Atopy, bronchial hyperresponsiveness, and peak flow variability in children with mild occasional wheezing

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Abstract

Background – Children who suffer from recurrent wheezy episodes are often promptly classified as asthmatic. The aim of this study was to evaluate a population of mild wheezy children with repeatedly normal spirometric tests at rest for atopy, bronchial hyperresponsiveness, and peak expiratory flow variability.

Methods – Thirty nine children aged 6–16 years with 1–12 wheezy attacks during the previous year were recruited from a community paediatric primary health care clinic serving an urban Israeli population. The conditions for inclusion were a physician-diagnosed wheeze on auscultation and normal spirometric tests at rest on at least three occasions. Evaluation included skin prick tests for atopy and a physician-completed questionnaire. In addition, two tests of bronchial hyperresponsiveness (BHR) were performed – namely, exercise-induced bronchospasm and inhaled methacholine hyperresponsiveness – as well as diurnal variability of peak expiratory flow (PV).

Results – One or more tests of BHR/PV were positive in 27 (69%) but repeatedly negative in 12 (31%). In terms of frequency of wheezing attacks, atopy, and questionnaire responses, there were no differences between BHR/PV and non-BHR/PV children, with the exception of a history of chest radiography proven pneumonia (only noted in the BHR/PV group). Overall, evidence of atopy (mainly indoor allergens) was noted in 21 (56%) of those tested and parental smoking in 29 (74%) of households. Thirty-two (82%) of the children complained of an exercise-related wheeze, yet exercise-induced bronchospasm was only demonstrated in nine (23%).

Conclusions – This selected group of wheezy children appears to be intermediate between a normal and clearly asthmatic population and, despite the recurrent wheezy attacks, some should probably not be classified as asthmatic by conventional criteria. Important aetiological factors in the symptomatology of these children may include parental smoking and atopy as well as other elements such as viral infections.

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A large number of children may present repeatedly with a history of wheezing. In practice, children with occasional wheezing are often promptly classified as asthmatics with implications both to the individual and in terms of the quality of the epidemiological data used to establish the true prevalence of asthma. Asthma awareness is increasing, and concurrently a disproportionate increase in wheezing illness is being reported.^{1,2} The prevalence of hayfever and eczema has increased substantially.^{3,4} Additionally, the role of house dust and other domestic allergens in the induction of asthma in children has recently been re-emphasised.⁵ Although the definition of asthma remains somewhat controversial, a low forced expiratory volume in one second (FEV₁) in the presence of a history of recurrent wheeze is consistent with asthma, especially if a reversible component can be demonstrated. Atopy and wheeze are associated with a reduced FEV₁.⁶

In the presence of normal spirometric parameters various provocation tests, including a 10% or more reduction in FEV₁ after exercise and methacholine inhalation challenge, as well as non-provoked spontaneous diurnal peak expiratory flow variability, are considered to be helpful in the diagnosis. Methacholine and histamine inhalation challenge tests have been used to screen populations for asthma but are thought to be somewhat oversensitive as a diagnostic tool in the asymptomatic population. In addition, variability in peak expiratory flow (which reflects spontaneous variations in airway calibre) not accompanied by any increase in methacholine responsiveness has been noted in the presence of respiratory symptoms.⁶ It has recently been suggested that asthma may be better defined as recent wheeze plus increased bronchial hyperresponsiveness (BHR).⁷

Some children wheeze from time to time in the presence of repeatedly normal spirometric values at rest. These children pose a clinical dilemma, frequently resulting in unnecessary diagnostic labelling and treatment. We hypothesised that if these children were really asthmatic, it would be appropriate to investigate some of the main aetiological factors known to be important in inducing asthma in this seemingly homogeneous population of wheezy children.

Methods

The population studied was aged between six and 16 years and referred by a specialist paediatrician working in a community clinic

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following a finding of wheezing on auscultation. The set-up of the services in that area is such that the clinic provides primary health care for a low socioeconomic urban population. The children who were referred from the community were subsequently studied at the Chaim Sheba Medical Center and had had 1–12 wheezing attacks a year over a two year period.

Additional conditions for referral were: (1) normal spirometric values at rest on at least three occasions over a two month period; (2) no hospital admissions during the previous three years; (3) no evidence of recent respiratory tract infection; and (4) no history of regular prophylactic asthma therapy. They were excluded if there was a history of cardiac or neuromuscular disorders or there were chest wall deformities. All subjects and parents were informed of the nature of the study before consenting to participate.

LUNG FUNCTION AND BRONCHIAL HYPERRESPONSIVENESS

Recordings of FEV₁ and FVC (forced vital capacity) were made with a dry bellows spirometer (Vitalograph, Buckingham, UK) taking the highest of the first three successive measurements within 5% of each other. Spirometric tests were only considered normal if the values for FEV₁, FVC, FEV₁/FVC, and Vmax₅₀ (maximal expiratory flow measured from the volume-time curve at 50% of vital capacity) were within normal limits for the Israeli population.⁸ Inhalation tests were performed with methacholine chloride using the Cockcroft protocol.⁹ The solutions were inhaled via a face mask in increasing doubling concentrations from 0.125 to 16 mg/ml by aerosol. The nebuliser had an output of 0.25 ml/min at an airflow rate of 5 l/min. The subject was asked to breathe with a normal tidal volume for two minutes and consecutive doses were administered at five minute intervals. The FEV₁ was measured at 30 and 90 seconds after each inhalation and the test was discontinued when the FEV₁ had fallen by 20% or more. The provocative concentration of methacholine required to lower the FEV₁ by 20% (PC₂₀) was considered significant if it was 8 mg/ml or less. The test was repeated after six months in subjects with a PC₂₀ of more than 8 mg/ml on the first occasion.

All exercise testing was performed in the same ambient conditions at the Respiratory Physiology Laboratory of the Chaim Sheba Medical Center. The exercise test involved running on a treadmill at an angle of 10 degrees at a speed of 8 km/hour for six minutes. A minimum pulse rate of 160/minute was obtained in all subjects. Measurements of FEV₁ were made before and at four, seven, and 10 minute intervals following the test. The exercise test was repeated in all subjects after three weeks.

All families were given a mini-Wright peak flow meter and children and parents were instructed as to its correct use. They were asked to record the highest of three daily morning and evening values over a three week period which were measured at approximately the

same time every day. Peak expiratory flow (PEF) variability (PV) was considered significant if a diurnal variation (difference between maximum and minimum PEF measured on the same day as a percentage of the maximum PEF) of more than 15% was calculated on at least three days in addition to an absolute difference between the peak and trough PEF values of more than 20% over the three week period. Every effort was made to keep to the same order of investigations and this was achieved in most cases – namely, the methacholine inhalation challenge, exercise testing, three weeks of PEF measurements, followed by a repeat exercise test. The exercise test and methacholine inhalation challenge were never performed on the same day.

ATOPIC STATUS

Atopic status was assessed by a skin prick test with the following inhalant allergens: olive pollen, mixed grasses (June, timothy, orchard, rye), weeds (sagebrush, cocklebur, Bermuda, Russian thistle), house dust mite (*D. farinae*), cockroach (*B. germanica* whole body and faecal) (cockroach allergens kindly supplied by S B Lehrer, Tulane University, USA).

Histamine and saline were used as positive and negative controls. A skin prick test was considered positive if it showed a wheal size similar to or larger than the histamine control (+3 or larger wheal)¹⁰ and negative if there was no response or the same response as to the saline control. The mean wheal size in this group was 5.8 mm (coefficient of variation 22.5%). A patient was considered atopic if one or more of the above tests was positive.

QUESTIONNAIRE

Details of the respiratory symptom history were obtained from both the subjects and parents by a physician-completed questionnaire. Questions were asked regarding a family history of asthma, number of wheezy attacks over past 12 months, nocturnal wheeze or cough, wheeze on exercise or rhinitis-associated wheeze, history of hayfever, eczema, vernal conjunctivitis as well as parental smoking. In addition, questions were asked about a history of well documented radiographically proven pneumonia.

DATA ANALYSIS

Correlation between each clinical parameter and the presence of BHR/PV was performed using the χ^2 test or Fisher's exact method for categorical variables and ANOVA for continuous variables. A logistic regression model was employed using BHR/PV as a dependent variable and clinical parameters as independent variables in order to determine the predicting factor (odds ratio) for the presence of BHR/PV. Statistical analysis was performed by STATVIEW package (Abacus Concepts, Berkeley, USA) and BMDP statistical software (Los Angeles, USA). All reported p values are two tailed and a p value of less than 0.05 was considered positive.

Table 1 Criteria for bronchial hyperresponsiveness (BHR/PV) in wheezing children (n = 39)

Test	No positive	% Positive
Methacholine	20	51.2
PEF diurnal variability (PV)	15	38.4
Exercise	9	23.0
BHR/PV*	27	69.2

* One or more positive tests.

Table 2 Mean (SE) demographics and frequency of wheezing in BHR/PV and non-BHR/PV children

	BHR/PV (n = 27)	Non-BHR/PV (n = 12)	Overall (n = 39)
Male/female	8/19	6/6	14/25
Age (years)	10.8 (0.5)	11.3 (0.7)	10.9 (0.4)
Attacks/year	3.4 (0.6)	2.5 (0.8)	3.1 (0.4)

Results

Fifty four children were referred for assessment, six of whom were excluded because of a subsequent finding of obstruction during spirometric testing at rest. Before initiation of the study five were deemed non-compliant and in four a repeat history was unsatisfactory. Thirty nine children met all of the above criteria and all completed the full evaluation with the exception of two subjects who declined skin prick testing.

Figure 1 Skin test results in both BHR/PV and non-BHR/PV subjects: overall atopy and response to individual allergen extracts. BHR = bronchial hyperresponsiveness.

Figure 2 Results of questionnaire in both BHR/PV and non-BHR/PV subjects (relating to details of past medical history). BHR = bronchial hyperresponsiveness. * $p < 0.05$.

BHR/PV was defined as a positive result in one or more of the three tests (methacholine inhalation, PEF variability, and exercise-induced bronchospasm) and was noted in 27 patients. Overlap was clearly present in these 27 children with BHR/PV, with a significant PC₂₀ to methacholine in 20 (74%), PEF variability (PV) in 15 (55.6%), and exercise-induced bronchospasm in nine (33.4%). The breakdown of BHR/PV in the whole population of wheezy children is as shown in table 1. In five children PV was clearly present despite no evidence of BHR by other methods when tested at the same time. All tests for BHR/PV were negative in 12 and in no case did the repeated methacholine inhalation challenge or exercise test result in a change in classification from non-BHR/PV to BHR/PV. We did not repeat methacholine inhalation challenge in the positive children. Table 2 gives the male/female ratio, mean age, as well as the mean number of attacks per year. Figure 1 shows the percentage of positive skin tests in children from both groups. Of the 37 subjects who were skin tested 21 (57%) were atopic, and most of these atopic children responded to dust mite (18, 86%) and cockroach (13, 67%) allergen extracts. There were no statistically significant differences in the presence or absence of atopy between the BHR/PV and non-BHR/PV groups.

Figure 2 gives the results of questionnaire responses. There were no statistically significant differences between the groups except for a history of radiographically proven pneumonia ($p < 0.05$, Fisher's exact method). This parameter has been shown to be predictive for BHR/PV (odds ratio 11.5, $p < 0.05$, confidence interval 90%).

No other anamnestic or clinical factor could predict the development of BHR/PV in this group of wheezy children. Symptoms of wheeze on exercise and nocturnal wheeze were common and were noted in 32 (82%) and 29 (74%), respectively.

At least one parent smoked in 29 (74%) of the households, but in 18 only the father smoked. Eleven (28%) of the mothers smoked during pregnancy. Figure 3 refers to a history of past atopic disease, asthma in the family, and parental and maternal smoking. There were no statistically significant differences between the groups.

Discussion

We decided to base the study of this carefully selected well characterised group of children on physician-diagnosed wheeze as many of the recent reports of asthma in children are based on reporting by a patient or parent. In one study 74% of non-atopic wheezy children with no evidence of histamine BHR were classified as asthmatic and 21% were receiving medication.⁷ Despite the fact that a universally acceptable definition of asthma remains elusive, much has been learned about atopy and BHR in a clearcut asthmatic population of children. Testing for BHR is intended to diagnose both provoked and spontaneous variations in airway

Figure 3 Results of questionnaire in both BHR/PV and non-BHR/PV subjects (relating to details of past medical history, particularly atopy, family history of asthma, and smoking). BHR = bronchial hyperresponsiveness.

calibre, and therefore we decided to investigate three indices of lung function variability with two provocation methods (methacholine and exercise) and spontaneous variation (diurnal peak flow measurements). Atopy was present in 80–90% of childhood asthmatics.^{6,7,9,11} Histamine or methacholine BHR has been noted in 66–85%,^{7,12,13} PEF variability in 60–72%,¹⁴ and exercise-induced bronchospasm in up to 89% of asthmatic children¹⁵ but is probably lower in milder asthma.¹⁶ Our local experience is consistent with the published data from various regions of the world. It has been shown that respiratory tract symptoms may be accompanied by changes in PEF without demonstrable methacholine BHR.⁶ Furthermore, clinical evaluation of children with mild occasional wheezing reveals that they frequently complain of wheezing on exercise and this was borne out by the results of our physician-completed questionnaire. It therefore seemed appropriate to include PEF variability as well as exercise testing in our evaluation.

It is likely that, with three different tests intended to evaluate spontaneous and provoked variations in airway calibre, which were repeated after six months, that BHR/PV was effectively excluded in 12 of the wheezy children. Atopy in the general paediatric population is between 25% and 35%,^{7,17} yet 56% of our wheezy children were atopic, regardless of the presence of BHR/PV. Reactions to domestic allergens such as house dust mite and cockroaches were detected in most of the atopic subjects. The majority of this population does not keep household pets and we therefore did not skin test for these allergens.

The children were recruited from a single community paediatric clinic serving a low socioeconomic population similar to that in the study by Gelber *et al.*¹⁸ Similarly, in our study 38% had positive skin tests to cockroach allergen (either whole body extract, faecal, or both).

It has been suggested that, for epidemiological purposes, current wheeze and BHR is consistent with a diagnosis of asthma⁷ and, based on these criteria, 27 (69%) of our

39 subjects could be diagnosed as asthmatic. In addition, despite repeated testing, overall exercise-induced bronchospasm was only detected in nine (23%) and, even in the BHR/PV group, in only nine of 27 (33%) which is considerably less than one would expect from an asthmatic population. It was remarkable that as many as 82% of the children in both the BHR/PV and non-BHR/PV groups had complained of wheezing on exercise. All of the children with a history of radiographically proven pneumonia had evidence of BHR/PV (eight of 39). Wheeze has been associated with low values of FEV₁⁶ and FEV₁/VC¹⁹ and atopy with a reduced FEV₁/VC.²⁰ Our very carefully selected group of subjects had repeatedly normal FEV₁, FEV₁/FVC and Vmax₅₀ at rest.

It must be noted that the sample size of this group was not predetermined by power based calculations, but rather was dependent on the number of children that could be recruited from a specific neighbourhood. They appeared to be homogeneous in terms of their symptomatology, physical and physiological findings, as well as area of residence. Careful scrutiny of the information, as shown in figs 1–3, points to many similarities between the groups.

More than half of our group were sensitive to domestic allergens and, in addition, parental smoking – which could be a significant contributory factor¹⁴ – was reported in three quarters of the households. This compares with a prevalence of 24–39% of smoking in the general Israeli population.²¹ Eleven (28%) of the mothers smoked (during and after pregnancy). However, if the fathers were considered, one or more parent smoked in 29 (74%) of households. As we were studying a low socioeconomic population with a high unemployment rate, it may be relevant that fathers spend more time at home than in other social groups. In addition, the role of viral respiratory tract infections, particularly rhinovirus, needs to be further investigated in these children as they may be an important trigger of symptoms.^{22,23}

We conclude that some children with occasional wheeze may not be asthmatic by conventional criteria. It is likely that various factors may be responsible for the symptomatology in certain “susceptible population groups”.

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