

Sensitivity to common aeroallergens in allergic rhinitis as a predictor of bronchial hyperreactivity and development of asthma

S. N. Gaur*, Raj Kumar, Amit Kumar Lohia, Kshitij Agarwal

Department of Respiratory Medicine, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi-110007.

Abstract

This study was conducted to investigate the association between rhinitis and asthma and to determine if atopy could predict the onset of lower airway inflammation in a patient of rhinitis. Thirty-two patients of allergic rhinitis above 12 years of age and without any history of breathlessness were investigated with skin prick test with 60 common aeroallergens. Bronchial reactivity was assessed with histamine diphosphate in all patients. All but 12 patients showed airflow obstruction. Twenty-six patients (81.2%) had both bronchial hyperreactivity (BHR) and skin test positivity, 6 were negative for BHR and 3 were SPT positive only. Patients with BHR had significantly higher number of Skin Prick Test (SPT) responses ($p < 0.0001$) and also, the number of positive antigens was an important factor for BHR in patients with allergic rhinitis. The mean histamine dose that induced BHR was significantly lesser in those with more than 4 positive antigens than in those with 1 and 2-4 positive antigens ($p = 0.004$ and $p = 0.03$ respectively). Those with no history of atopy and SPT negative did not show BHR and thus, no airway obstruction. In conclusion, perennial rhinitis can progress to airflow obstruction and is seen more in patients with a history of atopy and more number of allergen positivity. These parameters can be employed to predict progression of asthma in rhinitis patients.

Keywords: Rhinitis, asthma, bronchial hyperreactivity (BHR), skin prick test (SPT), atopy

INTRODUCTION

Allergic rhinitis (AR) represents a global health problem, affecting 10-25% of the world's population^{1,2} and is increasing over the last decade^{3,4}. It is common in clinical practice to see nasal and bronchial allergies existing together as do sinusitis, otitis media, nasal polyposis and recurrent respiratory tract infections. Most patients with asthma have rhinitis, and some with rhinitis go on to develop asthma^{5,6}. Moreover, epidemiological studies have shown that the two often co-exist in the same individual⁷⁻¹¹ or rhinitis frequently preceding the development of asthma¹²⁻¹⁶. Thus, it

may be said, the two could be off-shoots of the same process as was postulated by the 'One Airway, One Disease' hypothesis¹⁷⁻¹⁹. A Swedish study demonstrated that adults with a family history of asthma or rhinitis *i. e.* individuals with an atopic background have 3-4 fold greater risk of developing asthma and a 2-6 fold greater risk of developing rhinitis than in adults with negative history²⁰.

Rhinitis is associated in over 75% of patients of allergic asthma and in over 8% of those with non-allergic asthma^{21,22}. Small airway obstruction in asthma is well documented as evident that patients with mild asthmatic symptoms and normal FEV₁ may demonstrate impairment of FEF₂₅₋₇₅²³. Another study²⁴ reported both small as well as large airway obstruction in asthmatics is associated with rhinitis. In a previous study it was suggested that rhinitis

*Corresponding author: S. N. Gaur, Professor and Head, Department of Respiratory Medicine, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi-110007, India.

patients with mild spirometric impairment should be screened for allergy²⁵ and BHR should be suspected in AR patients with low FEF₂₅₋₇₅ values²⁶.

Bronchial hyperreactivity, a paramount feature of asthma, has also been observed in rhinitis²⁷ which could be indicative of a sub-clinical inflammation of the lower airways. It has been observed that in subjects with allergic rhinitis, sensitization to perennial allergens is associated not only with lower methacholine threshold values but also with lower prevalence and higher level of maximal response plateau on the concentration-response curve than sensitization to pollen allergens²⁸ and an increase in BHR is seen by performing nasal challenge with allergens²⁹. It has been shown that subjects of rhinitis who are sensitive to a greater number of allergens are more likely to have BHR³⁰. In an attempt to investigate the relationship between the degree of non-specific hyperresponsiveness and number of positive responses with skin prick test (SPT), Lombardi concluded, greater the number of SPT positives, greater is the BHR³¹. Thus, supporting the hypothesis that allergic-polysensitized individuals may exhibit greater BHR possibly due to an enhanced inflammatory component related to multiple allergen exposure.

The aim of this study was to find out the prevalence of airway obstruction in rhinitis having no breathlessness by spirometry, bronchial hyperresponsiveness to histamine challenge test in patients with allergic rhinitis and to investigate sensitivity with common aeroallergens. The study was done to explore whether sensitivity to aeroallergens can be used to predict BHR in patients of allergic rhinitis and can be used as a marker to indicate indirectly its progression towards asthma.

MATERIAL AND METHODS

Thirty two patients suffering from perennial allergic rhinitis, aged 12 years and above, who attended the out-patient clinics of the Department of Respiratory Medicine at V. P. Chest Institute during 2006-2008, were included in the study. All those patients who had symptoms compatible with rhinitis as per the guidelines laid down by the Allergic Rhinitis and its Impact on Asthma (ARIA) group *i.e.* having at least two of the four symptoms of blocked nose, runny

nose, itchy nose and sneezing for more than 2 years but with no history of breathlessness⁶ were included in the study. Smokers having associated respiratory or systemic illness, active or quiescent tuberculosis and pregnant and/or lactating women were excluded from the study. The project was cleared by the ethical committee of the Institute. A written informed consent was obtained from all patients enrolled in the study.

A detailed history of symptoms and a complete general physical examination including that of the upper respiratory tract was recorded. All patients were required to undergo a complete haemogram, X-ray chest, X-ray of the paranasal sinuses, urine-routine and microscopic examination, pulmonary function test (PFT), skin prick test with common aeroallergens and histamine (bronchoprovocation) challenge test. The PFT was performed on a computerized apparatus using a Morgan C model dry rolling seal type spirometer after taking height and weight of the patient. The parameters recorded were FEV₁, FVC, FEV₁/FVC and FEF₂₅₋₇₅ which were expressed as a percentage of the same values predicted for the weight and height of the patient which in turn were derived using the prediction equations based on age, gender and height³². Airway obstruction was diagnosed if the FEV₁ values were less than 80% of the predicted. SPT was performed and graded with 60 common aeroallergen extracts (1:20 w/v concentration) in 50% glycerinated buffered saline (All-cure Pharma Pvt. Ltd. ®) using the standard method³³.

Histamine challenge test was performed to see for BHR according to the protocol standardized by Cockcroft *et al*³⁴. Two hundred and sixty micro-grams of Histamine were delivered through a nebulizer (OMRON-flow of 9 L/min and MMD of 5.2µ) over 1 min 5 sec calculated by the particle size and flow rate. The test was performed using gradually increasing concentrations of histamine acid phosphate (HAP) in concentrations of 0.03, 0.06, 0.12, 0.25, 0.5, 1, 2, 4 and 8 mg/mL.

The percentage fall in FEV₁ was derived using the lowest post-saline FEV₁ (FEV_A) and the lowest post-histamine acid phosphate FEV₁ (FEV_B) values using the following formula:

$$100 \times (\text{FEV}_A - \text{FEV}_B) / \text{FEV}_A$$

The results were expressed as the provocation

concentration of histamine required to produce a 20% fall in FEV_1 (PC_{20}).

RESULTS

A total of 32 patients suffering from perennial allergic rhinitis with no previous history of breathlessness completed the study. Of the subjects studied, 1 (3.3%) showed mild airflow obstruction ($FEV_1 < 80\%$ predicted) while 19 (63.33%) demonstrated peripheral airflow obstruction ($FEF_{25-75} < 80\%$).

Bronchial hyperreactivity:

Out of 32 patients that underwent histamine challenge test, 26 (81.2%) had positive BHR and 6 patients (18.8%) had negative BHR.

Skin Prick Test:

Out of 32 patients tested, 29 (90.6%) were positive with SPT and 3 (9.4%) were negative with SPT.

Correlation between skin prick test positivity and bronchial hyper-reactivity

Out of 32 patients that underwent histamine challenge test, 26 (81.2%) had both BHR and skin test positivity, 6 patients (18.8%) had negative BHR, of which 3 were SPT positive. Thus, we found good agreement ($\kappa=0.619$) as defined by Cohen's κ ($K=0.61-0.80$) between SPT positivity and BHR in our study group.

Correlation between number of antigens positive with SPT and BHR

Results showed patients with BHR had significantly higher number of positive allergens with SPT. Histamine-responsive patients had a mean of 3.654 ± 2.96 allergen sensitivity while histamine-unresponsive patients had a mean of 0.5 ± 0.547 allergen sensitivity ($p < 0.0001$) which highly was significant.

Patients were divided into 3 sub-groups according to the number of allergens they tested positive for in SPT. Group A comprised of patients who had only 1 positive SPT response; group B comprised of those

with 2-4 positive responses and group C of those with 4 or more positive responses. In patients in group C, the mean histamine dose that induces BHR was significantly lesser *i.e.* more BHR than that in groups A and B ($p = 0.004$ and $p = 0.03$ respectively). However, there was no significant difference ($p = 0.78$) between groups A and B in mean BHR-inducing histamine dose but the dose inducing BHR in group B was found to be lesser than in group A. (Table 1)

Table 1: Correlation between response to SPT and PC_{20} value

SPT response BHR +^{ve} patient Histamine PC_{20} level,
Mean $\pm$ SD (mg/dL)

Group A	0-1	6	2.05 ± 1.2
Group B	2-4	12	1.936 ± 1.6
Group C	>4	8	0.682 ± 0.69

A vs. B, $p = 0.78$ B vs. C, $p = 0.03$ A vs. C, $p = 0.004$

DISCUSSION

Asthma and rhinitis are chronic conditions that impose a substantial economic burden on not just the affected individual but also on his family, the health-care system and the society as a whole. Epidemiological studies, done worldwide have consistently shown asthma and rhinitis to be co-existent in the same individual^{7-10,22}. In a study involving 20,000 households, of which 16,786 participated, the point prevalence of perennial rhinitis (those with at least 6 months of continuous symptoms) was 4.1%. A history of asthma was observed in 13.4% in those with perennial rhinitis vs. 3.8% in those without rhinitis (Odds ratio: 3.26)³⁵. The other way round, rhinitis has been seen to occur in over 75% of patients with allergic asthma and in over 8% patients with non-allergic asthma^{21,22}.

Many patients with allergic rhinitis also had increased bronchial sensitivity to methacholine or histamine^{6,36}. Patients with the seasonal form of allergic rhinitis have been shown to develop seasonal bronchoconstriction, not manifest clinically³⁷. Moreover, seasonal spurts in bronchial responsiveness to carbachol, histamine, methacholine and exercise have been observed commonly in those allergic to grass or birch pollen^{38,39}. Conversely, reversal of bronchial hyperactivity by instillation of intranasal

sodium cromoglycate⁴⁰, nedocromil sodium⁴¹ or glucocorticoids^{42,43} suggests that bronchial inflammation is associated with nasal inflammation⁴⁴.

Among the agents incriminated in asthma and rhinitis, allergens²² are known to be central to the pathogenesis of both asthma and rhinitis^{45,46}. In general, allergy to house dust mite and animal dander is a risk factor for asthma and rhinitis while that to pollen is a risk factor for rhinitis^{47,48}.

Through our study, we attempted to address the relationship between reactivity to SPT with BHR (PC_{20} -histamine, FEV_1) and investigated the spirometric impairment in patients with allergic rhinitis. In our study, 1 patient (3.3%) with allergic rhinitis showed mild airflow obstruction while 19 (63%) had peripheral airflow obstruction, while no airway obstruction was noted in the other 12 patients. In another study done on 50 patients of rhinitis without asthma demonstrated peripheral airway obstruction in 32% while 12% of patients showed mild airflow obstruction⁴⁹. In yet another study done on 100 patients of rhinitis sensitized only to perennial allergens showed reduced FEV_1 in 5% and impaired FEF_{25-75} in 48% of patients of allergic rhinitis and 72% patients showed positive methacholine challenge test⁵⁰. Another study was done in a group of subjects with seasonal allergic rhinitis both within and outside the pollen season. Out of 100 patients of rhinitis sensitized to pollen allergens, 54 were positive for methacholine challenge test and 17% showed impaired FEF_{25-75} ⁵¹. Our results were similar to the ones of this study excepting the fact that we found a greater prevalence of peripheral airway obstruction.

Previous studies have been done to find out the relationship between the degree of non-specific hyperresponsiveness and number of positive SPT to aeroallergens. Lombardi found that in patients with allergic rhinitis and asthma, the number of positive SPT response correlates well with the degree of BHR ($p = 0.0046$) (31). In particular, those with positivity to three or more allergens showed a greater degree of bronchial hyperreactivity. Asthmatic individuals with atopy were seen to be associated with lower PC_{20} value in a study done by Fowler⁵². Mete *et al* found BHR to be present in 39% of patients of allergic rhinitis, the BHR positive patients had a mean of 4 SPT responses whereas those with negative BHR had

a mean of 2.6 ($p = 0.04$). The mean PC_{20} dose was determined to be 5.05 ± 9.2 mg/mL in patients with more than 4 positive SPT responses, 2.36 ± 13.4 mg/mL in those with 2-4 positive SPT responses and 23.4 ± 14.10 mg/mL in those with 1 positive response ($p = 0.001$ for >4 vs. 2-4, $p = 0.002$ for >4 vs. 1) (30). In our study, we found similar results, 90 % of those with allergic rhinitis were found to be positive with BHR. The BHR positives had a mean of 3.65 positive SPT responses whereas those that had negative BHR had a mean of 0.5 ($p < 0.0001$). The mean PC_{20} dose was 0.682 ± 0.69 mg/mL in patients with >4 SPT responses, 1.93 ± 1.68 mg/mL in those with 2-4 positive responses and 2.05mg/mL in those with 1 positive responses to SPT, which was statistically significant ($p = 0.03$ for >4 vs. 2-4, $p = 0.04$ for >4 vs. 1).

Thus, as a corollary to these results, the number of positive allergens with SPT is an important indicator of bronchial hyperreactivity in patients with allergic rhinitis. Also, it was demonstrated that more the number of positive responses to SPT in an individual, lesser is the mean PC_{20} dose, implying thereby, a subject who has more allergen positivity has greater bronchial hyperreactivity in comparison to one with a lesser number of allergenic responses.

Through the findings of this study we can conclude that patients with the perennial form of allergic rhinitis but without any history of breathlessness may have airway obstruction especially in those with positive responses on SPT and also bronchial hyperreactivity and these can be used as a predictor for the development of asthma in patients of rhinitis. Thus, we recommend a thorough investigation for airway obstruction in any subject who presents with a history compatible with allergic rhinitis even without breathlessness. Also, the SPT can serve as a predictor of BHR, it would be prudent to investigate subjects of rhinitis for sensitivity to common aeroallergens which can indirectly reflect BHR or even airway obstruction.

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