

LETTER TO THE EDITOR

CONSEQUENCES OF LONG-LASTING PERSISTENT ALLERGIC RHINITIS IN ADOLESCENTS

G.L. MARSEGLIA, M. GRIGNANI, P. CIVALLERO, B. COLOMBO¹, M. DI GIOACCHINO²,
A. MARCHI, A. PERRONE² and G. CIPRANDI¹

Dipartimento di Scienze Pediatriche, Università di Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia; ¹Department of Internal Medicine, Azienda Ospedaliera Universitaria San Martino, Genoa; ²Allergy Related Disease Unit, "G. d'Annunzio University" Foundation, Chieti, Italy

Received November 16, 2007 – Accepted March 6, 2008

While it is well known that asthma is characterized by airway remodelling, only few studies have investigated this issue in patients affected by allergic rhinitis (AR). The aim of the present study is to investigate functional and structural consequences of long-lasting persistent AR (PER) in a cohort of adolescents. Eighty patients, forty with short-lasting and forty with long-lasting PER were prospectively and consecutively evaluated both clinically and by performing skin prick test, nasal cytology, and rhinomanometry. Eosinophils were significantly higher in patients presenting with long-lasting PER rather than in those with short-lasting PER ($P < 0.0001$). The degree of inflammation was significantly associated with impaired nasal airflow ($r_s = -0.81$). This study provides evidence that adolescents with long-lasting PER may show a progressive worsening of nasal function depending on the inflammation.

Allergic rhinitis (AR) is characterized by typical symptoms, the most important being nasal obstruction, which is actually dependent on allergic inflammation (1). Nasal obstruction may be roughly evaluated subjectively, by the perception of air passage throughout the nose, and objectively, by measuring the nasal airflow through rhinomanometry (2). It has been highlighted that allergic inflammation markers, such as Th2-type cytokines and nasal eosinophils, correlate well with nasal airflow limitation (3). AR has been recently re-classified by the ARIA (Allergic Rhinitis and its Impact on Asthma) workshop (4). The new classification of "intermittent" (ITR) and "persistent" rhinitis (PER) considers symptom duration (days/week and consecutive weeks), symptom severity (mild or

moderate-severe), and impact on quality of life.

Moreover, AR is a common chronic disorder and is frequently associated with asthma as underlined by the ARIA document (4). It is acknowledged that a batch of structural changes marks asthma, as they are encompassed within the term "airway remodeling"; these changes include epithelial disruption, goblet cell hyperplasia, mucus gland hypertrophy, enhanced airway collagen deposition, airway myofibroblast transformation, increased matrix protein deposition, and smooth muscle hypertrophy and hyperplasia (5).

Nevertheless, some recent reviews pointed out the paucity of studies concerning the evaluation of structural changes in AR (6-8): in fact, even though all of them concern the morphologic issue, none has

Key words: adolescents, allergic rhinitis, nasal airflow, duration, eosinophils

Mailing address: Giorgio Ciprandi, M.D.
Semeiotica Medica I,
Padiglione 3,
A.O.U. San Martino,
Largo R. Benzi 10, I - 6132 Genoa, Italy
Tel: ++39 10 35331820 Fax: ++39 10 3537573
e-mail: gio.cip@libero.it

0394-6320 (2008)

Copyright © by BIOLIFE, s.a.s.

This publication and/or article is for individual use only and may not be further reproduced without written permission from the copyright holder. Unauthorized reproduction may result in financial and other penalties

actually investigated functional changes. Therefore, the purpose of this cross-sectional study is to relate functional and structural consequences of long-lasting persistent AR (PER) in a cohort of adolescents.

MATERIALS AND METHODS

Study design

Eighty adolescents (44 males and 36 females) with persistent allergic rhinitis were prospectively and consecutively evaluated. Their mean age was 16.4 years, with a minimum age of 14 and a maximum of 18 years. A detailed clinical history was taken and a complete physical examination was carried out.

To be enrolled in the study patients were required to have moderate or severe nasal obstruction. Patients reporting concomitant or past asthma symptoms (one or more of: persistent cough, wheezing, dyspnoea, and shortness of breathing, either diurnal or nocturnal) were excluded. Subjects with acute upper respiratory infections, anatomic nasal disorders (i.e. septum deviation), nasal polyps, and patients using nasal or oral corticosteroids or decongestants, antileukotrienes and antihistamines within the previous 4 weeks were also excluded.

A history of nasal symptoms and positive results to skin prick test were sufficient in order to make a diagnosis of AR, according to validated criteria (8).

Nasal scraping and rhinomanometry were performed in all subjects. The study was approved by the Institutional Review Board and informed consent was obtained from both parents of each patient.

Subjects

Patients were recruited on the basis of disease duration: the first group included patients presenting with short-lasting rhinitis (disease lasting for no more than 1 year) ($n=40$) and the second one included patients presenting with long-lasting rhinitis (disease lasting for at least 8 years) ($n=40$).

Symptoms

The "nasal obstruction" symptom was assessed through questions asked by the investigator and evaluated on the following scale: 0 = absent, 1 = mild (symptom was present but was not annoying nor troublesome), 2 = moderate (symptom was frequently troublesome but did not interfere with either normal daily activity or sleep), and 3 = severe (symptom was sufficiently troublesome to have interfered with normal daily activity or sleep).

Skin prick tests

Allergy was assessed by skin prick test; the subjects

were considered as allergic in the presence of sensitization to the most common classes of aeroallergens. The test was performed as stated by the European Society of Allergy and Clinical Immunology (9).

Nasal cytology

Nasal cytology was obtained by scraping the inferior turbinate head with a cotton swab, as described in previous reports (4-5).

Rhinomanometry

Nasal airflow was measured by active anterior electronic rhinomanometry (ZAN 100 Rhino Flow Handy II, ZAN, Messgeraete GmbH, Germany) according to validated criteria (3, 6-7). 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.

Statistical analysis and data definitions

Comparison of qualitative variables between the two groups of subjects (patients presenting with short-lasting versus long-lasting rhinitis) was made by chi-square test. Comparison of quantitative variables between two groups of subjects (patients with short-lasting versus long-lasting rhinitis) was made by means of the non-parametric Mann-Whitney U test, as the parameters were not normally distributed. Correlation between quantitative variables was evaluated by means of the non-parametric Spearman's correlation coefficient (r_s).

All tests were two sided and in order to be considered statistically significant, the p-value had to be inferior to 0.05. The package "Statistica release 6" (StatSoft Corp., Tulsa, OK, USA) was used to carry out all the analyses.

RESULTS

Eighty adolescents, 40 with short-lasting and 40 with long-lasting rhinitis, were included in the study.

As shown in Fig. 1, the number of nasal eosinophils was significantly higher (median: 16.5) in patients with long-lasting rhinitis compared to patients with short-lasting rhinitis (median: 12) ($P<0.0001$). Nasal airflow values were significantly inversely correlated with nasal eosinophils either when evaluated in short-lasting rhinitis ($r_s = -0.83$) or when evaluated in patients with long-lasting rhinitis ($r_s = -0.81$) (Fig. 2, panel A and B).

Moreover, median nasal airflow values were significantly lower in the long-lasting group when

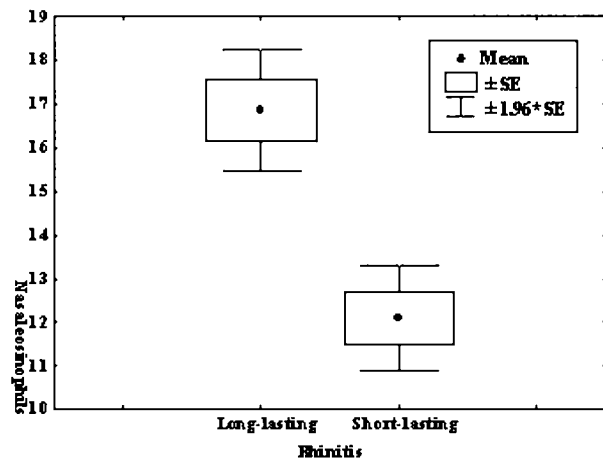


Fig. 1. Number of nasal eosinophils in adolescents with long-lasting and short-lasting persistent allergic rhinitis.

compared with the short-lasting one (348 ml/sec and 466 ml/sec respectively, $p < 0.0001$).

DISCUSSION

Allergic rhinitis is characterized by an inflammatory response that causes the occurrence of symptoms. In particular, nasal obstruction constitutes the symptom that expresses the most allergic inflammation, as it may be considered the key symptom in patients presenting with AR (11). Nasal obstruction may be evaluated both subjectively by symptom scoring and objectively by assessing airflow with rhinomanometry (2). Nasal airflow limitation may be reversible and the degree of recovery is associated to the grade of inflammation, for example, severe inflammation being characterized by a poor response to the test (10).

Allergic inflammation depends on allergen exposure and it persists until the patient inhales allergens, even though symptoms may not appear, in case of the so-called "minimal persistent inflammation" (12). The cascade of chronic inflammatory events determines the occurrence of structural changes which are more evident in lower airways where they have been deeply investigated.

Some recent reviews analyzed the features of airway remodeling in AR (6-8). Epithelial disruption and desquamation is poorly present in the nasal epithelium of patients with AR. Moreover, it seems

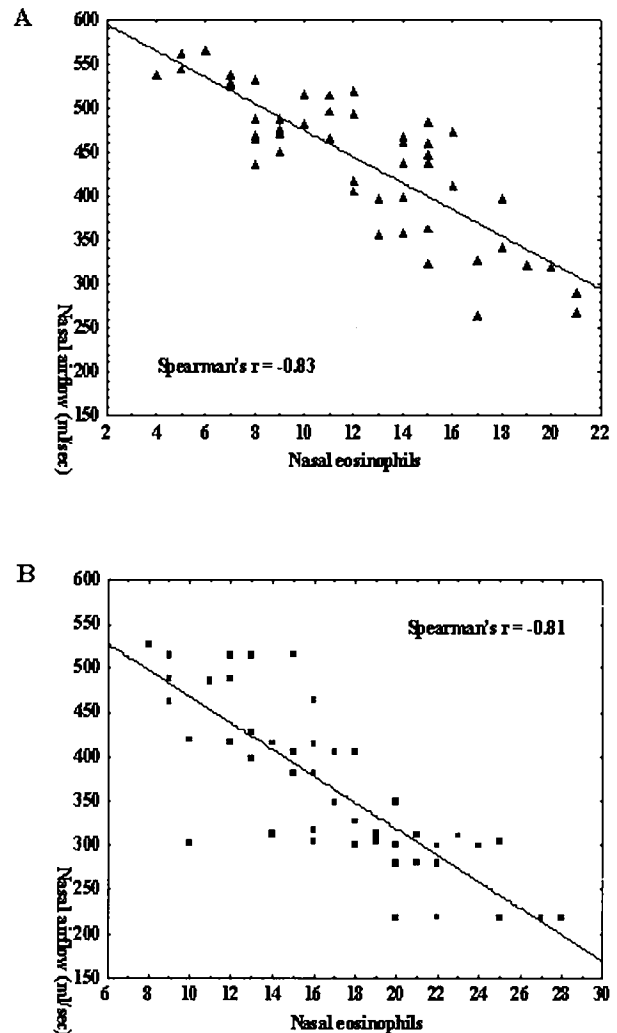


Fig. 2. Relationship between the number of nasal eosinophils and nasal airflow in adolescents with short-lasting (panel A) and long-lasting (panel B) persistent allergic rhinitis.

that there is some pseudo-thickening of the reticular basement membrane caused by collagen and fibrous protein deposition; nevertheless, this is true to a minor extent if compared to asthma (8). As for blood vessels, two recent studies provide evidence of increased expression of angiogenic markers in patients with pollen AR (13-14). Therefore, the most recent review concludes that airways remodeling exists in rhinitis, but it seems to be far less extensive

than in asthma (8). On the other hand, no study has investigated the morpho-functional consequences of nasal remodeling, while we have proof of it for the asthma model.

As a very recent study provided evidence that the duration of AR, as well as house dust mite sensitization, is a relevant risk factor for the worsening of FEV₁ (15), our study aims to evaluate functional and structural consequences of long-lasting persistent AR (PER) in a cohort of adolescents.

The first finding shows that the duration of PER may imply a more consistent inflammation grade, such as an increased number of nasal eosinophils.

Consequently, a significant limitation of nasal airflow can be detected in long-lasting PER patients. It appears evident that PER duration determines a worsening of nasal function, with a decrease in air passage throughout nasal cavities, and nasal inflammation. Indeed, the degree of nasal inflammation is significantly related to the impairment of nasal function.

A convincing explanation of this phenomenon might be associated to the persistence of allergic inflammation, a typical issue in patients presenting with PER (12). Chronic inflammation causes a characteristic anatomic feature: the hypertrophy of the turbinates. Hypertrophic turbinates are very frequently detectable in AR patients. An obvious consequence of turbinate enlargement is the reduction of nasal cavities which, in turn, causes airflow limitation.

Therefore, the present study points out the relevance of the progressive nasal airflow worsening that may depend on chronic remodeling. In addition, this phenomenon might be considered as a surrogate marker of nasal remodeling, mainly if turbinate hypertrophy is noticed.

In conclusion, this study provides evidence that adolescents presenting with PER may show a progressive worsening of nasal airflow, which varies depending on the duration of the disorder.

REFERENCES

1. Plaut M, Valentine MD. Allergic rhinitis. *N Engl J Med* 2005; 353:1934-9.
2. Kern EB. Committee report on standardization of rhinomanometry. *Rhinology* 1981; 19:231-46.
3. Ciprandi G, Cirillo I, Vizzaccaro A, Milanese M, Tosca MA. Nasal obstruction in patients with seasonal allergic rhinitis: relationships between allergic inflammation and nasal airflow. *Int Arch Allergy Immunol* 2004; 134:34-8.
4. Bousquet J, van Cauwenberge P, Khaltaev N, WHO Panel. Allergic rhinitis and Its Impact on Asthma. ARIA. In collaboration with the World Health Organization. *J Allergy Clin Immunol* 2001; 108: S1-S95.
5. Van Eerdekewegh P, Little RD, Dupuis J, Del Mastro RG, Falls K, Simon J. Association of the ADAM33 gene with asthma and bronchial hyper-responsiveness. *Nature* 2002; 418:426-33.
6. Shore SS. Modelling airway remodelling. The winner by a nose? *Am J Resp Crit Care Med* 2003; 168:910-18.
7. Salib RJ, Howarth PH. Remodelling of the upper airways in allergic rhinitis: is it a feature of the disease? *Clin Exp Allergy* 2003; 33:1629-34.
8. Bousquet J, Jacquot W, Vignola M, Bachert C, Van Cauwenberge P. Allergic rhinitis: a disease remodelling the upper airways? *J Allergy Clin Immunol* 2004; 113:43-50.
9. Dreborg S (Ed.). EAACI Subcommittee on Skin Tests. Skin tests used in type I allergy testing. Position Paper. *Allergy* 1989; 144(S10):22-41.
10. Ciprandi G, Cirillo I, Klersy C, Vizzaccaro A, Tosca MA, Marseglia GL. The response to decongestion test is associated with sensitizations and allergic inflammation. *Annals Allergy Asthma Immunol* 2006; 96:431-5.
11. Ciprandi G, Cirillo I, Klersy C, Marseglia GL, Caimmi D, Vizzaccaro A. Nasal obstruction is the key symptom in hay fever patients. *Otolaryngol Head Neck Surg* 2005; 133:429-34.
12. Ciprandi G, Buscaglia S, Pesce GP, Pronzato C, Ricca V, Permiani S. Minimal persistent inflammation is present at mucosal level in asymptomatic rhinitic patients with allergy due to mites. *J Allergy Clin Immunol* 1995; 96:971-7.
13. Kirmaz C, Ozbilgin K, Yuksel H, Bayrak K, Unlu H, Giray G. Increased expression of angiogenic markers in patients with seasonal allergic rhinitis. *Eur Cytokine Netw* 2004; 15:317-42.

14. Yuksel H, Kose C, Yilmaz O, Ozbilgin K, Degirmenci PB, Pinar F. Increased expression of tissue vascular endothelial growth factor and foetal liver kinase-1 receptor in seasonal allergic rhinitis and relevance to asthma component. Clin Exp Allergy 2007; 37:1183-8.
15. Ciprandi G, Cirillo I, Pistorio A. Impact of allergic rhinitis on asthma: effects on spirometric parameters. Allergy 2008; 63(3):255-60.