23	0.97	0.20	0.30	0.97	0.27	0.72	0.98	0.70
Shortness of breath when playing outdoors or walking up the staircase in the past 12 months ³	0.21	0.95	0.16	0.32	0.96	0.28	0.66	0.97	0.63
Dry cough at night apart from a cold or chest infection in the past 12 months ⁴	0.30	0.89	0.19	0.35	0.89	0.24	0.80	0.90	0.70
Attacks of shortness of breath with wheezing ever	0.55	0.87	0.42	0.59	0.87	0.46	0.78	0.87	0.65
(2) BHR tests only									
Pathological free running test ⁵							0.35	0.97	0.32
Pathological methacholine inhalation challenge ⁶							0.47	0.97	0.44
(3) Symptoms and BHR tests									
Wheeze* and pathological free running test							0.25	0.99	0.24
Wheeze* and pathological methacholine inhalation challenge							0.38	0.99	0.37

The sensitivity and specificity estimates have been adjusted for the sampling scheme of the study.^{15–16} Order of variable inclusions in the logistic regression analysis (see Methods and fig 2). *Wheezy chest apart from colds in the past 12 months—that is, symptom with the highest Youden's index v clinical asthma.

running test or methacholine challenge with the symptom of “wheezy chest apart from colds in the past 12 months” gave almost complete specificity for clinical asthma, but the sensitivity was low. The Youden's index was therefore only 0.24–0.37 (table 3).

DISCUSSION

Even highly specific and sensitive diagnostic tests may have little value in clinical practice if they do not give any additional information to the diagnostic grouping or to the selection of treatment.¹⁵ The main finding in our study, which is in agreement with other recent studies,^{17,18} was that, with a careful symptom history alone it was possible to distinguish reasonably well between asthmatic and non-asthmatic children. The free running test and methacholine inhalation challenge increased the diagnostic accuracy only to a small extent.

Definition of clinical asthma

There is no “gold standard” for the diagnosis of asthma in children. In our study subjects had to have both subjective symptoms and objective evidence of variable airway obstruction to be defined as having asthma.¹⁰ We therefore believe that our clinical definition was highly specific for asthma, as suggested also by the ROC analysis. To see whether this rather strict definition led to underdiagnosis we followed the children with “possible asthma” for 2 years.¹⁹ About one third of these children continued to have symptoms and showed objective evidence of asthma during the follow up, one third continued to have symptoms with no objective evidence of asthma, and one third grew out of their symptoms.¹⁹

The first third probably represented children who actually had mild asthma in the baseline study but in the cross sectional setting we were unable to demonstrate BHR because of the fluctuating course of the disease. When these nine children were included in the clinical asthma group in the analyses the results remained very similar. The areas under the ROC curves were only slightly though constantly lower than in the

original models (see fig 2); 0.86 for the model with symptoms alone and 0.91 for the model with both symptoms and BHR test results.

Clinical implications

When our results are considered from the primary care perspective, it seems that in most cases the diagnosis of asthma could be made with reasonable accuracy by taking a careful symptom history. A diagnosis of asthma made by trained primary care physicians can considerably shorten the delay in starting anti-inflammatory therapy.³ Although our results stress the role of symptoms in the diagnosis of asthma, sensitive and specific tests would obviously be beneficial to reach an objective diagnosis in clinical practice. Such tests would be especially useful in the evaluation of children with atypical symptoms or in the determination of asthma severity. The objective evidence of asthma would also be helpful in motivating the patient to undergo long term treatment, or it may be required for receiving social security and other benefits.

Our results show that in most cases the current BHR tests cannot provide such evidence. In order to avoid delays in the diagnosis of asthma, children with an obvious symptom history but no objective evidence of BHR should therefore be carefully followed and anti-inflammatory medication should be started when necessary.³ Although repeated BHR tests may help in reaching the diagnosis,¹⁹ the development of more sensitive and specific diagnostic tests²⁰ such as sputum biomarkers or measurement of NO in exhaled air may assist in identifying asthma cases at an early phase of the disease.

Epidemiological implications

Our results on the validation of the written symptom questionnaire confirm and expand previous findings.^{3,6,8} BHR alone, or in combination with the symptom history, was found to be a very insensitive measure of asthma. Similar findings have been reported by Jenkins *et al*⁷ who compared an

interview based physician's diagnosis of asthma with a symptom questionnaire and the results of a hypertonic saline challenge test and found that the symptoms alone had the best agreement with the physician's diagnosis. BHR alone, or in combination with symptoms, had a high specificity but low sensitivity, whereas the questionnaire had both a reasonably high sensitivity and specificity.⁷ On the basis of our present results and the results of Jenkins *et al.*⁷ we disagree with the suggestions that symptom history should be combined with BHR when defining asthma in epidemiological studies.^{2,21} Such suggestions have also been criticised in the study of Demissie *et al.*¹⁸ They used the Bayesian approach for sensitivity and specificity analysis and found that the exercise challenge test was clearly inferior to the symptom questionnaire in identifying asthmatic children in a community setting.

In addition to our study, only a few other studies have validated their symptom questionnaires by BHR tests or clinical assessment³ including two that have validated the currently used questionnaires in the ISAAC study.^{6,8} Both of these studies used only one type of BHR test on a rather small random population sample resulting in a small number of children with asthma. Our study had a relatively large source population from which we sampled symptomatic and non-symptomatic children into the clinical study. This kind of sampling selects more asthmatic children into the study, but it still retains the benefits of a population based sample.³ On the other hand, it is necessary to adjust the results by the sampling scheme to avoid verification bias.¹⁵ Another strength of our study was that we performed two different BHR tests and a careful clinical evaluation to differentiate "true" clinical asthma cases from the population of symptomatic and asymptomatic children. Taking the validation results together, our study gives further support to the evidence that use of a symptom questionnaire is a highly valid method for studying the prevalence of asthma in epidemiological studies.^{3,7,17,18}

Free running test and methacholine inhalation challenge

In our study the free running test was specific for asthma and profound responses in terms of ΔFEV_1 (%) were found only among the children with clinical asthma. The few studies reporting false positive reactions in free running tests have used PEF measurements in the response follow up instead of FEV_1 .²²⁻²³ On the other hand, the sensitivity of the free running test was low. Previous studies have suggested that exercise challenge is useful in the characterisation of asthmatic children and in the differential diagnosis of asthma from other lung diseases.²⁴⁻²⁶ Some authors have even suggested the free running test as a screening tool for undiagnosed asthma,²⁷ but its usefulness is certainly limited by its minor additional value after symptoms are known and the low sensitivity, as shown in our study and in some earlier studies.^{28,29}

The methacholine inhalation challenge seemed to be almost as specific for asthma as the free running test but it was more sensitive, which is in accordance with previous observations.^{3,4} Similarly, our findings support the previously reported complexity in the association between the responses of asthmatic children to physical and pharmacological stimuli.³⁰ Pathological responses to both exercise and methacholine were rare, indicating that these tests reflect different pathophysiological mechanisms in the asthmatic airways. The high specificity of the methacholine inhalation challenge in our study was probably due to the rather strict criterion for a positive test result ($PD_{20}FEV_1 \leq 400$ μg).

In summary, our study showed that a careful symptom history still forms the most important basis for defining asthma in both clinical and epidemiological settings. Tests of BHR give only marginal "added value" to the diagnostic accuracy based on symptom history. We therefore emphasise that the diagnosis of childhood asthma should not be overlooked in cases

with an obvious symptom history but no objective evidence of BHR. We conclude that a written symptom questionnaire is a valid method for studying the epidemiology of asthma, and BHR should not be required for defining asthma in epidemiological studies.

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