Allergy 2004: 59: 1074–1079
Printed in UK. All rights reserved

Copyright © Blackwell Munksgaard 2004
ALLERGY
DOI: 10.1111/j.1398-9995.2004.00559.x

Original article

Bronchial hyperresponsiveness in children with atopic rhinitis: a 7-year follow-up

Background: A high prevalence of bronchial hyperresponsiveness (BHR) was found in atopic subjects with rhinitis. Those subjects may be at higher risk for developing bronchial asthma. We evaluated, in a 7-year follow-up, BHR and atopy in a homogeneous population of nonasthmatic children with allergic rhinitis (AR), and their role in asthma development.
Methods: Twenty-eight children (6–15 years) with AR were studied. At enrollment (T_0), skin tests, total serum IgE assay, peak expiratory flow (PEF) monitoring and methacholine (Mch) bronchial challenge were performed. BHR was computed as the Mch dose causing a 20% forced expiratory volume $(FEV)_1$ fall ($PD_{20}FEV_1$) and as dose–response slope (D_{RS}). Subjects were reassessed after 7 years (T_1) using the same criteria.
Results: At T_0, 13 children (46%), showing a $PD_{20}FEV_1 < 1526$ μg of Mch, had BHR (Mch +), although PEF variability (PEFv) was within normal limits. None of the children with negative methacholine test developed bronchial asthma after 7 years. Of the 13 Mch +, only two reported asthma symptoms after 7 years. No significant change was seen in the other parameters of atopy considered.
Conclusion: Children with allergic rhinitis present a high prevalence of BHR. Nevertheless, their PEFv is normal and the rate of asthma development low.

F. Cibella[1], G. Cuttitta[1], S. La Grutta[2], M. R. Hopps[3], G. Passalacqua[4], G. B. Pajno[5], G. Bonsignore[1]

[1]Istituto di Biomedicina e Immunologia Molecolare del C.N.R., Palermo, Italy; [2]Allergy Unit, Childrens Hospital, ARNAS, Palermo, Italy; [3]Clinica Pneumologica dell'Università, Palermo, Italy; [4]Allergy & Respiratory Diseases, Department of Internal Medicine, Genoa University, Genoa, Italy; [5]Clinica Pediatrica dell'Università, Messina, Italy

Key words: allergic rhinitis; asthma; children; methacholine test; nonspecific bronchial hyperresponsiveness.

Fabio Cibella, MD
Istituto di Biomedicina e Immunologia Molecolare `Alberto Monroy' del C.N.R
via U. La Malfa, 153
I 90146 Palermo, Italy

Accepted for publication 8 March 2004

Non-specific bronchial hyperresponsiveness (BHR) is considered both a distinctive functional characteristic of bronchial asthma and a significant risk factor for the future onset of asthma itself, expecially in children (1). Asymptomatic BHR has been found to occur more frequently in atopic subjects (2) and in those with rhinitis; therefore, patients with BHR and allergic rhinitis are supposed to be at higher risk for subsequent development of bronchial asthma (3, 4). Indeed, several studies have demonstrated a strict association between atopic status, BHR, and asthma (5, 6), but the real clinical outcome of asymptomatic BHR, has not still been fully ascertained (7). In parallel, although a relationship exists between BHR and spontaneous changes in bronchomotor tone as evaluated by peak expiratory flow (PEF) monitoring in children (8), there is still no clear demonstration of a clinical outcome of this relationship. Moreover, despite the suggestive epidemiological evidence, the possible evolution of BHR towards asthma in atopic patients has not been convincingly clarified in clinical conditions, e.g. in a selected population of patients with well-ascertained BHR, and followed up for a long enough time period (5).

The aim of the present long-term longitudinal study was to determine the clinical role of BHR in the development of asthma. A selected homogeneous population of children with allergic rhinitis alone was therefore assessed at baseline conditions and after 7 years, in order to evaluate the time course of BHR and atopy and their possible role in asthma development.

Material and methods

Study design

The study is a prospective evaluation with two time-point assessments: baseline (T_0) and after 7 years (T_1). At both time-points, several parameters were evaluated including: presence of allergic rhinitis, presence and severity of asthma, skin-prick test (and allergy score), allergen-specific IgE measurements, total serum IgE, pulmonary function tests and methacholine (Mch) challenge. All parents of the patients granted their availability for follow-up visit and signed a written informed consent. The study was approved by the inner Ethical Committee. According to the Italian law, the respect of individual privacy concerning clinical data was granted.

Patients and diagnosis

Twenty-eight children (15 female, 13 male, mean age 10.4 years, age range 6–15 years) were enrolled in the study (T_0). The subjects were selected from outpatients consecutively referred to the Allergy Unit of the Department of Pediatrics, Palermo University, according to the following strict criteria. All children had to suffer from allergic rhinitis (9), assessed by a clinical history of nasal blockage, sneezing, itching and discharge (not caused by common cold), in the last 2 years. The allergic mechanism had to be confirmed through skin-prick test and allergen-specific IgE measurements. None of the subjects had a personal history of diurnal/nocturnal dry cough, isolated or recurrent diurnal/nocturnal episodes of wheezing, recurrent episodes of difficult breathing and/or chest tightness at rest or with physical activity (10). Skin tests were performed with a standard panel of commercial allergen extracts (Lofarma S.p.A, Milan, Italy) including: *Dermatophagoides pteronyssinus*, grasses, *Parietaria judaica*, *Phleum pratense*, *Artemisia*, olive, dog and cat dander, *Alternaria*, and *Cladosporium*, plus a positive (histamine 1%) and a negative (saline) control. Following the EAACI recommendations, the positivity was measured after 15 min as the mean of the major diameter of the wheal plus its orthogonal. Reactions of 5 mm or greater were considered positive (11). The allergy score was defined as the number of positive skin reactions. Total serum IgE were determined by latex nephelometry (Behring Institute, L'Aquila, Italy), log transformed and expressed as *Z*-scores (12), according to the age groups 6–10 and 11–15 years. Allergen-specific IgE were measured by FEIA-CAP System (Pharmacia, Upssala, Sweden). The cut-off limit for specific IgE was 0.35 kU/l: levels above this limit were considered positive (CAP class I). The age of onset and duration of rhinitis, passive and active smoking were assessed. Familial atopic risk was classified according to the criteria of Croner and Kjellman (13). At T_0, rhinitis was re-defined as persistent (symptoms at least 4 days/week and >4 weeks/year) or intermittent (symptoms <4 days/week or <4 weeks/year), according to the ARIA guidelines (14). As expected, the subjects with persistent rhinitis were those with positive skin tests for *Dermatophagoides* and/or *Parietaria*: in fact, in the southern Mediterranean area, *Parietaria* has a very long period of pollination. At T_1, all subjects were again interviewed to ascertain whether (i) asthma symptoms had developed during the preceding 7 years; (ii) diagnosis of bronchial asthma had been made by a physician; (iii) clinical symptoms of bronchial asthma were actually present. Skin-prick test and Mch challenge were repeated, and any pharmacological treatment (nasal steroids, or specific immunotherapy) was also recorded. All children were free of upper or lower respiratory infections in the 30 days preceding the clinical evaluations (15).

Pulmonary function tests and Mch challenge

Pulmonary function tests (PFT) were performed in all subjects at T_0 and T_1 by a computerized water-sealed spirometer (Biomedin, Padua, Italy). Methacholine bronchial provocation tests were performed at T_0 and T_1 at the same hour of the day and under the same environmental conditions. Subjects with positive skin tests for seasonal pollens were challenged outside the pollen season. Moreover, to minimize exposure to *Parietaria* pollen, subjects were tested in the period December–February at both T_0 and T_1. An ampoule-dosimeter (Mefar Elettromedicali, Bovezzo, Brescia, Italy) was used. An inspiratory effort activated a solenoid valve for 0.5 s delivering 5 µl of solution. After using a saline solution as control, Mch was administered in doubling increasing amounts beginning with a starting dose of 50 µg. The forced vital capacity (FVC) and the forced expiratory volume (FEV) in the first second (FEV_1) were recorded approximately 2 min after each inhalation (15). The cumulative administered dose of Mch causing a reduction of 20% of the baseline FEV_1 (PD_{20}) was calculated by interpolating the cumulative doses immediately preceding and following the 20% FEV_1 fall. Subjects showing a PD_{20} <7.8 µmol Mch, equivalent to 1526 µg (16), were considered as responders (Mch+). We defined persistent Mch− subjects nonresponders at both T_0 and T_1; transient Mch− nonresponders at T_0 and responders at T_1; transient Mch+ responders at T_0 and nonresponders at T_1; and persistent Mch+, the responders at both T_0 and T_1.

Dose–response slopes (D_{RS}) were calculated for each subject as the ratio between percent decline in FEV_1 (from the postsaline value) over the cumulative dose of Mch (17). Using this procedure, a continuous index of BHR was also obtained in the nonresponders (Mch−) in which a FEV_1 fall $>20\%$ was not obtained.

At T_0, the subjects were instructed to use twice daily (after awakening and at bedtime) a portable peak expiratory flow rate meter (Mini Wright Peak Flow Meter, Clement Clarke Ltd, London, UK), selecting the best of three consecutive measurements. PEF measurements and any respiratory symptom occurring over a 14-consecutive day period were recorded on a diary card. PEF variability (PEFv) was computed as the mean on 14 days of the daily differences between the highest and lowest values expressed as the percent of the daily mean.

Changes in D_{RS} from T_0 to T_1 were considered significant if the absolute value of the difference of D_{RS} values between T_1 and T_0 (ΔD_{RS}) was ≥2 SD of D_{RS} at T_0.

Statistical analysis

As the distribution of D_{RS} values was highly skewed, results of all analyses were expressed as values after natural log transformation (ln D_{RS}) (18). The differences between the two groups were analysed using the ANOVA and chi-squared analysis. For paired comparison, Student's *t*-test for paired data and Wilcoxon signed rank test were used. The relationships between different variables were tested by simple and multiple linear regression analysis. A *P*-value <0.05 was considered significant.

Results

At baseline, 13 of 28 patients (46%) were MCh+. The clinical characteristics of our sample are summarized in Table 1. Baseline FVC and FEV_1 were $>80\%$ of the predicted value in all subjects (Table 2). Predicted values were those from Polgar for subjects <18 years of age and ECCS for subjects ≥18 years. In the overall sample, the number of positive skin-prick tests was in the range 1–6 at T_0 and in the range 1–7 at T_1 (Table 2). Disease duration was not significantly different between Mch+ and Mch−

Table 1. Clinical characteristics of the sample at baseline time-point (T_0)

	Mch+	Mch−
No. patients ($n = 28$)	13	15
Mean age (years; ±SD)	9.2 ± 1.8	11.5 ± 1.9
Mean height (cm; ±SD)	139 ± 10	144 ± 12
Sex (M/F)	8/5	5/10
Persistent/intermittent rhinitis (*n*)	12/1	12/3

Table 2. Clinical and pulmonary function test characteristics of the studied population at enrollment (T_0) and at follow-up visit (T_1)

	T_0		T_1		*P*-value
	Mch+ ($n = 13$)	Mch− ($n = 15$)	Mch+ ($n = 14$)	Mch− ($n = 14$)	N.S. (chi-squared test)
Age (years)*	9.2 ± 1.8	11.5 ± 1.9	16.6 ± 2.6	17.0 ± 2.2	N.S. (anova)
Disease duration (years)*	4.6 ± 3.1	3.6 ± 2.7	9.1 ± 1.9	11.8 ± 3.3	N.S. (anova)
Familial atopic risk*	1.2 ± 1.2	0.7 ± 0.9			N.S. (anova)
Passive smoke (Y/N)	8/5	5/10	10/4	3/11	$P = 0.008$ at T_1 (chi-squared test)
Allergy score†	2.7 (1–6)	2.3 (1–6)	2.0 (1–7)	2.0 (1–3)	N.S. (anova)
IgE *Z*-score*	0.28 ± 0.97	−0.11 ± 1.11			N.S. (anova)
FVC (% pred)*	110 ± 9	113 ± 11	111 ± 16	112 ± 16	N.S. (anova)
FEV_1 (L)*	2.2 ± 0.3	2.7 ± 0.7	3.5 ± 0.6	3.8 ± 0.8	N.S. (anova)
FEV_1 (% pred)*	109 ± 113	113 ± 11	111 ± 16	117 ± 15	N.S. (anova)
FEV_1/FVC (%)*	91 ± 7	93 ± 6	88 ± 6	91 ± 5	N.S. (anova)
PEFv (%)*	5.4 ± 2.4	5.2 ± 2.4			N.S. (anova)
$PD_{20}^{\ddagger}$ (μg Mch)	660 (195–1415)		431 (82–1225)		N.S. (WSRT)
$D_{RS}^{\ddagger}$ (%FEV_1/μg Mch)	0.038 (0.016–0.102)	0.003 (0.0006–0.0127)	0.036 (0.017–0.211)	0.0038 (0.0002–0.0118)	N.S. (WSRT)

PD_{20}, cumulative administered dose of methacholine causing a reduction of 20% of the baseline FEV_1. Those subjects with $PD_{20} \leq 1526$ μg were considered Mch+ (responders).

D_{RS}, methacholine dose–response slope.

Data are shown as mean ± SD*, as mean and range†, and as median and range‡.

N.S., *P*-value not significant; anova, one-way analysis of variance; WSRT, Wilcoxon signed rank test.

Table 3. Contingency tables relevant to distribution of subjects with different rhinitis course in responder (Mch+) and non responder (Mch−) groups, at enrollment (T_0) and at follow-up visit (T_1)

	Persistent	Intermittent	Total
T_0			
Mch+	12	1	13
Mch−	12	3	15
T_1			
Mch+	9	5	14
Mch−	9	5	14

Differences in frequency distribution were not statistically significant at both T_0 and T_1 (chi-squared test).

subjects at both T_0 and T_1 (Table 2). None of the subject was a smoker at T_0; only five were active smokers at T_1, but none of them had a smoke history of >1 pack-year. The exposure to passive smoke was not significantly associated with Mch response at T_0. Conversely, at T_1, Mch+ subjects were 10 of 13 among those exposed to passive smoke, and only four of 15 among those not exposed ($P = 0.008$, chi-squared test; Table 2). The frequency distribution of the course of rhinitis did not differ between Mch+ and Mch− subjects at both T_0 and T_1 (chi-squared test; Table 3). Baseline FVC, FEV_1 (% of predicted) and FEV_1/FVC ratio were not significantly different between Mch+ and Mch− subjects at both T_0 and T_1 (ANOVA; Table 2). Moreover, the individual FEV_1/FVC ratio did not significantly change between T_0 and T_1 (*t*-test for paired data; $P = 0.11$).

At T_0, the 13 Mch+ subjects had a median PD_{20} of 660 μg; their median D_{RS} was 0.038%FEV_1/μgMch (Table 2). At T_1, 14 of 28 subjects were Mch+, with a median PD_{20} of 431 μg and a median D_{RS} of 0.036, as summarized in Table 2. No significant difference was found in overall D_{RS} between T_0 and T_1 (Wilcoxon signed rank test). The frequency distribution of Mch+ and Mch− subjects was not significantly different between T_0 and T_1 (chi-squared), nevertheless, only eight Mch+ subjects were persistent Mch+ and nine Mch− were persistent Mch−. Moreover, six subjects were transient Mch− and five transient Mch+ after 7 years (Fig. 1). The subgroup of persistent Mch+ was significanly associated with passive smoke exposure ($P = 0.03$; chi-squared test). Only four subjects showed changes in D_{RS} >2 SD; BHR was increased in three subjects and decreased in one. All the four subjects were persistent Mch+.

Only five subjects followed a regular therapeutic regimen with nasal steroids and five subjects underwent specific immunotherapy during the 7 years preceding the follow-up visit. None of the therapeutic regimens (regular nasal steroids or specific immunotherapy) was associated to any class of change in Mch response. In particular, among subjects who underwent specific immunotherapy, two were persistent Mch+, two transient Mch−, and one transient Mch+; among subjects who used regular nasal steroids, two were transient Mch−, two transient Mch+, and one persistent Mch−. At T_0, ln D_{RS} showed a significant inverse linear relationship with age ($R^2 = 0.147$, $P = 0.044$; Fig. 2). At T_1, ln D_{RS} showed a significant inverse linear relationship with disease duration ($R^2 = 0.146$, $P = 0.044$; Fig. 3). The linear regression analysis between disease duration and age was not significant at T_1 ($P = 0.60$). A significant positive linear relationship was found between ln D_{RS} at T_1 and ln D_{RS} at T_0 ($R^2 = 0.303$, $P = 0.0024$; Fig. 1).

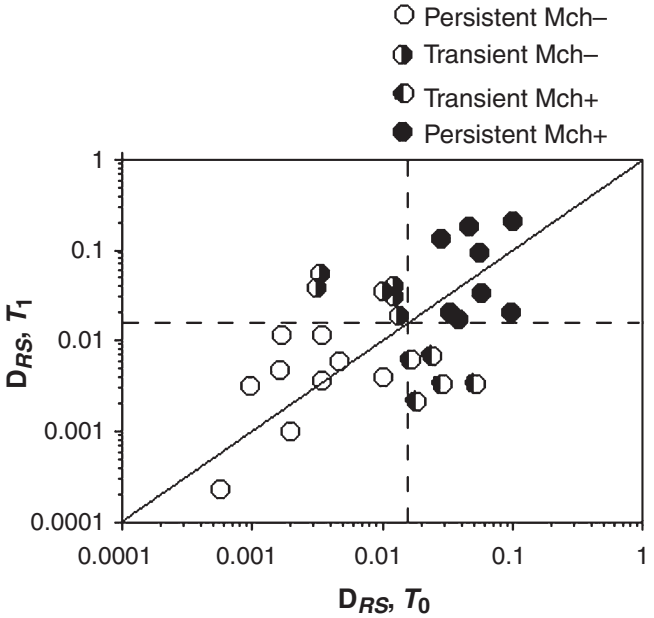

Figure 1. Relationship between individual values of methacholine dose–response slope (%FEV_1/μg Mch, D_{RS}) obtained at the follow-up visit (T_1) *vs* D_{RS} at the enrollment (T_0). Axis are traced in a log–log scale. For each subject, the change in bronchial responsiveness between T_0 and T_1 is shown. Horizontal and vertical dashed lines depict the D_{RS} value corresponding to $MchPD_{20}$ of 1526 μg of methacholine. The identity line is plotted. Persistent Mch−: nonresponders at both T_0 and T_1; transient Mch−: nonresponder at T_0 and responder at T_1; transient Mch+: responder at T_0 and nonresponder at T_1; persistent Mch+: responder at both T_0 and T_1.

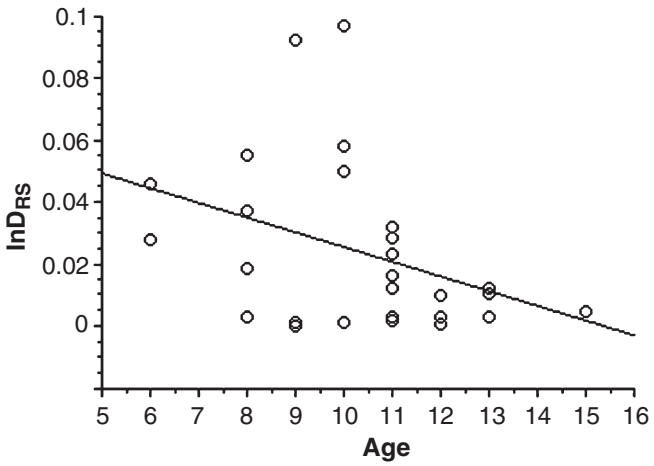

Figure 2. Relationship between the natural log of methacholine dose–response slope (%FEV_1/μg Mch, ln D_{RS}) and age (years), at enrollment (T_0). The linear regression was significant ($P = 0.044$, $R^2 = 0.147$).

Age, IgE *Z*-score, allergy score, familial atopic risk, age of disease onset, active or passive smoke exposure and duration of disease were not significantly different within

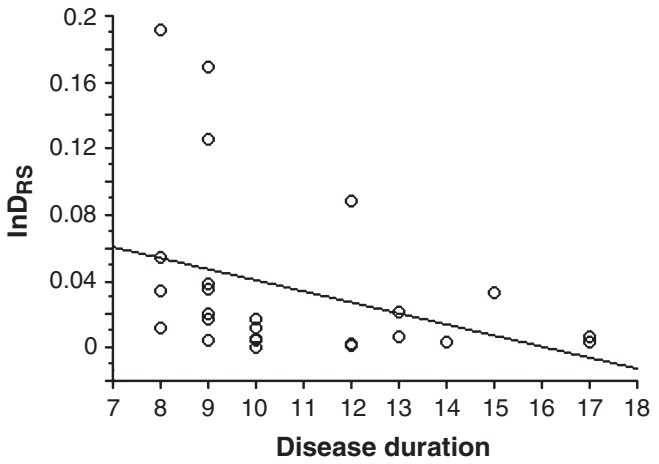

Figure 3. Relationship between the natural log of methacholine dose-response slope (%FEV_1/Mch, ln D_{RS}) and disease duration (years), at the follow-up visit (T_1). The linear regression was significant ($P = 0.044$, $R^2 = 0.146$).

groups. At T_0, the presence of mite skin positivity was significantly associated with the Mch+ subgroup (chi-squared test; $P = 0.017$), whereas the association disappeared at T_1.

No significant difference was found in PEFv between Mch+ and Mch− subgroups at T_0 (Table 2). Only one subject persistent Mch+ showed a high PEFv (11.6%). The ln D_{RS} at T_1 was significantly related to PEF variability at T_0 ($P = 0.008$, $R^2 = 0.239$). Multiple linear regression between BHR level at T_0, PEF variability, IgE *Z*-score, presence/absence of indoor allergens (*Dermatophagoides*), and exposure to passive smoke as independent variables and BHR at T_1 as dependent variable produced a large increase in R^2 (0.492).

At T_1, only three subjects reported development of mild intermittent asthma (10) during the 7-year follow-up: all three subjects were Mch+ at T_0, but only two were persistent Mch+. Consequently, we assumed that only two of 28 subjects developed bronchial asthma during the 7-year interval. These two subjects showed PD_{20} at T_0 of 240 and 388 μg of Mch, and PEFv of 7.7 and 3.9% respectively. Their PD_{20} values at T_1 were 82 and 220 μg of Mch, respectively. Both were positive to mites, had a familial atopic risk of 1 and an allergy score of 2 and 3, respectively. Only one reported asthma symptoms in the last year, showing an $FEV_1 < 80\%$ of the predicted value (78%) at T_1.

Discussion

Our study on a small homogeneous population reflects the high prevalence of BHR among children with allergic rhinitis described previously in larger studies. BHR was completely asymptomatic, as no spontaneous variability of airway patency, evaluated by daily PEF

variability, could be detected. Our 7-year follow-up showed that two of the 13 Mch+ subjects at T_1 (15%) developed mild intermittent asthma, whereas the overall BHR degree and atopic status did not change. At T_1, BHR was related to baseline BHR and to PEF variability. Moreover, also IgE *Z*-score, sensitization to mites, and exposure to passive smoke appeared to maintain BHR.

A high prevalence (37%) of BHR was found in a previous study by Koh et al. (19), in a sample of nonasthmatic children with allergic rhinitis. Rasmussen et al. (20) showed that among children with asymptomatic BHR at the age of 9 years, 13% had developed asthma at age of 15 years. Similar results were obtained in adults by Laprise and Boulet (6), who suggested that asymptomatic BHR may represent an intermediate stage between normal and asthmatic subjects, although it is not clear how many patients skew from normality to illness and why. Moreover, in this above-mentioned study, allergen exposure appeared to be one of the main risk factors for asthma development. In agreement, we found that the two subjects who developed asthma symptoms were sensitized to indoor allergens.

In our study, none of the Mch− subjects at T_0 developed asthma during the subsequent 7-year follow-up. This confirms the good predictive value of a negative Mch bronchial challenge. Among the 13 Mch+ at T_0, we found a low rate of asthma development: only three subjects reported intermittent asthma symptoms in the subsequent follow-up, but one of them had become Mch− at T_1. Therefore, during the 7-year follow-up, we assumed an asthma development rate of 15% (two among 13 subjects Mch+ at T_0). One of the two subjects reporting asthma showed asthmatic symptoms in the last year before T_1 and had a FEV_1 of $<80\%$ of the predicted value. Our results are in agreement with those of Prieto et al. (21) who showed that asymptomatic adult subjects with allergic rhinitis and Mch positivity did not show an increased susceptility to asthma onset over a follow-up period of 3.5 years.

The scarce relationship between BHR and asthma development seems to be confirmed by the high rate of individual changes in airway reactivity. In fact, although no significant difference was found in the number of Mch+ subjects between T_0 and T_1, 11 children (39% of the total) changed their class of responsiveness, moving from Mch+ to Mch−, or vice-versa (Fig. 1). These results confirm that nonspecific BHR is only one of the mechanisms underlying airflow obstruction in asthma and its relationship with the clinical expression of asthma is still uncertain or weak.

In our sample, all but one patient showed a PEFv value lower than 9.26%, the value previously found as the upper (95th percentile) limit for asymptomatic nonasthmatic children (22). Because PEF variability describes the spontaneous daily changes in airway patency (23), the finding of a low rate of asthma development is not surprising in our subgroup with BHR. This seems to suggest that a low PEFv has a greater clinical significance than a positive response to Mch challenge test.

Interestingly, we found a significant inverse linear correlation between D_{RS} and age at T_0 (Fig. 2): this result suggests that, in childhood, airway geometric factors play a fundamental role in non specific BHR, as previously demonstrated in normal subjects (24). Thus, a potential confounding effect on changes in BHR may be played by changes in airway caliber, that are expected during growth. However, despite this assumption, in the present work, in the overall sample, no significant change in FEV_1/FVC ratio, an index of airway caliber (24), was found between T_0 and T_1.

Moreover, an inverse linear relationship was found between D_{RS} and disease duration at T_1 (Fig. 3). Because disease duration and age were not correlated at T_1, we suppose that disease duration has an independent effect on BHR. Similarly, in young adults, the duration of disease may affect the mechanisms underlying BHR as suggested by previous results obtained in young asthmatics, in which the maximum long-term response to bronchodilator treatment was significantly lower than in subjects having asthma for a long time (25). This suggests that, in asthmatics, the progression of disease reduces the changes in airway motor tone, possibly because of airway remodeling. In subjects with allergic rhinitis and asymptomatic BHR, it remains to be established if that relationship recognizes similar underlying mechanisms.

We found that all the subjects showed positive SPT at T_1 without any significant change in allergy score over time. The exposure to mites was associated with positive BHR response at T_0. Exposure to indoor allergens and to passive smoke, BHR degree, and PEFv at T_0 were the only factors significantly related to keeping of BHR at T_1: this was demonstrated by the R^2 increase in the multiple linear regression between BHR at T_1 as a dependent variable, and BHR at T_0, PEFv, IgE *Z*-score, presence/absence of indoor allergens, and exposure to passive smoke as independent ones. However, in our sample, such relationship did not show any clinical relevance in terms of asthma development. In fact, the asthma development rate we found (15%) was clearly lower than previously reported among children with asymptomatic BHR (26, 27).

In conclusion, this study suggests that in a 7-year follow-up, children affected by allergic rhinitis maintain a high prevalence of bronchial hyperresponsiveness. Nevertheless, the rate of asthma development remains low and associated to a spontaneous daily variability of PEF within normal limits and to no significant change in their atopic status. It remains to be ascertained if a 7-year interval is long enough for the development of clinical evidences of asthma symptoms.

References

1. Hopp RJ, Towley RG, Biven RE, Bewtra AK, Nair NM. The presence of airway reactivity before the development of asthma. Am Rev Respir Dis 1990;**141**:2–8.
2. Ramsdale EH, Morris MM, Roberts RS, Hargreave FE. Asymptomatic bronchial hyperresponsiveness in rhinitis. J Allergy Clin Immunol 1985;**75**: 573–577.
3. Braman SS, Barrows AA, DeCotiis BA, Settipane GA, Corrao WM. Airway hyperresponsiveness in allergic rhinitis. A risk factor for asthma. Chest 1987;**91**:671–674.
4. Grosclaude M, Pletan J, Perrin-Fugolle M. Proposed rationale for a pragmatic attitude for indicating hyposensistization therapy in seasonal allergic rhinitis sufferers. A two years prospective study in 31 patients. Allergy 1992;**47**(Suppl):25.
5. Ulrik CS, Backer V, Hesse B, Dirksen A. Risk factors for development of asthma in children and adolescents: findings from a longitudinal population study. Respir Med 1996;**90**:623–630.
6. Laprise C, Boulet L-P. Asymptomatic airway hyperresponsiveness:a three-year follow-up. Am J Respir Crit Care Med 1997;**156**:403–409.
7. Grembiale RD, Camporota L, Naty S, Tranfa CME, Djukanovic R, Marsico SA. Effects of specific immunotherapy in allergic rhinitic individuals with bronchial hyperresponsiveness. Am J Respir Crit Care Med 2000;**162**:2048–2052.
8. Gibson PG, Mattoli S, Sears MR, Dolovich J, Hargreave FE. Increased peak flow variability in children with asymptomatic hyperresponsiveness. Eur Respir J 1995;**8**:1731–1735.
9. The International Rhinitis Management Working Group. International Consensus Report on the Diagnosis and Management of Rhinitis. Allergy 1994;**49** (Suppl 19):1–34.
10. NHLBI/WHO Workshop Report. Global strategy for asthma management and prevention. National Institutes of Health. Publication No. 95–3659. Bethesda, MD: National Heart, Lung, and Blood Institute, 1995.
11. Dreborg S, Frew A. Position paper; Allergen standardization and skin tests. Allergy 1993;**48**(Suppl 14):49–82.
12. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MA. Association of asthma with serum IgE levels and skin-test reactivity to allergens. New Engl J Med 1989;**320**:271–277.
13. Croner S, Kjellman NI. Development of atopic disease in relation to family history and cord blood IgE levels: eleven-years follow-up in 1654 children. Pediatr Allergy Immunol 1990;**1**:14–20.
14. Bousquet J, Van Cauwenberge P, Khaltaev N. ARIA Workshop Group; World Health Organization. Allergic Rhinitis and its Impact on Asthma. J Allergy Clin Immunol 2001; **108**(Suppl 5):S147–S334.
15. American Thoracic Society. Guidelines for methacholine and exercise challenge testing-1999. Am J Respir Crit Care Med 2000;**161**:309–329.
16. Sterk PJ, Fabbri LM, Quanjer PhH, Cockcroft DW, O'Byrne PM, Anderson SD et al. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Eur Respir J 1993;**6**(Suppl 16):53–83.
17. O'Connor G, Sparrow D, Taylor D, Segal M, Weiss S. Analysis of dose-response curves to methacholine. Am Rev Respir Dis 1987;**36**:1412–1417.
18. Paoletti P, Carrozzi L, Viegi G, et al. Distribution of bronchial responsiveness in a general population:effect of sex, age, smoking and level of pulmonary function. Am J Respir Crit Care Med 1995;**151**:1770–1777.
19. Koh YY, Lee MH, Kim CK, Min YG, Kim YK, Min KU et al. A familial predisposition in bronchial hyperresponsiveness among patients with allergic rhinitis. J Allergy Clin Immunol 1998;**702**:921–926.
20. Rasmussen F, Taylor DR, Flannery EM, Cowan JO, Greene JM, Herbison GP et al. Outcome in adulthood of asymptomatic airway hyperresponsiveness in childhood: a longitudinal population study. Pediatr Pulmonol 2002;**34**:164–171.
21. Prieto L, Bertó JM, Gutierrez V. Airway responsiveness to methacholine and risk of asthma in patients with allergic rhinitis. Ann Allergy Asthma Immunol 1994;**72**:534–539.
22. Siersted HC, Hansen HS, Hansen N-CG, Hyldebrandt N, Mostgaard G, Oxhøj H. Evaluation of peak expiratory flow variability in an adolescent population sample. Am J Respir Crit Care Med 1994;**149**:598–603.
23. Ryan G, Latimer KM, Dolovich J, Hargreave FE. Bronchial responsiveness to histamine: relationship to diurnal variation of peak flow rate, improvement after bronchodilator, and airway calibre. Thorax 1982;**37**:423–429.
24. Peat JK, Salome CM, Xuan W. On adjusting measurements of airway responsiveness for lung size and airway caliber. Am J Respir Crit Care Med 1996;**154**:870–875.
25. Bellia V, Cibella F, Cuttitta G et al. Effect of age upon airway obstruction and reversibility in adult asthmatics. Chest 1998;**114**:1336–1342.
26. Zhong NS, Chen RC, Yang MO, Wu ZY, Zheng JP, Li YF. Is asymptomatic bronchial hyperresponsiveness an indication of potential asthma? A two-year follow-up of young students with bronchial hyperresponsiveness. Chest 1992;**102**:1104–1109.
27. Jones A. Asymptomatic bronchial hyperreactivity and the development of asthma and other respiratory tract illnesses in children. Thorax 1994;**49**:757–761.