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RELATIONSHIP BETWEEN RESPONSES TO BRONCHODILATION TESTING AND TO NASAL DECONGESTION TESTING IN PATIENTS WITH ALLERGIC RHINITIS ALONE

G. CIPRANDI, A. PISTORIO[1], M.A. TOSCA[2], I. CIRILLO[3] and G.L. MARSEGLIA[4]

Department of Internal Medicine, Azienda Ospedaliera Universitaria San Martino, Genoa; [1]Epidemiology and Statistics Unit, IRCCS G. Gaslini, Genoa; [2]Pneumology and Allergy Center, IRCCS G. Gaslini, Genoa; [3]Pneumology and Allergy, Navy Medical Service, La Spezia; [4]Clinica Pediatrica, Foundation IRCCS San Matteo, University of Pavia, Pavia, Italy

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A remarkable relationship exists between upper and lower airways. Bronchial obstruction is a paramount feature of asthma as well as nasal obstruction of allergic rhinitis (AR). This study aims to evaluate the response to both bronchodilation and decongestion testing and their relationships in a large group of patients with moderate-severe persistent AR alone. Two hundred eleven patients with moderate-severe persistent AR were prospectively and consecutively evaluated. Clinical examination, skin prick test, spirometry, bronchodilation test, rhinomanometry, and decongestion test were performed on all patients. Seventeen subjects (8%) did not respond to any of the tests, 55 subjects (26.1%) were responders only to the decongestion test, 31 (14.7%) only to the bronchodilation test, and 108 subjects (51.2%) responded to both these tests. Longer AR duration was significantly associated with positive response to both tests ($p<0.01$). In conclusion, this study provides the first evidence that patients with moderate-severe persistent AR may frequently show reversibility to both bronchodilation and decongestion tests.

Allergic rhinitis is characterized by typical symptoms, including nasal itching, sneezing, rhinorrhea, and obstruction, induced by an IgE-mediated inflammatory response of the nose to allergen exposure. The critical role of inflammation as an essential component of allergic rhinitis is now well accepted and infiltration by inflammatory cells, including T cells, mast cells, and especially eosinophils, provides the hallmark cellular signature of allergic inflammation (1-2). The cytokine pattern is typically characterized by a Th2 polarization (3). Th2-derived cytokines account for recruitment and activation of many of the inflammatory cells in the airways, including eosinophils which may be considered a reliable cellular marker of allergic inflammation (4). Although asthma is classically defined as a chronic inflammatory disorder of lower airways (5), allergic airway inflammation may also contribute to airflow limitation both at the nasal and bronchial levels (6) and the close linkage between allergic rhinitis and asthma has now been widely accepted (7-8). Moreover, allergic rhinitis has been demonstrated to be a strong risk factor for the onset of asthma in adults (9).

From a pathophysiological point of view, asthma is typically characterized by attacks of airflow

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Mailing address:
Giorgio Ciprandi, M.D.
Semeiotica e Metodologia Medica I, DIMI
Viale Benedetto XV 6,
16132 Genoa, Italy
Tel: ++39 10 35338120 Fax: ++39 10 3537573
e-mail gio.cip@libero.it

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obstruction (10-11). Although bronchial airflow is easily assessed by the measurement of several spirometric parameters, the gold standard predictive marker of asthma is FEV_1, as recommended in the GINA guidelines (5) In addition, reversibility of airflow obstruction is considered a pathognomonic and diagnostic characteristic of asthma. This reversibility may be spontaneous or induced by drugs, such as bronchodilators. Bronchial reversibility, is commonly assessed in the clinical setting by the bronchodilation test (10-11).

Obstruction of the nasal passages has also been defined as the key pathogenetic event in allergic rhinitis (12) and may be objectively evaluated by measuring the nasal airflow through rhinomanometry (13). Moreover, the nasal decongestion testing consists of evaluating the reversibility of nasal airflow obstruction after administering an intranasal vasoconstrictor (such as an α-adrenoreceptor stimulant) (14). The degree to which obstruction is relieved by decongestants is related to both the sensitizing allergen as well as to allergic inflammation (15). The percentage values of increases in nasal airflow after decongestants have been established and are useful in the interpretation of positive responses and in diagnosing nasal obstruction reversibility (16).

Very recently, up to 2/3 of patients with persistent allergic rhinitis alone and with normal values of FEV1, have been reported to have a positive response to the bronchodilation test (17). Therefore, since bronchial impairment without symptoms is frequently encountered in allergic rhinitis, the bronchodilation test may provide an important predictive detection marker (17). However, no studies have been performed to evaluate the contemporaneous response to bronchodilation and decongestion tests in the same patient in order to investigate the relevance of airflow limitation reversibility. The purpose of the present study is to evaluate a large group of patients with moderate-severe persistent allergic rhinitis alone to determine the reversibility to both bronchodilation and decongestion tests and the relationship of the response to the two tests.

MATERIALS AND METHODS

Study design

The study included patients with moderate-severe persistent allergic rhinitis, all of whom were evaluated with skin prick tests, spirometry, bronchodilation test, rhinomanometry, and decongestion test. The study was performed during the spring.

Subjects

Two hundred and eleven patients with moderate-severe persistent allergic rhinitis were prospectively and consecutively evaluated. Demographic and functional characteristics, including gender, age, and duration of rhinitis (expressed in years), are reported in Table I. All of them were sailors in the Navy who were obliged to undergo regular fitness check-ups at the Navy Hospital. Informed consent was obtained from each patient, and the procedures were approved by the Navy Review Board

A detailed clinical history was taken and a complete physical examination was carried out. The patients were included in the study on the basis of positive skin prick test, clinical history of persistent allergic rhinitis, and presence of moderate-severe nasal symptoms according to validated criteria (6). Exclusion criteria included: any prior history of asthma or presence of asthma symptoms, including cough, wheezing, dyspnea, and shortness of breathing, abnormal spirometry (e.g. FEV1 <80% of predicted), acute or chronic upper respiratory infections, anatomical nasal disorders (i.e. nasal polyps, septum deviation, etc.), previous or current smoking (screened by expired-CO assessment), previous or current specific immunotherapy, and use of nasal or oral corticosteroids, nasal or oral vasoconstrictors, antileukotrienes, and antihistamines during the previous 4 weeks (if they assumed pharmacologic treatment, they were asked to return after suspending medications for 4 weeks). All subjects had been previously treated exclusively with drugs and had not received immunotherapy.

Diagnostic testing

The diagnosis of persistent allergic rhinitis was made on the basis of a history of nasal symptoms and positive skin prick test according to validated criteria (6).

Skin prick tests

Skin prick tests were performed as recommended by the European Academy of Allergy and Clinical Immunology (18). The panel consisted of: house dust mites (*Dermatophagoides farinae* and *pteronyssinus*), cat, dog, grasses mix, *Compositae* mix, *Parietaria officinalis*, birch, hazel, olive tree, *Alternaria tenuis*, *Cladosporium*, *Aspergilli* mix (Stallergenes, Milan, Italy).

Spirometry

Spirometry was performed with a computer-assisted spirometer (Pulmolab 435-spiro 235, Morgan, England) and according to international guidelines (5, 10-11). Briefly, 3 blows (every 5 min) were performed and the

best result was considered.

Test of bronchodilation

Bronchodilation testing was performed according to international guidelines, using a salbutamol metered dose of 400 mcg. Reversibility was considered if an increase of at least 12% of FEV1 from baseline was achieved (10-11).

Rhinomanometry

Nasal airflow was measured by active anterior electronic rhinomanometry (ZAN 100 Rhino Flow Handy II, ZAN, Messgeraete Gmbh, Germany) according to validated criteria (13). Nasal airflow was considered as the sum of recorded airflow through the right and left nostrils, measured in milliliter per second at a pressure difference of 150 Pa across the nasal passage.

Decongestion testing

The responses to decongestants was performed according to validated criteria (14-15). After baseline rhinomanometry, two sprays of naphazoline (1 mg/mL) were applied per nostril. This drug is a potent α-adrenostimulator that induces rapid vasoconstriction. Rhinomanometry was performed 5 and 10 min later. The higher response was considered in analogy with bronchodilation test. Total nasal airflow volume and percentage of reversibility were evaluated. The test was considered positive when the percentage of reversibility was $\geq$ 34% (16).

Statistical analysis

Descriptive statistics were firstly performed and quantitative parameters were reported as means and standard deviations (SD), or as medians with quartiles in case of skewed distribution. Qualitative data were reported as frequencies and percentages. Comparison of qualitative data among various groups of patients was made by the chi-square test (or by the Fisher's Exact test in case of expected frequencies less than five). Comparison of quantitative variables between the four groups of patients was made by means of the non-parametric Analysis of Variance (Kruskal-Wallis test) as the normality assumption was not fulfilled; *post-hoc* comparisons were performed using the non-parametric Dunn's test. The correlation between quantitative parameters was evaluated by means of the non-parametric Spearman's correlation coefficient (r_s).

All tests were two sided and a *P* value less than 0.05 was considered statistically significant. The package "Statistica release 6" (StatSoft Corp., Tulsa, OK, USA) was used for all the analyses.

RESULTS

Two hundred and eleven patients, 168 males (79.6%) and 43 females (20.4%) were included in the study. The mean age was 23.9 years (SD: 2.2) with a minimum age of 19 and a maximum of 32 years. The subjects were well-matched with regard to the clinical severity.

Globally, 163 patients (77.3%) had a positive response to the decongestion test, and 139 patients (65.9%) showed positive responses to the bronchodilation test.

Patients were divided into four groups according to their positive response to the bronchodilation test and to the decongestion test: there were 17 subjects (8%) who did not respond to either of the two tests (D-/B-), 55 subjects (26.1%) who were only responders to the decongestion test (D+/B-), 31 (14.7%) who were only responders to the bronchodilation test (D-/B+), and 108 subjects (51.2%) who responded to both tests (D+/B+), as shown in Table II. There was a similar gender distribution in the 4 groups of patients (p=0.18); age at study visit was very similar among the 4 groups of patients (p=0.21) as well as FVC% of predicted values (p=0.22). In contrast, the 4 groups were very different in terms of rhinitis duration (p=0.0009), and in terms of the two major spirometric parameters at baseline: FEV_1% of predicted values (p<0.0001) and FEF_{25-75}% of predicted values (p=0.03); moreover they were statistically different in terms of nasal airflow at baseline (p<0.0001).

Of particular interest was the finding that group D+/B+ had a significantly longer disease duration (p<0.01) compared to all patients with a negative response to the bronchodilation test (D-/B- and D+/B- patients) (Fig. 1).

Globally, there is no correlation between the response to decongestion test (measured as percentage change of nasal airflow) and the response to the bronchodilation test (measured as percentage change of FEV_1 % of predicted values) (r_S = 0.15).

The description of sensitizations in the 4 groups of patients is shown in Table III. No differences emerged among the 4 groups of patients in terms of allergen sensitization.

DISCUSSION

Allergic rhinitis and asthma may be considered as a single syndrome involving two parts of the respiratory tract, as documented by two

Table I. *Characteristics of the study patients (N=211).*

Characteristics	**Median** [1st – 3rd quartiles]
Sex: Male - N (%)	168 (79.6%)
Age (yrs): Median [1st – 3rd quartiles]	24 [22 – 25]
Rhinitis duration (years): Median [1st – 3rd quartiles]	4 [2 – 7]
pre-test Nasal airflow (ml / sec)	459 [328-523]
pre-test FEV_1 % of predicted	91 [89-94]
pre- test FVC % of predicted	100 [98-105]
pre- test FEF_{25-75} % of predicted	71 [66-73]
% Δ Nasal Air flow > 34% - N (%)	163 (77.3%)
% Δ FEV1 > 12% - N (%)	139 (65.9%)

Table II. *Demographic and clinical parameters of the patients divided into 4 groups.*

	D- / B- N= 17	D+ / B- N= 55	D- / B+ N= 31	D+ / B+ N= 108	P
Gender - Males, N *(%)*	10 (58.8)	46 (83.6)	26 (83.9)	86 (79.6)	0.18 #
Age (yrs):	23 [22-24]	25 [23-26]	24 [22-25]	23 [22-25]	0.21°
Rhinitis duration (yrs)	3 [2-5]	3 [1-5]	4 [3-8]	5 [3-8]	0.0009°
Nasal airflow (ml / sec)	522 [510-560]	440 [282-466]	500 [483-556]	400 [303-523]	<0.0001°
FVC % of predicted	103.0 [91-104]	100.0 [97.5-104.5]	105.0 [100-106]	101.5 [86-102]	0.22°
FEV_1 % of predicted	98.0 [94-103]	90.0 [89-95]	94.5 [91-95]	84.5 [83-86]	<0.0001°
FEF_{25-75} % of predicted	79.0 [72-100]	72.0 [71-74]	73.0 [71-73]	63.0 [57-72]	0.03°

All percentages in round brackets are calculated over the total number of subjects reported at top of the column. All numbers in the Table are medians and numbers in square brackets represent 1st-3rd quartiles, unless otherwise specified.
 # Chi-square test; ° Kruskal-Wallis test

Table III. *Description of allergen sensitizations in the four groups of patients.*

	D- / B- N= 17	D+ / B- N= 55	D- / B+ N= 31	D+ / B+ N= 108	P
House dust mites, N *(%)*	12 (70.6)	41 (74.6)	19 (61.3)	78 (72.2)	0.61°
Trees, N (%)	4 (23.5)	10 (18.2)	9 (29.0)	24 (22.2)	0.69°
Parietaria, N (%)	11 (64.7)	36 (65.4)	19 (61.3)	63 (58.3)	0.83#
Graminae, N (%)	4 (23.5)	16 (29.1)	12 (38.7)	28 (25.9)	0.54°
Moulds, N (%)	3 (17.6)	15 (27.3)	4 (12.9)	15 (13.9)	0.18°
Dog or cat, N (%)	2 (11.8)	8 (14.5)	2 (6.4)	17 (15.7)	0.66°
Compositae, N (%)	1 (5.9)	4 (7.3)	0 (0.0)	4 (3.7)	0.37°
Perennial allergens: yes, N *(%)*	13 (76.5)	43 (78.2)	19 (61.3)	81 (75.0)	0.38°
Polysensitization: yes, N *(%)*	14 (82.3)	43 (78.2)	21 (67.7)	77 (71.3)	0.59°

All percentages in round brackets are calculated over the total number of subjects reported at top of the column. #Chi-square test; ° Fisher's Exact test

experimental studies (19-20). Patients with allergic rhinitis may frequently present with the obstructive symptoms of asthma and/or its impaired spirometric manifestations. Indeed, impaired FEV_1 values may be detected in some patients with allergic rhinitis who manifest nasal symptoms alone (21). This finding not only underscores the link between upper and lower airway disease but also illustrates the concept that allergic rhinitis may usually precede overt asthma.

Asthma is characterized by airflow obstruction that is typically reversible, spontaneously or pharmacologically. The demonstration of bronchial reversibility is a main step in the diagnosis of asthma and is performed by a bronchodilation test. The bronchodilation test should be considered as an integral part of spirometry since it is easily carried out and may also provide important diagnostic clues for patients without overt bronchial airflow obstruction. The present study investigates the response to both the bronchodilation and decongestion tests in a large cohort of patients with moderate-severe persistent allergic rhinitis alone, who presented solely with nasal symptoms.

Several interesting observations resulted from this study. Firstly, a large percentage (about 2/3) of patients with moderate-severe persistent allergic rhinitis showed reversibility with increases >12% of basal FEV_1 values. It should be noted that all patients had normal initial basal FEV_1 values, i.e., > 80% of predicted values. This finding suggests that a positive response elicited by the bronchodilation test might provide evidence of early bronchial impairment in allergic rhinitis, confirming observations from previous studies (17, 21).

A second study finding was that approximately 80% of patients showed a positive nasal decongestion

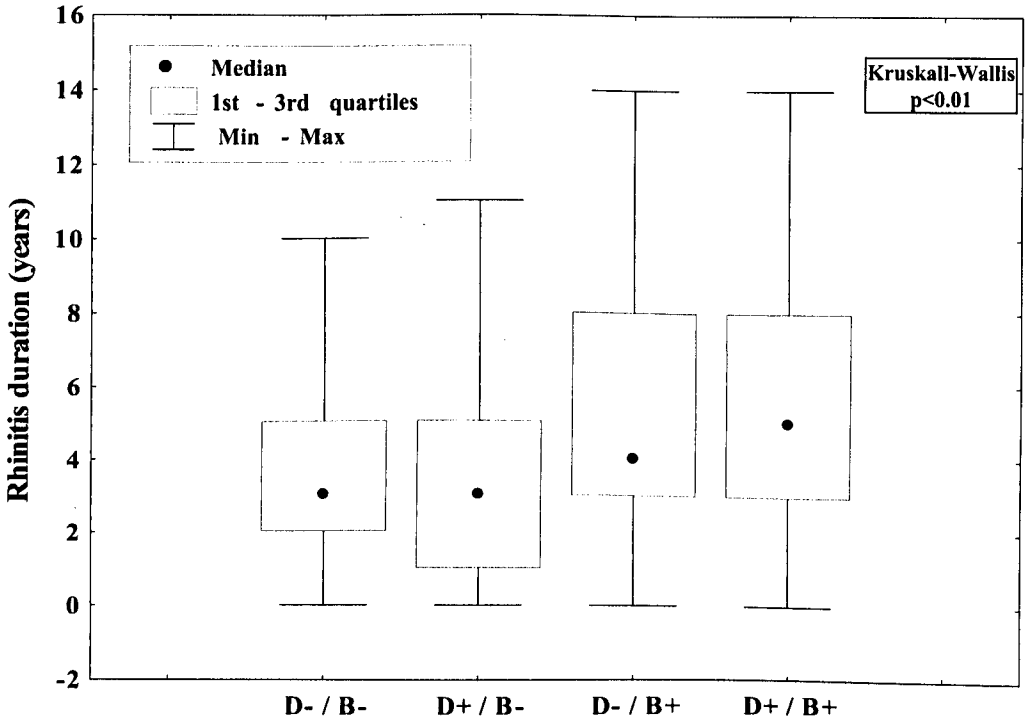

Fig. 1. *Rhinitis duration (years) in the four groups of patients: non-responders to both tests (D-/B-), responders only to decongestion test (D+/B-), responders only to bronchodilation test (D-/B+) and responders to both tests (D+/B+). Data are expressed as medians; boxes represent first and third quartiles and bars represent minimum (Min) and maximum values (Max).*

test. Although the responses to the decongestion test depend largely on baseline airflow limitation, this observation confirms the results of previous studies and underscores the relevance of this finding in allergic rhinitis (14-16).

Another outcome of the present study is the contemporaneous positive responses to both tests seen in the study population. Most patients (about 50%) elicited positive responses to both tests in contrast to < 10% who were non-responsive to the paired test procedures. About 30% of patients showed positive responses only to the decongestion test and 15% only to the bronchodilation test. Of the several possible factors that could have influenced the type of response seen, duration of rhinitis, baseline values of both FEV_1 and nasal airflow seem most likely. There was no relationship of these responses with the type or number of positive skin test responses. The duration of rhinitis symptomatology appears to be the most relevant basis for the dual responses, in contrast to baseline airflow limitation in the nose or bronchi which appear to be more relevant for the responses to specific nasal or bronchial testing, respectively..The duration of allergic rhinitis implies the obligatory contribution of chronic nasal inflammation typical of persistent allergic rhinitis. Moreover, since allergic inflammation is strictly related to the persistence of allergen exposure, the magnitude of the manifestations of allergic rhinitis correlate with the degree of exposure and subsequent inflammation, as described in the phenomenon of minimal persistent inflammation (22-23). Chronic nasal inflammation causes impairment of nasal airflow and successively of bronchial airflow, which may be detected early by the degree of obstructive reversibility.

The possible clinical implications of this study relate to the finding that some patients with allergic rhinitis may also have lower airway inflammation, causing both diminished but still normal FEV1 values but with significant bronchial reversibility.

However, the responses to the two tests are not related probably because the two organs, i.e. the nose and the bronchi, though sharing common pathophysiologic mechanisms, are characterized by different anatomic and physiologic structures. Indeed, nasal obstruction is mainly sustained by vascular congestion, whereas bronchial obstruction is mainly consequent to smooth muscle contraction. Therefore, the response to the two tests, even though present in the same patient, may not relate to intensity of disease manifestations.

In conclusion, this study provides the first evidence that patients with moderate-severe persistent allergic rhinitis may frequently show reversibility to both decongestion and bronchodilation tests. These findings may also account for early symptomless bronchial involvement in patients presenting solely with nasal symptoms alone.

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