

Prevalence and predictors of bronchial hyperresponsiveness in children aged 7–16 years

V. BACKER,¹ N. BACH-MORTENSEN² & A. DIRKSEN³

¹Dept. of Medicine B, Laboratory of Respiratory Physiology, ²Dept. of Pediatrics G, and ³Dept. of Medicine TTA, Allergy Unit, State University Hospital, Copenhagen, Denmark

To study the prevalence and possible predictors of bronchial responsiveness we examined a cross-section of 527 children aged 7–16 years from Copenhagen. The method used included an interview with the child and the parents, skin prick test with common allergens and se-IgE. Bronchial responsiveness was measured by a histamine inhalation test. We found that 79 (16%) of the children had bronchial hyperresponsiveness (BH), defined as a 20% fall in FEV₁ with a provoking concentration of histamine (PC₂₀) at 8 mg/ml or less. Atopic symptoms defined as asthma, rhinitis or eczema were significantly ($P < 0.001$) correlated to BH both in prevalence and degree of BH. None of the children with urticaria had BH. The degree of bronchial responsiveness was also significantly influenced ($P < 0.001$) by family disposition to atopy, whereas we found no correlation between BH and “passive” smoking, specific skin test in unselected children, or elevation of IgE in children without atopic symptoms. We conclude that BH is severest in children with asthma, independent of elevated IgE or positive skin prick test. Children with rhinitis, dermatitis, or asymptomatic BH have the same degree of BH; this differed from that in children with asthma.

Key words: allergy; asthma; bronchial hyperresponsiveness; children.

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CLINICAL ASPECTS

Asthma symptoms appear to be the most important predictors of BH, and asthmatics were also found to have the severest BH. Other predictors of BH were found to be dermatitis, rhinitis and disposition to atopic diseases in asymptomatic children. Elevated IgE or positive skin prick test were not predictors of BH in children without allergic symptoms. Thus latent allergic diseases do not predict BH. We believe that asymptomatic BH in children with disposition to allergy might be the strongest predictor of the development of asthma.

Bronchial hyperresponsiveness (BH) to histamine is an almost universal feature of asthma (7, 8). Knowledge of the distribution of bronchial responsiveness in the general population is primarily based on surveys in adults (5, 16). A few epidemiologic studies are concerned with the prevalence of bronchial hyperresponsiveness to methacholine in unselected children (2, 13). In studies of both adults and children, BH to methacholine has been found in individuals

without clinical symptoms of asthma (9, 16). Sears (14) found that 20% of asymptomatic children with BH developed asthma over a period of 2 years.

The cause of BH is still not clearly identified. BH may develop at any age (8) and Cockcroft (4) proposes that BH is due to a combination of heredity and environmental factors.

The purpose of this study is to determine the prevalence and some possible predictors of BH

in a randomly selected population of children from Copenhagen.

MATERIAL AND METHODS

Subjects

The children were selected from the population register list in Denmark. All children aged 7 to 16 years within the University Hospital area were selected for study. All were born in the first week of a month. Of the 983 children invited to participate, 527 (53.6%) (265 girls and 262 boys) accepted and were examined. Of these 94% (495) underwent a histamine challenge test. The remaining 32 children refused or were excluded from the histamine challenge because of chronic diseases.

A sample of 100 non-responders (families who did not respond when contacted by letter) were contacted by telephone. The families of these children were asked the same questions about allergy as the visiting children. There was no difference in gender, age or disposition to atopy between responders and non-responders, but there were significantly fewer children with atopy in the group of non-responders (Table 1).

This study was completed with the approval of the local medical ethics committee

and was in accordance with the Helsinki II declaration.

Methods

At the out-patient clinic, the children and their parents were interviewed by one of us (V.B.) about atopic diseases or disposition, pulmonary symptoms and recent respiratory infection (11). The children were classified as having *symptoms of atopy* (asthma, rhinitis, eczema urticaria) or *no symptoms*. Asthmatic children were named as *asthma*, independent of other symptoms of atopy. Children with urticaria as their single symptom, were identified as *urticaria* and the remainder with symptoms were named *other atopy*. Further, a past history of *wheezing* was noted separately.

The children were asked not to smoke for 2 h before their appointment, not to take theophylline or antihistamine for at least 24 h (astemizole 6 weeks), not to take oral beta-agonist for 18 h and not to use inhaled bronchodilators for 6 h before testing.

Bronchial challenge tests were performed according to Cockcroft (3). Histamine was inhaled from a Wright's nebulizer. The concentration was doubled until either a maximum of 8 mg/ml had been reached or a decrease of at least 20% of the FEV₁ baseline readings was observed. The

Table 1

527 responders and a sample of 100 non-responders by atopic symptoms (atopy), disposition to atopic diseases in first degree relatives (disposition), sex and age. Information was obtained by interview in the clinic (responders) or by telephone (non-responders)

		Responders	Non-responders
Atopy**	yes	111	11
	no	415	89
Disposition	yes	205	32
	no	332	68
Sex	girl	265	42
	boy	262	58
Age (mean)		12.0	13.0

**Chi-square *P* < 0.05

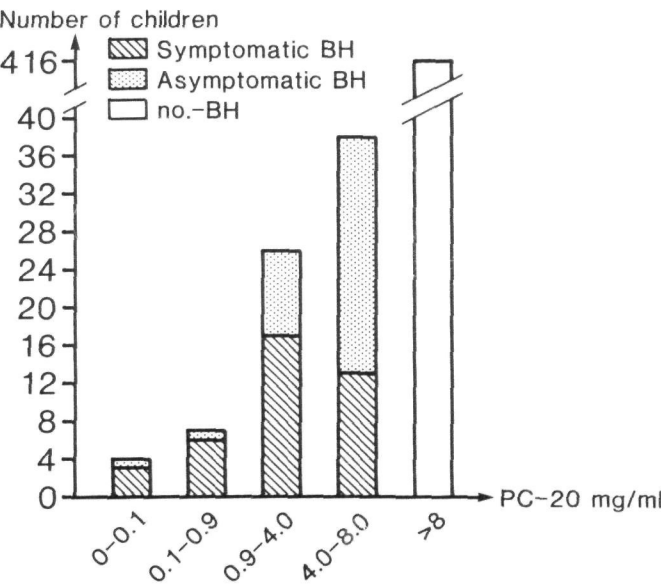


Fig. 1. Bronchial hyperresponsiveness of 495 children, and atopic symptoms.

Table 2

495 children and the degree of bronchial hyperresponsiveness in relation to asthma, other atopy than asthma and children without atopic symptoms

		Bronchial hyperresponsiveness					Total
		Yes			No		
		<i>n</i>	(%)	Mean PC ₂₀ mg/ml	<i>n</i>	(%)	
Symptoms							
Yes	Asthma	28	(100)	1.47*	0		28
	Other atopy	13	(15)	5.60	65	(85)	78
No		38	(10)	4.27	351	(90)	389
Total		79	(16)	2.92	416	(84)	495

**P* < 0.05 (Mann-Whitney test) in comparison with other groups of reactors.
Chi-square *P* < 0.001. Numbers in parenthesis are rowpercent.

Table 3

Bronchial hyperreactivity of children by atopic symptoms either without elevated IgE and positive prick test (No) and with either one of the factors or both (Yes)

		Bronchial hyperresponsiveness	
		Yes	No
Asthma			
no	IgE/prick	9	0
yes	IgE/prick	19	0
Other atopy			
no	IgE/prick	8	34
yes	IgE/prick	5	20 NS
Urticaria			
no	IgE/prick	0	9
yes	IgE/prick	0	2 NS
Total atopic symptoms			
no	IgE/prick	17	43
yes	IgE/prick	24	22 <i>P</i> < 0.01
No symptoms			
no	IgE/prick	34	293
yes	IgE/prick	4	36 NS

Table 4

Bronchial hyperreactivity of 459 children by various predictors, such as atopy symptoms and either elevated IgE or positive prick (allergy), wheezing, and smoking. BH was defined as PC₂₀ < 8.0 mg/ml

		Bronchial hyperresponsiveness	
		Yes	No
Atopy**	yes	41	65
	no	38	351
Allergy**	yes	24	23
	no	55	375
Disposition	yes	34 (11)	164 (129)
	no	45 (27)	252 (222)
Wheezing**	yes	16 (7)	25 (20)
	no	69 (38)	366 (300)
Cigarette smoking	yes	53 (25)	280 (237)
	no	31 (18)	130 (101)

Chi-square ***P* < 0.001; Numbers in parenthesis are children without atopic symptoms.

concentration (PC₂₀) of histamine that produced a 20% reduction in FEV₁ was read from the individual log-dose response relation.

Skin prick test using nine common allergens was performed. The allergens were: birch, grass,

mugwort, horse, dog, cat, house dust mite (*D. Pt.*) and two molds (*Alternaria iridis* and *Cladosporium herbarum*). The strength was 100,000 BU (Pharmacia). After 15 min the largest diameter of the wheal and its perpendicular were recorded. Ten mg/ml histamine was used as positive reference, and a positive reaction was defined when the reaction was at least the

same size (classified as 3) as histamine reaction.

Blood IgE. Blood samples were taken and kept at -20°C for approx. 30 days and then analysed with PRIST (Pharmacia). As in Kjellman (10) the IgE elevation (+ 2SD) was recorded.

Data analysis. Data were analysed in contingency tables using the chi-square statistic. The Mann-Whitney rank test was used to compare the severity of BH in different groups.

RESULTS

A satisfactory histamine challenge test was conducted in 495 children, 79 (16 %) of whom had BH to histamine defined as a PC₂₀ value of 8 mg/ml or less. 41 (52 %) of the 79 children with BH had atopic symptoms. The degree of BH was pronounced in the presence of symptoms (Fig. 1). We found that 28 (5.3 %) of the children had clinical asthma (PC₂₀ mean 1.47 mg/ml) with a significantly (*P* < 0.05) increased reactivity to histamine compared with children having other atopic symptoms than asthma (PC₂₀ mean 5.60 mg/ml) (Table 2).

In the symptomatic groups no significant correlation was found between BH and either elevated IgE, positive skin prick test or both (Table 3). None of the children with urticaria, of whom two had elevated IgE, proved to have BH. It appears from Table 4 that the most important predictors of BH are atopic symptoms and allergic diseases. Children with a history of wheezing bronchitis did not show increased bronchial responsiveness if they were without present atopic symptoms. We found no correlation between having BH and the different allergens, or smoking among parents.

The degree of BH in atopic children (Table 5) was independent of disposition to atopic diseases. In contrast, the BH in asymptomatic children was significantly higher in those who had an atopic disposition (*P* < 0.004).

DISCUSSION

The definition of BH is necessarily arbitrary since no detailed description of the distribution of normal responsiveness has been made. In adult studies a PC₂₀ at 8 mg/ml often appears as the distinction between normal and abnormal test response. This corresponds with our study,

Table 5

Bronchial responsiveness (mean PC₂₀ mg/ml) of 495 children by atopic symptoms (atopy) and atopic disposition (disposition) in first degree relatives. Bronchial hyperresponsiveness was defined as PC₂₀ < 8 mg/ml

	Bronchial hyperresponsiveness					Total
	Yes			No		
	<i>n</i>	(%)	Mean PC ₂₀ mg/ml	<i>n</i>	(%)	
Atopy						
Yes						
disposition						
yes	23	(42.6)	2.16	35	(57.4)	58
no	18	(37.6)	1.94	30	(62.4)	48
No						
disposition						
yes	11	(7.9)	2.03	129	(92.1)	140
no	27	(10.8)	5.77*	222	(89.2)	249
Total	79	(16.0)	2.92	416	(84.0)	495

Chi-square *P* < 0.001; **P* < 0.004 (Mann-Whitney test) in comparison with any of the other groups of reactors; Numbers in parenthesis are rowpercent.

as none of the asthmatics showed PC_{20} over 8 mg/ml. Symptoms of asthma were the most important predictors of BH, and it has earlier been shown that BH in asymptomatic children is an important predictor of asthma (14). Asthma not only predicts BH but also predicts the development of the more severe degrees of BH which differ from the BH in asymptomatic children.

As previously shown (9), we found more frequent and more severe BH in children with atopic symptoms than in children without. Among atopic symptoms, dermatitis and rhinitis were found to be of some predictive value, whereas urticaria was unimportant.

Elevation of IgE or presence of positive prick test are known to be predictors of BH (15). We can confirm these results, but elevated IgE or positive skin prick test were not predicted in children without allergic symptoms. Thus children at risk of a developing allergic (latent allergy) disease did not appear to have an increased risk of having BH. Similarly, we found no correlation between IgE elevation or results of prick test and BH in children with dermatitis and rhinitis.

We found that a positive family history of atopy was predictive of BH, and the number of children in our group who had asymptomatic BH and disposition to atopy corresponds well with the 20% asymptomatic children who developed asthma, as found by Sears (14). We believe that asymptomatic BH in children with a family history of atopy may be a strong predictor of the development of asthma. When coupled with BH, allergic rhinitis (1) as well as dermatitis are known to be predictors of asthma. However, it is unknown whether the strength of this predictive factor will be independent of present IgE-mediated allergy.

As in other studies (12) there appeared to be no single cause for the development of BH; it was most strongly correlated to allergy or a positive family history of atopy. Provocation of the bronchial system, such as parents' smoking or earlier wheezing bronchitis, were of minor importance, as also shown by others (12).

Because of a response rate of 54%, estimates of asthma or asymptomatic bronchial respon-

siveness will be subject to some uncertainty. The selection bias will tend to increase the total percentage of BH in our population – but will probably have less influence on the number of asymptomatic children with BH.

In the entire group of children, the prevalence of clinical asthma ("responders" and "non-responders") was approximately 4%, which is less than found by some authors (13) but similar to findings of others (6).

However, we are still unable to determine who will develop asthma. A repeat of the present study might reveal whether a certain degree of BH, elevated IgE, a positive skin prick test or other factors are predictors of children susceptible to asthma.

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- Address:
Vibeke Backer
Dept. of Infectious Diseases M
Rigshospitalet
Copenhagen
Denmark

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