

# Evolution of patients with nonallergic rhinitis supports conversion to allergic rhinitis

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**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 ■■■■;■■■:■■■-■■■.)

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

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%,<sup>1-3</sup> affecting approximately 19 million subjects in the United States<sup>4</sup> and more than 200 million persons worldwide.<sup>5</sup> *Idiopathic rhinitis* is a term

## Abbreviations used

AR: Allergic rhinitis  
ARIA: Allergic rhinitis and its impact on asthma  
FEV<sub>1</sub>: Forced expiratory volume in the first second  
FVC: Forced vital capacity  
NAPT: Nasal allergen provocation test  
NAR: Nonallergic rhinitis  
SPT: Skin prick test

used for a group of rhinitis disorders, which include some NAR cases of unknown etiology that are diagnosed by exclusion.<sup>6,7</sup> 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.<sup>5</sup>

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

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

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”<sup>12</sup> or “local AR.”<sup>13</sup> 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 and serum specific IgE at the first evaluation. The patients were

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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.<sup>14</sup> *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"<sup>15</sup> 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.<sup>16</sup> The decreases in forced expiratory volume in the first second (FEV<sub>1</sub>) and FEV<sub>1</sub>/forced vital capacity (FVC) ratio were

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

|                                      | Patients with NAR<br>(n = 180) |
|--------------------------------------|--------------------------------|
| Age                                  |                                |
| Mean $\pm$ SD                        | 43.80 $\pm$ 13.72              |
| <35 y (%)                            | 35                             |
| 35–55 y (%)                          | 40                             |
| >55 y (%)                            | 25                             |
| Rhinitis duration (y), mean $\pm$ SD | 12.91 $\pm$ 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                              |

expressed as a percentage of the predicted value and were used to quantify the degree of airway obstruction.

### Statistical analysis

Descriptive statistics (frequency, mean, median, SD, and range) were used to describe the population at the first and second evaluations.  $\chi^2$  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).

**TABLE II.** Clinical evolution of patients with NAR

|                                    | Patients with NAR (n = 180) |               |         |
|------------------------------------|-----------------------------|---------------|---------|
|                                    | FE (%)                      | SE (%)        | P value |
| ARIA classification (%)            |                             |               |         |
| Intermittent                       | 23                          | 11            | .002    |
| Persistent                         | 77                          | 89            | .002    |
| Mild                               | 47                          | 38            | NS      |
| Moderate-to-severe                 | 53                          | 62            | NS      |
| Clinical evolution (%)             |                             |               |         |
| Disappearance                      | —                           | 0             | NA      |
| Improvement                        | —                           | 8             | NA      |
| Worsening                          | —                           | 52            | NA      |
| No change                          | —                           | 40            | NA      |
| Hyposmia (%)                       | 7                           | 18            | <.05    |
| Comorbidities (%)                  |                             |               |         |
| Asthma                             | 52                          | 76            | .001    |
| Conjunctivitis                     | 32                          | 55            | .001    |
| Nasal polyps                       | 28                          | 43            | .003    |
| Nasal polyps                       | 4                           | 9             | NS      |
| Chronic rhinosinusitis             | 0                           | 7             | <.05    |
| Aspirin hypersensitivity           | 2                           | 6             | NS      |
| Total IgE (IU/mL)*                 | 63.43 ± 78.41               | 59.84 ± 83.52 | NS      |
| FEV <sub>1</sub> /FVC % predicted  |                             |               |         |
| >80%                               | 90                          | 80            | <.05    |
| 70% to 80%                         | 4                           | 3             | NS      |
| <70%                               | 6                           | 17            | <.05    |
| FEV <sub>1</sub> % predicted       |                             |               |         |
| >80%                               | 89                          | 78            | <.05    |
| 70% to 80%                         | 6                           | 17            | <.05    |
| <70%                               | 5                           | 5             | NS      |
| Aeroallergen sensitization (%)     |                             |               |         |
| SPT response, positive             | 0                           | 24            | .001    |
| Specific IgE measurement, positive | 0                           | 15            | .001    |

FE, First evaluation; SE, second evaluation; ARIA, Allergic Rhinitis and Its Impact on Asthma; NS, not significant; NA, not applicable.

\*Data represent the mean ± SD.

The clinical evolution of the patients is shown in Table II. According to the ARIA criteria, in the second evaluation the majority of the patients with NAR reported persistent symptoms (89%) and moderate-to-severe rhinitis affecting their quality of life (62%). Hyposmia was present in 18% of the subjects. Worsening symptoms were reported by 52% of the patients, with an increase in the persistence (increased by 12%,  $P = .002$ ) of nasal symptoms and new comorbidities (increased by 24%,  $P = .001$ ). Asthma was the most frequent associated condition (increased by 23%,  $P = .001$ ), followed by conjunctivitis (increased by 15%,  $P = .003$ ). No significant differences were found in severity, effect on quality of life, or comorbidities between persistent and intermittent NAR.

Comparison between those who developed AR and those who did not showed a similar presence of specific triggering factors, comorbidities, persistence, and rhinitis severity (Table III). However, comparison of specific symptoms showed that rhinorrhea was more bothersome in patients with NAR ( $P < .05$ ) and sneezing was bothersome in patients with AR ( $P = .001$ ). Nasal obstruction (patients with NAR) and sneezing (patients with AR) were the symptoms that patients most wanted to prevent (Table III). When nonspecific triggering factors were compared, we detected that only irritant smells were more frequent in patients with NAR ( $P < .05$ ), whereas temperature changes were similar in both groups. The distribution of comorbidities at the final evaluation was similar in the patients with NAR who remained negative and those who had

**TABLE III.** Comparison between patients with NAR and those with AR: Allergic Rhinitis and Its Impact on Asthma classification of rhinitis, frequency of nasal symptoms that patients most wanted to prevent, and triggering factors

|                         | Patients with NAR<br>(n = 137) | Patients with AR<br>(n = 43) | P<br>value |
|-------------------------|--------------------------------|------------------------------|------------|
| ARIA classification (%) |                                |                              |            |
| Intermittent            | 13                             | 15                           | NS         |
| Persistent              | 87                             | 85                           | NS         |
| Mild                    | 36                             | 35                           | NS         |
| Moderate-to-severe      | 64                             | 65                           | NS         |
| Nasal symptoms (%)      |                                |                              |            |
| Itching                 | 16                             | 21                           | NS         |
| Sneezing                | 31                             | 58                           | .001       |
| Rhinorrhea              | 51                             | 30                           | <.05       |
| Obstruction             | 58                             | 49                           | NS         |
| Triggering factors (%)  |                                |                              |            |
| House dust exposure     | 33                             | 43                           | NS         |
| Pollen exposure         | 20                             | 26                           | NS         |
| Irritant                | 27                             | 9                            | <.05       |
| Temperature changes     | 16                             | 13                           | NS         |
| Animal dander           | 13                             | 17                           | NS         |
| Others                  | 5                              | 5                            | NS         |

ARIA, Allergic Rhinitis and its Impact on Asthma; NS, not significant.

**TABLE IV.** Distribution of comorbidities in patients with NAR and those with AR

|                            | Patients with NAR<br>(n = 137) | Patients with AR<br>(n = 43) | P<br>value |
|----------------------------|--------------------------------|------------------------------|------------|
| Asthma (%)                 | 55                             | 60                           | NS         |
| Conjunctivitis (%)         | 39                             | 56                           | <.05       |
| Nasal polyps (%)           | 9                              | 7                            | NS         |
| Chronic rhinosinusitis (%) | 7                              | 7                            | NS         |
| Aspirin sensitization (%)  | 9                              | 0                            | <.05       |

NS, Not significant.

AR, except for conjunctivitis, which was reported more frequently in patients with AR (56%,  $P < .05$ ), and aspirin hypersensitivity, which was only reported by patients with NAR (9%,  $P < .05$ ; Table IV). Three subgroups of patients were defined according to the duration of rhinitis (<6 years, 6–14 years, and >14 years). When we examined the presence of new comorbidities at the second evaluation, no significant differences in new comorbidities were detected between these subgroups.

### SPTs and specific IgE measurement

*De novo* sensitization to aeroallergens was detected by means of SPTs, serum specific IgE measurements, or both in 21% and 15% of patients, respectively ( $P = .001$ ). Allergic sensitization to pollens was the most prevalent (18%), followed by house dust mite and animal epithelia (Fig 1). The most frequent specific aeroallergen was *D pteronyssinus* (11.54%), followed by *O europeae* (7.69%), *C arizonica* (5.13%), and grass, dog, and cat epithelia (3.85% each). These results were in agreement with the triggering factors reported by the patients and the seasonality of their symptoms. No significant differences were found in allergy sensitization between the patients with persistent and those with intermittent NAR.

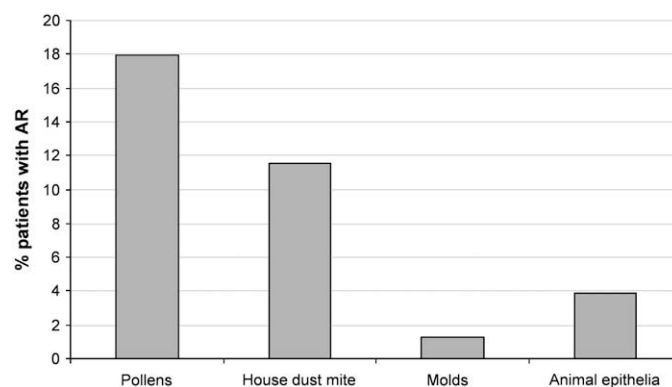


**FIG 1.** Incidence of new aeroallergen sensitization in patients with AR detected by means of SPTs, serum specific IgE measurements, or both.

### Lung function tests

The majority of patients originally showed normal lung function, with an FEV<sub>1</sub> and FEV<sub>1</sub>/FVC >80% of predicted value (Table II). At the second evaluation, 11% of patients with NAR showed a decrease in FEV<sub>1</sub> from >80% to 70%-80% of predicted value ( $P < .05$ ), with a decrease in the FEV<sub>1</sub>/FVC ratio from >80% to < 70% in 10% of the patients ( $P < .05$ ). The proportion of patients with bronchial obstruction and an FEV<sub>1</sub> of less than 70% of predicted value remained around 5% at the second evaluation.

### DISCUSSION

The clinical evaluation of the persistence and severity of rhinitis showed that the majority of patients with NAR reported persistent and moderate-to-severe symptoms at the same frequency as the patients with AR. These data demonstrate that NAR is no less important in severity or persistence than AR, as shown in previous studies.<sup>3,6</sup> In contrast with these results, Bachert et al<sup>2</sup> reported in a questionnaire survey in Belgium that patients with AR had more persistent and severe symptoms than patients with NAR. The great heterogeneity of patients with idiopathic rhinitis might explain the different clinical<sup>2,3,6</sup> and histologic<sup>17-20</sup> results. Further studies including different subsets of idiopathic rhinitis might help elucidate this question.

Although it is common to find that patients with NAR might react to nonspecific environmental triggers, such as temperature changes, humidity, and exposure to tobacco smoke, perfumes, strong odors, or spicy foods,<sup>5,6</sup> few data are available about how these patients might react to specific triggering factors. In this study we found no significant differences between specific and nonspecific triggers. In fact, 2 potential specific triggers, house dust and pollen exposure, were the most frequently reported by the patients with NAR. These findings could indicate the presence of an undetected sensitization, a local AR with nasal synthesis of IgE,<sup>12,21</sup> and/or a misattribution of symptoms by patients caused by nonspecific nasal hyperresponsiveness (temperature or weather changes, irritant odorants, or others). Clarification of this question would require a nasal provocation test with allergens<sup>21,22</sup> and with nonspecific triggers,<sup>23-25</sup> as well as measurement of local nasal-specific IgE levels.<sup>21</sup> The NAPT is a useful tool for diagnosis and pathophysiologic studies in both patients with idiopathic rhinitis<sup>13,21,22</sup> and those with AR,<sup>26,27</sup> but responses to NAPTs evaluated only based on nasal symptom scores or performed with multiallergens in one session might result in false-positive results that are not reproducible.<sup>28</sup> To

obtain a good level of accuracy, the response to the NAPT could be monitored by using 2 parameters, nasal symptom scores and objective data of nasal obstruction (acoustic rhinometry, inspiratory peak flow, or anterior rhinomanometry), as well as attempting to evaluate the existence of immediate, late, or dual responses to the NAPT by using just 1 allergen per session.<sup>13,21,22</sup>

AR has a large effect on the quality of life of patients, affecting sleep and social, educational, and professional areas.<sup>6,12,29,30</sup> However, few data are available about the importance of the social effect of NAR.<sup>5</sup> In our study 64% of the patients with NAR reported moderate-to-severe rhinitis affecting their quality of life. Further studies with generic and disease-specific questionnaires on quality of life are needed to assess the real state of this common disease.

After a long disease course, 52% of the patients with NAR reported worsening and 8% reported an improvement, but no cases were reported of spontaneous disappearance. In contrast, previous studies carried out in patients with AR found a better evolution, with a higher rate of improvement (39%)<sup>1</sup> and disappearance of rhinitis (1% to 10%).<sup>1,31,32</sup>

Patients with NAR and AR may present similar nasal symptoms, but there are a few distinct features that might help differentiate them.<sup>6</sup> When we compared both groups, we found that rhinorrhea was more severe in patients with NAR and sneezing was more severe in patients with AR. In agreement with previous studies, rhinorrhea and nasal obstruction were the symptoms that patients with NAR most wanted to prevent.<sup>3,33</sup>

Evidence exists that both AR and NAR are often associated with asthma.<sup>2-8</sup> This association has been reported to be more prevalent in patients with AR than in patients with NAR.<sup>2,3</sup> AR can also be associated with other comorbidities, such as conjunctivitis, sinusitis, and otitis media.<sup>6</sup> NAR has also been found to be associated with sinusitis,<sup>2,3</sup> skin allergy,<sup>2</sup> food allergy, and headache.<sup>2,3</sup> Our study found that asthma (32%) and conjunctivitis (28%) were the most frequent entities associated with NAR at the initial evaluation. An interesting finding was the increase in comorbidities detected in the second evaluation. Patients with NAR reported more asthma (increasing from 32% to 55%) and conjunctivitis (increasing from 28% to 43%) than at the initial evaluation. These patients also showed impairment in lung function over time, with an increase in the number of patients with a low FEV<sub>1</sub> or FEV<sub>1</sub>/FVC ratio and asthma. The prevalence of the other comorbidities evaluated (nasal polyps, chronic rhinosinusitis, and aspirin hypersensitivity) also increased at the final evaluation, although not significantly so.

Another interesting finding was *de novo* aeroallergen sensitization in 24% of patients with NAR, with the highest positivity to pollens followed by house dust mite and animal epithelia. We found no differences in association with asthma, severity, or effect on quality of life between the patients with NAR and those with AR. Asymptomatic IgE sensitization has been reported as a risk factor for the development of AR.<sup>34</sup> However, few data are available on the natural history of NAR or about its progression toward AR.<sup>34,35</sup> Bodtger et al<sup>34</sup> observed a positive trend for later sensitization to pollen in patients with NAR with pollen-related rhinitis, but the association was not significant. One reason for this detection of a lower rate of *de novo* sensitization could be that only serum specific IgE measurement was performed but no SPTs. Previous studies have shown that the serum specific IgE test is less sensitive than SPTs for detecting aeroallergen sensitization.<sup>36,37</sup> In our study SPT responses were positive in 21% and specific IgE measurements were positive in 15% of patients with NAR with aeroallergen-related symptoms.

Whether a certain proportion of these patients had only a nasal allergic response cannot be ascertained, but previous results from our group suggest that this percentage might be greater than 50%.<sup>13,17</sup> Comorbidities were similar in patients with NAR and AR, although aspirin hypersensitivity was only found in patients with NAR.

In conclusion, this study confirms that *de novo* sensitization to aeroallergens, new comorbidities, and worsening in the persistence, severity, and effect on quality of life are frequent in the natural evolution of adults with NAR. NAR is a common and important health care problem associated with serious conditions, such as asthma, nasal polyps, or aspirin hypersensitivity. The natural evolution and heterogeneity of NAR warrant a clinical and allergologic re-evaluation over time and the undertaking of prospective studies to define more accurately the natural evolution of these patients.

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**Clinical implications: Patients with NAR need to be evaluated over time to identify new comorbidities, including the appearance of AR.**

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