Evolution of patients with nonallergic rhinitis supports conversion to allergic rhinitis

Carmen Rondón, MD, PhD, Inmaculada Doña, MD, Maria J. Torres, MD, PhD, Paloma Campo, MD, and Miguel Blanca, MD, PhD *Malaga, Spain*

Background: Nonallergic rhinitis (NAR) affects a significant number of patients in clinical practice. However, the different entities involved within NAR require further study. Once allergy has been ruled out, most of these patients are not usually followed up in allergy clinics, despite the persistence of rhinitis symptoms. Thus few data are available concerning the natural evolution of these patients.

Objective: We sought to re-evaluate over time the severity, accompanying disorders, and possible allergen sensitizations in subjects with NAR.

Methods: A representative sample of 180 patients given diagnoses of NAR during 2000-2004 was re-evaluated in 2007 by using sociodemographic and clinical questionnaires, spirometry, skin prick testing, and measurement of specific IgE to common aeroallergens.

Results: Patients with NAR generally experienced worsening disease (52%), with an increase in the persistence (12%) and severity of nasal symptoms (9%) and new comorbidities (24%) over time. The most frequent comorbidities at the re-evaluation were asthma (increasing from 32% to 55%) and conjunctivitis (from 28% to 43%), followed by chronic rhinosinusitis. Sensitization to aeroallergens not present at the initial evolution was detected by means of skin prick testing, serum specific IgE measurement, or both in 24% of the patients.

Conclusions: Persistent moderate-to-severe rhinitis associated with asthma, conjunctivitis, or both and sensitization to aeroallergens are likely to appear at a later date in adults initially given diagnoses of NAR. A periodic re-evaluation of these patients might therefore be necessary. (J Allergy Clin Immunol 2009;123:1098-102.)

Key words: *Allergy, comorbidities, evolution, nonallergic, quality of life, rhinitis*

Abbreviations used
AR: Allergic rhinitis
ARIA: Allergic rhinitis and its impact on asthma
FEV_1: Forced expiratory volume in the first second
FVC: Forced vital capacity
NAPT: Nasal allergen provocation test
NAR: Nonallergic rhinitis
SPT: Skin prick test

Nonallergic rhinitis (NAR) affects a significant number of patients in clinical practice. The prevalence in the adult population with rhinitis varies from 23% to 70%,[1-3] affecting approximately 19 million subjects in the United States[4] and more than 200 million persons worldwide.[5] *Idiopathic rhinitis* is a term used for a group of rhinitis disorders, which include some NAR cases of unknown etiology that are diagnosed by exclusion.[6,7] Once an allergic cause has been ruled out by a negative skin prick test (SPT) response and a lack of serum specific IgE against aeroallergens, these patients are usually given diagnoses of NAR, and in our clinic the majority of them are followed up by general practitioners. Few data are therefore available about the natural evolution of these patients.[5]

The majority of patients with NAR have persistent symptoms with no well-defined season during the year.[2,3,6] The severity has been reported to be equal to or less than that of allergic rhinitis (AR),[2,3] although the number of studies is limited.

Both AR and NAR are commonly associated with asthma.[7-9] This association supports the concept of "one airway, one disease."[10] Rhinitis, mainly the allergic type, can also be associated with other comorbidities, including conjunctivitis, sinusitis, and otitis media.[6] These associations not only produce an effect on the quality of life of the patients but also represent an important economic health burden.[11]

Evidence indicates that subjects with NAR can have local production of IgE antibodies and are therefore considered allergic. This concept has been defined as "entopy"[12] or "local AR."[13] Whether in the long run these patients will have systemic evidence of allergy is a matter of research. Thus to examine this possibility, a group of subjects with NAR was re-evaluated at a later time by repeating the SPT and the study of serum specific IgE. The persistence and severity of the symptoms and the presence and effect of comorbidities were also analyzed. Results indicated that an important group of patients had *de novo* aeroallergen sensitization, suggesting that patients with NAR might evolve to AR.

METHODS

Study approach

To determine whether patients with NAR could experience new comorbidities, as well as AR, as part of the natural evolution of the disease, we randomly selected 180 patients given diagnoses of NAR in our allergy clinic between 2000 and 2004. All the patients had rhinitis symptoms and a negative SPT response

From the Allergy Service, Carlos Haya Hospital.
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Reprint requests: Carmen Rondón, MD, PhD, Allergy Service, Hospital Civil, pabellón 6, sótano, Plaza del Hospital Civil, 29009 Málaga, Spain. E-mail: carmenrs61@gmail.com.
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and serum specific IgE at the first evaluation. The patients were selected from a total of 16,000 adult rhinitis subjects seen over this period, of whom 3,000 had NAR. In July and August 2007, 230 of these were randomly selected for re-evaluation from a nameless database and asked to participate in the study, 180 (88%) of whom accepted and completed the study. Patients with NAR were screened for eligibility and randomized by means of simple random sampling with a computer-generated list. The study was approved by the institutional review board, and all participants provided written informed consent.

Clinical questionnaire and medical interview

Data on the initial evaluation were extracted from the medical history obtained at the patient's first visit to our center and included a clinical questionnaire and a complete respiratory and allergy evaluation with a physical examination, spirometry, and allergy testing (SPTs and serum total and specific IgE measurements). No nasal allergen provocation test (NAPT) was carried out. At the re-evaluation, the same clinical questionnaire as that administered at the initial evaluation and a new detailed sociodemographic questionnaire were applied to obtain information about the persistence and severity of the disease, the symptoms, the effect, and the comorbidities. Before the survey, its content was run as a pilot study with a limited number of other patients with rhinitis.

NAR was defined by the presence of 2 or more nasal symptoms (sneezing, itching, rhinorrhea, or nasal obstruction) plus a negative SPT response and serum specific IgE level to aeroallergens.

The persistence and severity of NAR were classified according to the Allergic Rhinitis and Its Impact on Asthma (ARIA) 2008 updated criteria as intermittent or persistent and as mild or moderate to severe.[14] *Intermittent* was defined as symptoms that were present on less than 4 days a week or for less than 4 consecutive weeks. If the symptoms were present on more than 4 days a week or for more than 4 consecutive weeks, NAR was classified as *persistent*. *Mild* was defined as symptoms that were present but not reported to be troublesome, and none of the following were impaired: sleep; daily activities; leisure, sport, or both; and school or work attendance. The rest of the patients with NAR were classified as having moderate-to-severe disease.

Chronic rhinosinusitis was defined according to the criteria for epidemiologic studies in the "European position paper on rhinosinusitis and nasal polyps 2007"[15] as the presence of 2 or more symptoms, one of which should be either nasal obstruction or nasal discharge with or without facial pain/pressure and reduction or loss of smell for more than 12 weeks.

SPTs and specific IgE measurement

SPTs were performed at both the initial and final evaluations with the same panel of the most prevalent aeroallergens, including *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Lepidoglyphus destructor*, *Blomia tropicalis*, *Poa*, *Phleum*, *Lolium*, *Casuarina*, *Eucalyptus*, *Cupressus arizonica*, *Platanus*, *Olea europea*, *Helianthus*, *Chenopodium*, *Plantago*, *Artemisia*, *Parietaria judaica*, *Salsola kali*, *Rumex*, *Ricinus*, *Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, *Penicillium notatum*, and animal epithelia of dog, cat, and hamster (ALK-Abelló, Madrid, Spain). Histamine (10 mg/mL) and saline were used as positive and negative controls, respectively. A positive SPT response was defined as a wheal diameter of 3 mm or larger to at least 1 of these aeroallergens. The participants were requested to stop taking any medications that contained antihistamine at least 8 days before skin testing.

In the initial and final evaluation serum specific IgE to *D pteronyssinus*, *O europea*, grass, *Cupressus arizonica*, *P judaica*, *Alternaria alternata*, *Aspergillus fumigatus*, cat, and dog were determined in patients with a negative SPT response by means of ImmunoCAP (Phadia, Uppsala, Sweden), according to the manufacturer's instructions. A value of 0.35 kU/L or greater was considered positive.

Lung function tests

Flow-volume spirometry was performed with a Spirobank spirometer (Medical International Research, Rome, Italy) according to American Thoracic Society recommendations.[16] The decreases in forced expiratory volume in the first second (FEV_1) and FEV_1/forced vital capacity (FVC) ratio were expressed as a percentage of the predicted value and were used to quantify the degree of airway obstruction.

TABLE I. Sociodemographic and clinical data of patients with NAR at the initial evaluation

	Patients with NAR (n = 180)
Age	
Mean ± SD	43.80 ± 13.72
<35 y (%)	35
35–55 y (%)	40
>55 y (%)	25
Rhinitis duration (y), mean ± SD	12.91 ± 9.83
Sex (%)	
Male	40
Female	60
Smoking status (%)	
Nonsmoking	76
Smoking	24
Family history of atopy (%)	
Yes	32
No	68
Dwelling (%)	
City	54
Rural	46
Coast	63
Inland	37
Triggering factors (%)	
House dust	36
Pollen exposure	22
Irritant	20
Temperature changes	15
Animal dander	14
Others	5

Statistical analysis

Descriptive statistics (frequency, mean, median, SD, and range) were used to describe the population at the first and second evaluations. χ^2 analysis was used to test differences for nominal variables, and *t* tests were used for interval variables with 2 groups. A *P* value of less than .05 was considered significant. The data were analyzed with the statistical software package SPSS for Windows 15.0 (SPSS, Inc, Chicago, Ill).

RESULTS

Clinical questionnaire and medical interview

The sociodemographic data are shown in Table I. A total of 180 patients completed the whole evaluation. Their age ranged from 19 to 69 years, with an average of 49 years and a mean of 12.91 years' evolution of rhinitis. There was a predominance of women (male/female ratio of 1:1.5), and most were nonsmokers, had no family history of atopy, and lived in the city or on the coast (Table I). The 50 (22%) nonparticipating subjects were 31 women and 19 men. There were no significant demographic or clinical differences between the enrolled and nonenrolled subjects.

At the first evaluation, 117 (65%) patients with NAR reported responding to at least 1 specific (environmental pollen, house dust exposure, or animal epithelia) or nonspecific triggering factor (irritant, temperature change, or others). House dust exposure was the most prevalent triggering factor, reported by 36% of patients with NAR. There were no differences between the patients according to whether they reported specific or nonspecific triggering factors (Table I).