

## Original article

## Impact of allergic rhinitis on asthma in children: effects on bronchodilation test

**Background:** Relevant relationship exists between upper and lower airways. Bronchial obstruction is a paramount feature of asthma and its reversibility is considered a diagnostic step for asthma diagnosis.

**Objective:** This study aimed at evaluating a large group of children with allergic rhinitis alone for investigating the degree of bronchodilation and possible factors related to it.

**Methods:** Two hundred patients with allergic rhinitis and 150 normal subjects were consecutively evaluated. Clinical examination, skin prick test, spirometry, and bronchodilation test were performed in all patients.

**Results:** Rhinitics showed a significant FEV<sub>1</sub> increase after bronchodilation test ( $P < 0.0001$ ) in comparison both to basal values and to controls' levels. More than 20% of rhinitics had reversibility ( $\geq 12\%$  basal levels). Patients with reversibility had lower FEV<sub>1</sub> levels, longer rhinitis duration, and perennial allergy.

**Conclusion:** This study highlights the close link between upper and lower airways and the relevance of performing bronchodilation test in patients with allergic rhinitis and these characteristics.

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IgE-mediated inflammation characterizes allergic rhinitis. Indeed, inflammation may be considered a *condicio sine qua non* of allergic rhinitis (1, 2). Th2-derived cytokines account for recruiting and activating eosinophils in the airways: actually, eosinophil infiltration may be considered as a reliable marker of allergic inflammation (3, 4).

On the other hand, asthma is defined as chronic inflammation of bronchi (5). The allergic airway inflammation may therefore induce airflow obstruction both at nasal and bronchial level (6). Allergic rhinitis has been demonstrated to be a strong risk factor for the onset of asthma in adults (7). Allergic rhinitis and asthma are therefore two disorders closely associated (8, 9).

From a pathophysiological point of view, asthma is characterized by airflow obstruction (10, 11). Bronchial airflow may be easily assessed by spirometry. Several spirometric parameters may be considered, but the gold standard to detect asthma is FEV<sub>1</sub>. In addition, reversibility of airflow obstruction is considered a characteristic of asthma. This reversibility may be spontaneous or induced by drugs, such as bronchodilators. To assess reversibility, the bronchodilation test is commonly performed in clinical setting.

As allergic rhinitis may be frequently associated with asthma or precedes it, the WHO document 'the impact of allergic rhinitis on asthma' (ARIA) clearly underlines the role of allergic rhinitis as risk factor for asthma development and suggests of considering a bronchial involvement in patients with allergic rhinitis (6). Concerning this issue, it has been previously reported that FEV<sub>1</sub> may be impaired in about 5% patients with allergic rhinitis and perceiving nasal symptoms alone (12). Moreover, slight spirometric impairment, such as reduced FEF<sub>25-75</sub> values, may be frequently found in rhinitics and it might be a reliable marker of early bronchial involvement (13). Therefore, allergic rhinitis may be considered as the first step of a progression of respiratory allergy toward asthma.

Recently, it has been conducted a study in patients with moderate-severe persistent allergic rhinitis to investigate the degree of reversibility to bronchodilation test (14). This study provided evidence that 2/3 of patients with allergic rhinitis had a reversibility after bronchodilation test and had lower FEV<sub>1</sub> levels, longer rhinitis duration, and mites and trees allergy in comparison with other patients (14).

Therefore, this study aimed at evaluating a large cohort of children with allergic rhinitis and perceiving nasal symptoms only for investigating these aspects.

## Materials and methods

### Study design

The study included children with allergic rhinitis. All of them were evaluated performing skin prick test, spirometry, and bronchodilation test. The Review Board approved the study and an informed consent was obtained from the parents of each patient. The study was performed during the spring, i.e. the pollen season.

### Subjects

Two hundred children (118 males and 82 females) and 150 control subjects (81 males and 69 females) were consecutively included in the study. Patients' mean age was 11.3 years (SD 2.6) and controls' mean age was 11.7 (SD 2.8). Healthy controls were enrolled during visits for sport qualification, they had to be negative to skin prick test.

Demographic characteristics, including gender, age, and duration of rhinitis (expressed in years), are reported in Table 1. All of them referred to Ave Gratia Plena Hospital for allergic rhinitis.

Detailed clinical history and complete physical examination were performed. The patients were included in the study on the basis of a clinical history of allergic rhinitis and presence of nasal symptoms according to validated criteria (6). We excluded all the subjects who met the following exclusion criteria: any prior history of asthma or presence of asthma symptoms, including cough, wheezing, dyspnoea, and shortness of breathing, acute or chronic upper respiratory infections, anatomical nasal disorders (i.e. nasal polyps, severe septum deviation, etc.), previous or current specific immunotherapy, and use of nasal or oral corticosteroids, nasal or oral vasoconstrictors, antileukotrienes, and antihistamines during the previous 4 weeks. All patients were previously treated only on demand with drugs (e.g. antihistamines) alone.

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

*Skin prick tests* were performed as stated by the European Academy of Allergy and Clinical Immunology (15). 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* was performed with a computer-assisted spirometer (Pulmolab 435-spiro 235, Morgan, UK) and according to international guidelines (5, 10, 11). Briefly, three blows (every 5 min) were performed and the best result was considered.

*Test of bronchodilation* was performed according to international guidelines and using a salbutamol metered dose of 400 mcg.

Reversibility was considered if an increase of at least 12% of FEV<sub>1</sub> from baseline was achieved, according to international guidelines (10, 11).

### Statistical analysis

Descriptive statistics were performed and quantitative parameters were reported as means and standard deviations (SD), or as medians with minimum (min) and maximum (max) values 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. Comparison of quantitative normally distributed data between two groups of patients was made by means of the Student's *t*-test; whenever the homoscedasticity assumption was not fulfilled the Mann–Whitney *U*-test was used as nonparametric counterpart (e.g. age of the patients). Comparison of quantitative variables between the three groups of subjects (such as patients with PER and reversibility, patients with PER and without reversibility, and normal subjects) was made by means of the Analysis of Variance or by the nonparametric Kruskal–Wallis test; *post hoc* comparisons were performed using the Scheffé or the nonparametric Dunn's test.

Comparison of quantitative variables (e.g. FEV<sub>1</sub> percentage of predicted) for paired data (pre- and post-test values) was made by means of the Wilcoxon test.

All tests were two sided and a *P*-value less than 0.05 was considered statistically significant. A statistical software program (STATISTICA; STATSOFT ITALIA S.r.l. 2005, Vigonza, Italy) was used for all the analyses.

## Results

The patients' mean age (11.3 years, SD 2.6) was comparable with controls' mean age (11.7 years, SD 2.8) (Mann–Whitney *U*-test; *P* = 0.4). All of the included subjects have clinically relevant sensitisation to at least one allergen to which they were exposed at the time of testing.

Demographic and clinical characteristics of the patients are shown in Table 1; as can be seen in the table, patients had a median rhinitis duration of 2 years (mean 2.7). Table 2 shows the list of allergens to which skin prick tests were positive in patients.

Thus, the subjects were studied on the basis of their response to bronchodilation test. In Fig. 1 (Panel A) are shown pretest FEV<sub>1</sub> values in patients and controls; as shown, patients mean pretest FEV<sub>1</sub> is 89.3% of predicted (SD 11.6; median 89) and reach a mean post-test value of 99.8% of predicted (SD 9.1; median 100). This increase is statistically significant (Wilcoxon test *P* < 0.001). Controls' FEV<sub>1</sub> value is higher than patient's value; pre- and post-test values in the controls' also show a statistically significant increase (pretest FEV<sub>1</sub> values: mean = 99.5%; SD = 11.5; median = 100 and post-test FEV<sub>1</sub> values: mean = 104.8%; SD = 1.2; median = 104) (Wilcoxon test *P* < 0.001). Moreover, patients' post-test FEV<sub>1</sub> values remain lower than those of the control group (Mann–Whitney *U*-test *P* < 0.01).

Table 1. Demographic characteristics of the evaluated patients (*N* = 200)

| Characteristic                                         | Value       |
|--------------------------------------------------------|-------------|
| Age, median (range)                                    | 11 (8–16)   |
| Gender: males, <i>n</i> (%)                            | 118 (59%)   |
| Rhinitis duration, median (range)                      | 2 (1–7)     |
| FEV <sub>1</sub> , median (range), % of predicted      | 89 (65–120) |
| FEF <sub>25–75%</sub> , median (range), % of predicted | 85 (60–120) |

FEV<sub>1</sub>, forced expiratory volume in the first second; FEF, forced expiratory flow at the 25% and 75% of the pulmonary volume.

Table 2. Number of the clinically relevant sensitizations of the evaluated patients

| Allergen         | Number |
|------------------|--------|
| House dust mites | 69     |
| Parietaria       | 55     |
| Grasses          | 36     |
| Birch            | 31     |
| Cat              | 7      |
| Dog              | 2      |

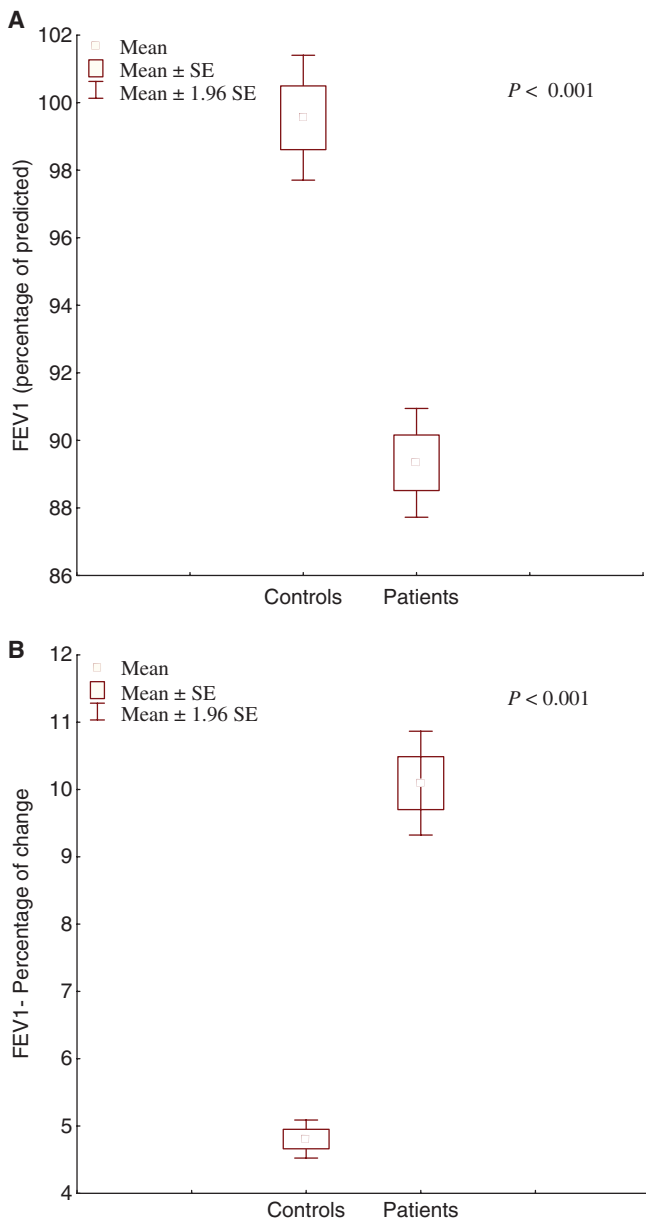


**Figure 1.** (A) Pretest forced expiratory volume in 1 s (FEV<sub>1</sub>) values in patients and controls. (B) Percentage change in FEV<sub>1</sub> values is significantly higher in patients vs controls. Error bars represent SD.

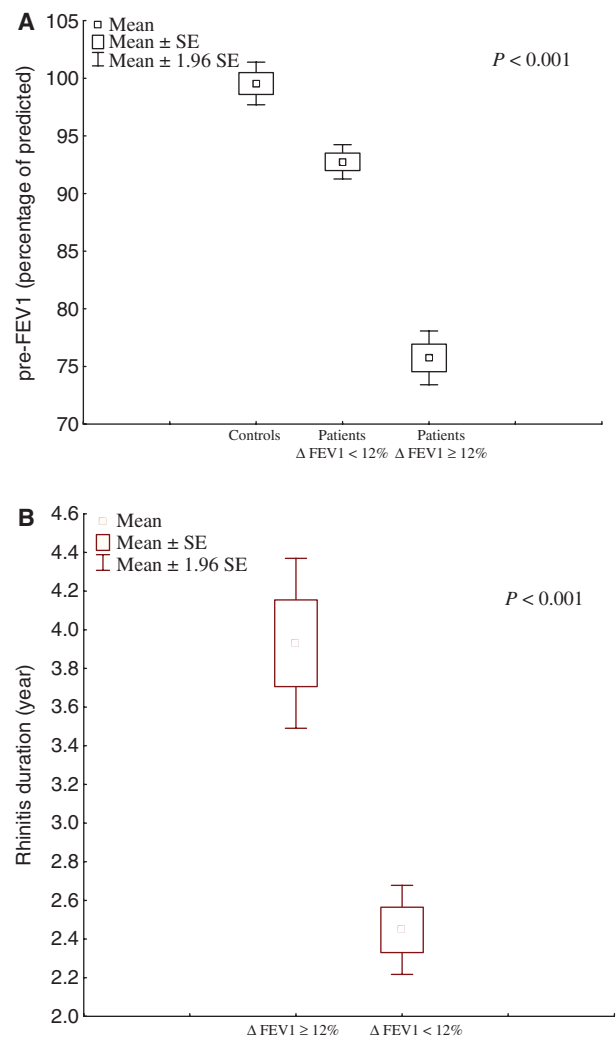


**Figure 2.** (A) Mean pretest FEV<sub>1</sub> values in the three groups of subjects: patients with a percentage change ( $\Delta$ ) of FEV<sub>1</sub> % of predicted  $\geq 12\%$ , patients with a  $\Delta$  FEV<sub>1</sub> < 12% and controls (all with a  $\Delta$  FEV<sub>1</sub> < 12%). (B) Rhinitis duration is significantly higher in patients with a percentage change ( $\Delta$ ) of FEV<sub>1</sub> % of predicted  $\geq 12\%$ .

The percentage of change in FEV<sub>1</sub> values (with respect to pretest values) is significantly higher in patients with respect to controls (Fig. 1, Panel B) (Mann–Whitney *U*-test;  $P < 0.0001$ ).

Among the patients, there were 43 (21.5%) subjects that showed a percentage of increase of FEV<sub>1</sub>  $\geq 12\%$  and therefore had reversibility, whereas 157 (78.5%) showed a percentage of increase of FEV<sub>1</sub> < 12%. None of the controls was ‘reversible’; in fact all the percentages of increase of FEV<sub>1</sub> in the control group of subjects were < 12%.

Mean FEV<sub>1</sub> values at baseline in the three groups of subjects are shown in Fig. 2 (Panel A): patients with a percentage change ( $\Delta$ ) of FEV<sub>1</sub> % of predicted  $\geq 12\%$  have lower levels of pretest FEV<sub>1</sub> either with respect to

Table 3. Description of allergen sensitization in the patients divided in two groups according to their reversibility

| Sensitisation to                  | Percentage change of FEV <sub>1</sub> (% of predicted) |                        | <i>P</i> |
|-----------------------------------|--------------------------------------------------------|------------------------|----------|
|                                   | ≥12% ( <i>N</i> = 43)                                  | <12% ( <i>N</i> = 157) |          |
| Perennial allergens, <i>N</i> (%) | 38 (88)                                                | 40 (25.5)              | 0.005    |
| Seasonal allergens, <i>N</i> (%)  | 5 (12)                                                 | 117 (74.5)             | 0.001    |

All percentages in round brackets are calculated over the total number of subjects reported at top of the column. All *P*-values in the table refer to the chi-square test.

patients with a  $\Delta$  FEV<sub>1</sub> < 12% (Dunn's test *P* < 0.01) or with respect to controls (Dunn's test *P* < 0.01) (Panel A). As shown in Fig. 2 (Panel B), rhinitis duration is significantly higher in patients with a percentage change ( $\Delta$ ) of FEV<sub>1</sub> ≥ 12% with respect to patient with a  $\Delta$  FEV<sub>1</sub> < 12%.

Description of allergen sensitization in the two groups of patients (patients with a  $\Delta$  FEV<sub>1</sub> ≥ 12% vs patients with a  $\Delta$  FEV<sub>1</sub> < 12%) is shown in Table 3; patients with  $\Delta$  FEV<sub>1</sub> ≥ 12% are more frequently positive to perennial allergens and are less frequently positive to seasonal.

## Discussion

Allergic rhinitis and asthma may be considered as a single syndrome involving two parts of the respiratory tract as surely documented by two elegant experimental studies (16, 17).

The present study investigated the response to the bronchodilation test in a large cohort of children with allergic rhinitis alone, such as perceiving only nasal symptoms. Several interesting findings have been observed in this survey.

First, this study provides evidence that a discrete percentage (> 20%) of children with allergic rhinitis show reversibility to bronchodilation test, such as an increase > 12% of basal FEV<sub>1</sub> values. Moreover, a relative bronchodilation has been observed also in patients without reversibility, such as < 12% of increase of basal FEV<sub>1</sub> values, and the increase percentage of FEV<sub>1</sub> values is significantly higher than in normal subjects. Therefore,

it appears conceivable to formulate the hypothesis that the response to bronchodilation test might be considered a further proof of bronchial impairment in allergic rhinitis.

Second, the response degree to bronchodilation test depends on basal FEV<sub>1</sub> values. Indeed, patients with reversibility had significant lower FEV<sub>1</sub> values than patients without reversibility. This issue underlines the concept that reversibility to bronchodilation test is associated with early bronchial airflow limitation, even though in presence of borderline FEV<sub>1</sub> values.

Third, reversibility is associated with longer duration of rhinitis. This finding confirms a previous study providing evidence that spirometric impairments are more frequent in patients with long lasting rhinitis (18). The duration of allergic rhinitis constitutes an important factor that promotes the development of bronchial involvement. The possible explanation of this phenomenon might depend on the allergic inflammation that persists over the time and tends to progress from the nose into the bronchi (6).

Fourth, the reversibility is associated with specific sensitizations, such as to perennial allergens. This fact confirms the previous outcome: mite allergy is characterized by the well-known concept of minimal persistent inflammation (19). The continuous exposure to causal allergen induces persistence of inflammation that may favour complications. In addition, it has been evidenced that also birch allergy is characterized by this phenomenon (20). Therefore, as in asthmatic patients also in rhinitis the response to bronchodilation test appears to be dependent on airway inflammation.

In addition, this study confirms the previous report in adults, even though the percentage of patients positive to the bronchodilation test was higher in adult population. This finding probably depends on the duration of allergic rhinitis: longer in adults.

In conclusion, this study provides the evidence that children with allergic rhinitis may quite frequently show reversibility to bronchodilation test. This event may account for early bronchial involvement as patients were perceiving nasal symptoms alone. The reversibility is also associated with lower basal FEV<sub>1</sub> values, longer duration of rhinitis, and sensitization to mites.

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