

Follow-up study in local allergic rhinitis shows a consistent entity not evolving to systemic allergic rhinitis

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Background: Local allergic rhinitis (LAR) is a common disease that affects 25.7% of the rhinitis population and more than 47% of patients previously diagnosed with nonallergic rhinitis. Whether LAR is the first step in the natural history of allergic rhinitis (AR) with systemic atopy or a consistent entity is unknown.

Objective: The aim was to evaluate the natural history of a population with LAR of recent onset and the development of AR and asthma.

Methods: A prospective 10-year follow-up study with initial cohorts of 194 patients with LAR of recent onset and 130 healthy controls is being undertaken. A clinical-demographic questionnaire, spirometry, skin prick test, and specific IgE to aeroallergens were done yearly. Nasal allergen provocation tests with *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Olea europea*, and a mix of grass pollen were performed at baseline and after 5 years.

Results: At disease onset, most of the patients with LAR had moderate-to-severe persistent-perennial rhinitis; conjunctivitis and asthma were the main comorbidities (51.1% and 18.8%, respectively), and *D pteronyssinus* was the most relevant aeroallergen (51.1%). After 5 years of follow-up, a worsening of rhinitis was detected in 26.2%, with an increase in symptom persistence and severity, and new associations with conjunctivitis and asthma. Atopy was detected by skin prick test and/or serum specific-IgE in patients with LAR (6.81%) and in controls (4.5%).

Conclusions: This study shows a similar rate of development of systemic atopy in LAR and controls, which suggests that LAR is an entity well differentiated from AR. To determine the natural course of LAR more precisely, this study is in progress to complete 10 years of follow-up. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: Allergic rhinitis, local allergic rhinitis, natural history, nasal allergen provocation test, systemic atopy

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Abbreviations used

AR: Allergic rhinitis

DP: *Dermatophagoides pteronyssinus*

LAR: Local allergic rhinitis

NAPT: Nasal allergen provocation test

sIgE: Specific IgE

SPT: Skin prick test

VAS: Visual analog scale

Different studies have shown that local allergic rhinitis (LAR) is a common allergic respiratory disease in the rhinitis population. The prevalence in adult patients with rhinitis has reached 25.7%¹ and exceeded 47% in patients previously diagnosed with nonallergic rhinitis.²⁻⁶ Studies in progress have shown similar data in different populations.^{7,8} The clinical and immunologic characteristics of LAR show that the majority of patients with LAR and patients with allergic rhinitis (AR) have persistent perennial rhinitis symptoms, frequently associated with conjunctivitis and asthma, and more than 36% of subjects with LAR report rhinitis onset in childhood.¹ The immunologic phenotype of LAR is characterized by local production of specific IgE (sIgE),^{4,5,9,10} a nasal cellular T_H2 immune response during natural exposure to aeroallergens^{3-5,11,12} and a positive response to nasal allergen provocation test (NAPT)^{1,2,4-10} with a negative skin prick test (SPT) and nondetectable serum sIgE. In addition, local production of sIgE, as well as tryptase and eosinophil cationic protein release, occurs after allergen challenge.^{9,10} Important studies also have demonstrated an increase in local free light chain expression in nasal mucosa of patients with nonallergic rhinitis,^{13,14} and class switching to IgE in patients with chronic rhinosinusitis and nasal polyps.¹⁵ However, important questions about the natural history of this newly recognized entity need to be explored. Is LAR the first step in the development of AR with systemic atopy, or does it represent a distinct phenotype with an independent natural history? Is there an equivalent to the atopic march in the LAR population, with an evolution toward asthma?¹⁶

The aim of this study was to follow a large series of patients with LAR and healthy controls over a long time to evaluate the natural history of LAR and the development of AR and/or asthma over time. The present work provides the results of the first 5 years of follow-up. Analysis of our data shows that similar rates of adult patients with LAR and healthy controls developed systemic atopy, which suggests that LAR and AR may be 2 independent entities. To better define the consistency of these results, a longer follow-up study is currently in progress.

METHODS

Study subjects

An initial 10-year follow-up study, divided into 2 phases of 5 years, was designed to investigate the natural history of LAR and its possible conversion to AR with systemic atopy and the association with asthma over time. The required sample size with a significance level of 95%, a study power of 80%, and 20% losses, was 179 subjects in the case cohort (patients with LAR) and 129 in the normal subjects (healthy controls). A total of 194 patients with LAR who were diagnosed between 2005 and 2006 in the allergy unit of Carlos Haya Hospital and 130 age- and sex-matched healthy controls were finally included. Carlos Haya Hospital is a tertiary care center that covers the city and the surrounding area, with a catchment population of 1,500,000 people. Because there are no primary or secondary allergy centers in our system, almost all subjects with suspected AR are referred to us for evaluation. Healthy controls were obtained from the same area and consisted of nonrelated friends, neighbors, or persons who accompany the study subject. The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committees. All the participants and parents of patients younger than 16 years of age were informed and signed the corresponding informed consent.

All the patients with LAR were diagnosed consecutively at their first visit. They had to have had a recent onset of the disease, with a history of rhinitis no longer than 2 years. Patients with immunologic diseases were excluded as well as patients younger than 14 years old because the hospital referral system only covers subjects older than 14 years of age. LAR was diagnosed by the presence of a suggestive clinical history plus a positive NAPT response to at least one aeroallergen and a negative SPT and serum sIgE. A detailed, self-administered demographic and clinical questionnaire, physical examination, spirometry, SPTs, and serum total IgE and sIgE measurements were performed yearly throughout the study period. NAPT with *Dermatophagoides pteronyssinus* (DP), *Alternaria alternata*, *Olea europea*, and a mix of grass pollen were performed at the initial evaluation and after 5 years of follow-up.

Demographic and clinical data

The demographic and clinical questionnaire was similar to that used at our previous evaluation for the nonallergic rhinitis study.¹⁷ The main items were personal demographic data, family history of atopy, smoking habits, profession, environmental conditions, structural features of the house, triggering factors of nasal symptoms, keeping domestic animals, months with nasal symptoms, persistence and severity of the rhinitis, presence of individual nasal symptoms, comorbidities, and subjective perception of disease evolution (disappearance, improvement, no change, worsening), health related to the rhinitis (excellent, very good, good, normal, bad), and impairment of quality of life (none, mild, moderate, severe). The use of medical emergency services due to severe symptoms of rhinitis and/or conjunctivitis (with moderate or severe chemosis) or asthma attacks triggered by natural exposure to aeroallergens were also included.

Different types of rhinitis were defined according to the time of exposure to the allergen and to the persistence and severity of symptoms. When depending on the time of exposure, rhinitis was divided into "perennial" or "seasonal." The persistence of rhinitis symptoms was classified according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines¹⁸ as "intermittent" (symptoms present <4 d/wk and/or for <4 consecutive weeks), and "persistent" (symptoms present ≥4 d/wk and for ≥4 consecutive weeks). The severity was defined by following the modified ARIA severity classification¹⁹: the number of impaired items (sleep; daily activities, sport, leisure; work or school performance; and troublesome symptoms) was used to grade the rhinitis severity as "mild" (no affected items), "moderate" (1-3 affected items), or "severe" (4 affected items). "Local allergic rhinitis" or "LAR" was defined by the presence of a suggestive clinical history plus a positive NAPT response and a negative SPT and serum sIgE. "Systemic atopy" was defined by the demonstration of a positive SPT or serum sIgE antibodies to at least one of the aeroallergens tested. "Comorbidities" were defined as medical conditions that exist simultaneously with rhinitis. Asthma was diagnosed clinically by the presence of recurrent symptoms of wheezing, shortness of breath, cough, and the demonstration of objective signs of reversible airway obstruction.²⁰

SPT and serum total IgE and serum sIgE

The SPTs were performed with a wide panel of allergens, including those most prevalent in our area: house dust mite (DP, *Dermatophagoides farinae*, *Lepidoglyphus destructor*), pollens (*Phleum*, *Lolium*, *Cupressus*, *Platanus*, *Olea*, *Chenopodium*, *Plantago*, *Artemisia*, *Parietaria*, and *Salsola kali*), molds (*Alternaria*, *Aspergillus*, *Cladosporium*, and *Penicillium*) and animal epithelia (dog, cat, and hamster) (ALK-Abelló, Madrid, Spain). Total and sIgE in serum to the same panel of aeroallergens evaluated in the SPT were determined by fluoroenzyme immunosorbent assay (UNICAP; Pharmacia Diagnostics, Uppsala, Sweden). The positive cutoff value of the sIgE was 0.35 kU/L.

Lung function tests

Flow-volume spirometry was performed with a Spirobank spirometer (Medical International Research, Rome, Italy) at baseline and every year throughout the survey. The decrease in FEV₁, expressed as a percentage of the predicted value, was evaluated.

Nasal symptoms

The presence and intensity of individual nasal symptoms (nasal obstruction, rhinorrhea, itching, and sneezing) were recorded by the visual analog scale (VAS) of 100 mm. The total VAS was the sum of the 4 VAS scores (total range, 0-400 mm).

Nasal allergen provocation test

The allergic response to NAPT was assessed at the initial evaluation and after 5 years. Four NAPT with a single aeroallergen per session were performed at weekly intervals by following previously described methods.^{4,5} After negative saline solution challenge to exclude nasal hyperreactivity, a bilateral NAPT was performed by applying 2 puffs (100 µL) of 4 increasing concentrations of freshly reconstituted freeze-dried allergen solution (ALK-Abelló, Madrid, Spain) at room temperature by using a metered spray. The allergen concentrations were the following: DP (*Der p1* 0.04, 0.4, 2, and 4 mcg/mL), *A alternata* (0.0025, 0.025, 0.125, and 0.25 mcg/mL), grass (0.001, 0.01, 0.05, and 0.1 mcg/mL), and *O europea* pollen (0.006, 0.06, 0.3, and 0.6 mcg/mL).

Responses were monitored by means of objective plus subjective parameters: acoustic rhinometry (SRE 2000 rhinometer; Rhinometrics, Lynge, Denmark) and symptom scores, respectively. Acoustic rhinometry (objective parameter) was performed by following the Guidelines of the Standardization Committee on Acoustic Rhinometry,²¹ by measuring the volume of the nasal cavity that corresponds to the lower turbinate (vol 2-6 cm) in each nostril. Symptoms of nasal obstruction, rhinorrhea, itching and sneezing, and ocular symptoms (subjective parameters) were monitored at each time point by placing a vertical mark on a horizontal VAS of 100 mm. A positive NAPT was considered to be an increase ≥30% in the total VAS and a decrease ≥30% in the total sum of vol 2-6 cm of both nasal cavities compared with the baseline test.^{4,5} The nasal response was monitored at baseline, 15 minutes after saline solution challenge, 15 minutes after each aeroallergen concentration, and 1 hour and 24 hours after the last concentration. The NAPT was stopped when a positive response occurred.

Statistical analysis

SPSS version 15.0 (SPSS Inc, Chicago, Ill) was used for the statistical analysis. Continuous data were expressed as median and range, and categorical data as percentages. The clinical and demographic data were compared between the groups by using the χ^2 analysis and the Mann-Whitney *U* test. All *P* values less than .05 were considered statistically significant.

RESULTS

Demographic characteristics

From the total group of 194 adults with LAR, 18 dropped out (9.3%), and, from the total group of 130 controls, 15 dropped out (11.5%) for work or personal reasons. Thus, 176 patients with LAR and the 115 controls completed the study. No significant

TABLE I. Baseline demographic characteristics of patients with LAR and healthy controls

	LAR patients (n = 176)	Healthy controls (n = 115)	P value
Sex, no. (%)			.886
Male	55 (31.3)	35 (30.4)	
Female	121 (68.8)	80 (69.6)	
Age (y), mean (SD)	27.2 ± 11.3	29.5 ± 13.6	.895
Age groups, no. (%)			
14-20 y	62 (35.2)	39 (33.9)	
21-30 y	57 (32.4)	40 (34.8)	
31-40 y	39 (22.2)	29 (25.2)	
41-50 y	15 (8.5)	5 (4.3)	
51-60 y	3 (1.7)	2 (1.8)	
Family history of atopy, no. (%)	74 (42)	30 (26.1)	.018
Dwelling, no. (%)			.806
City	114 (64.8)	73 (63.5)	
Country	62 (35.2)	42 (36.5)	
Smoking habit, no. (%)			.676
Current smoker	13 (7.4)	11 (9.6)	
Ex-smoker	18 (10.2)	14 (12.2)	
Nonsmoker	145 (82.4)	90 (78.2)	

demographic or clinical differences were found between the participating and the nonparticipating subjects. The baseline demographic data of the study subjects are shown in [Table I](#). The mean age of the patients with LAR was 26.5 years, and 67% were 14-30 years old. The LAR group contained a predominance of women who were nonsmokers and city dwellers ([Table I](#)). A family history of atopy was significantly more frequent in the LAR group; no other significant demographic differences were detected between patients and controls.

Clinical evolution

At the onset of the disease, 73.9% of patients with LAR had perennial rhinitis. With regard to seasonality, 64.8% of patients had persistent symptoms. In terms of severity of symptoms, these were moderate for 59.7% of the cases. The objective evaluation after 5 years showed a significant worsening of the rhinitis in 26.1% of the patients, with an increase in the persistence (86.9%, $P = .001$) and severity of nasal symptoms (39.2%, $P = .001$) ([Table II](#)). Conjunctivitis was the most frequent associated disease at the initial evaluation, being present in 52.3% of the patients, followed by asthma in 18.8%. Eleven patients (6.25%) were diagnosed with other nonrespiratory allergy processes at baseline (food, drug, or hymenoptera allergy). Three cases had food allergy (oral allergy syndrome to fruits), 2 had immediate hypersensitivity to betalactams, and 2 had hypersensitivity to Hymenoptera, diagnosed by a positive skin test and/or serum sIgE. Four cases with nonsteroidal anti-inflammatory drug hypersensitivity were diagnosed by a single-blind drug provocation test ([Table II](#)). After 5 years, conjunctivitis increased by 7.9% and asthma by 5.6%. One patient developed food allergy, and, another, Hymenoptera allergy during this period. No significant differences in comorbidities were found between the evaluation at baseline and after 5 years of follow-up ([Table II](#)).

Second-generation oral antihistamines and intranasal corticosteroids were the most frequent medical treatments used by patients with LAR during the study. After 5 years, there was an increase in the use of oral antihistamines ($P = .053$) and a

TABLE II. Allergologic evaluation of LAR clinical evolution

	Baseline (n = 176)	After 5 y (n = 176)	P value
Seasonality of nasal symptoms, no. (%)			.258
Perennial	130 (73.9)	139 (79.0)	
Seasonal	46 (26.1)	37 (21.0)	
Persistence of nasal symptoms, no. (%)			.001
Persistent	114 (64.8)	153 (86.9)	
Intermittent	62 (35.2)	23 (13.1)	
Severity of rhinitis, no. (%)			.001
Mild	38 (21.6)	28 (15.9)	
Moderate	105 (59.7)	79 (44.9)	
Severe	33 (18.8)	69 (39.2)	
Emergency assistance			
Patients, no. (%)	31 (17.6)	63 (35.8)	.017
Rhinitis or conjunctivitis, no. (%)	11 (6.4)	24 (13.9)	.001
Asthma attack, no. (%)	20 (11.4)	39 (22.2)	.007
No. visits/patient, mean (SD)	0.31 ± 0.799	0.61 ± 1.082	.037
Rhinitis medical treatment, no. (%)			
Antihistamines			
Oral	163 (92.6)	171 (97.2)	.053
Ocular	65 (36.9)	75 (42.6)	.276
Corticosteroids			
Intranasal	137 (77.8)	140 (79.5)	.696
Systemic	9 (5.1)	11 (6.3)	.645
Decongestant			
Oral	10 (5.7)	9 (5.1)	.814
Intranasal	9 (5.1)	2 (1.1)	.032
NSAIDs	11 (6.3)	2 (1.1)	.011
Comorbidities, no. (%)			
Asthma	33 (18.8)	43 (24.4)	.195
Conjunctivitis	92 (52.3)	106 (60.2)	.133
Food allergy	3 (1.7)	4 (2.3)	—
Drug allergy	2 (1.1)	2 (1.1)	—
NSAID hyp	4 (2.3)	4 (2.3)	—
Hymenoptera allergy	2 (1.1)	3 (1.7)	—
Atopic dermatitis	4 (2.3)	4 (2.3)	—
Urticaria-angioedema	2 (1.1)	2 (1.1)	—
Hypothyroidism	6 (3.4)	8 (4.5)	—
High blood pressure	4 (2.3)	4 (2.3)	—
FEV ₁ lung function test, mean % predicted (SD)	94.1 ± 10.7	93.2 ± 9.7	.464

—, Not performed; *hyp*, hypersensitivity; *NSAID*, nonsteroidal anti-inflammatory drug.

significant reduction in the use of intranasal decongestants ($P = .032$). Nonsignificant changes in the use of ocular antihistamines and of intranasal, inhaled, and oral corticosteroids were detected ([Table II](#)).

The analysis of the use of medical emergency services during these first 5 years revealed a significant increase in the percentage of patients who required emergency assistance due to severe symptoms of rhinitis and/or conjunctivitis (with moderate or severe chemosis) or asthma attacks triggered by natural exposure to aeroallergens (initial, 17.8%; fifth year, 35.6%; $P = .001$) and in the mean (SD) number of visits per patient (initial, 0.31 ± 0.799 ; fifth year, 0.61 ± 1.082 ; $P = .037$). More detailed information is shown in [Table II](#). Lung function explored by FEV₁, which was normal at the initial evaluation in 94.1% of the patients, showed no significant change during the study period ([Table II](#)).

The subjective evaluation by the patients with LAR is shown in [Table III](#). After 5 years, 36.9% of the patients reported a worsening of the disease; 17.6% reported a worsening in health perception related to rhinitis, with a significant decrease in

TABLE III. Patients' subjective evaluation of LAR at baseline and after 5 years

	Baseline, no. (%)	After 5 y, no. (%)	P value
Clinical evolution			
Disappearance	NA	0 (0)	NP
Improvement	NA	58 (33)	NP
Worsening	NA	65 (36.9)	NP
No change	NA	53 (30.1)	NP
Health perception			
Health impairment	NA	31 (17.6)	NP
Excellent	141 (80.1)	121 (68.7)	.015
Very good	23 (13.1)	30 (17.0)	.297
Good	12 (6.8)	11 (6.3)	.829
Normal	0 (0)	10 (5.7)	.002
Bad	0 (0)	4 (2.3)	.123
Impairment of QoL	NA	71 (40.3)	NP
No	79 (44.9)	30 (17.0)	.001
Mild	57 (32.4)	89 (50.6)	.001
Moderate-severe	40 (22.7)	57 (32.4)	.043
Moderate	38 (21.6)	50 (28.4)	NP
Severe	2 (1.1)	7 (4.0)	NP

NA, Not applicable; NP, not performed; QoL, quality of life.

"excellent health" from 80.1% at disease onset to 60.7% after 5 years ($P = .015$), and a significant increase in "normal health," from 0% to 5.7% ($P = .002$) at the expense of patients with excellent or very good or good health at the onset of the disease. Also, after this period, 40.3% of the patients with LAR reported an impairment in the quality of life related to rhinitis, with a significant increase in the categories of mild ($P = .001$) and moderate-severe ($P = .043$) over this time (Table III).

Allergen inductors of nasal allergic response

A total of 261 aeroallergen sensitizations were detected by NAPT at the initial evaluation. Most common specific nasal sensitizing aeroallergen was DP (51.1%) followed by *A alternata* (35.2%). After 5 years, 5.7% of the patients with LAR developed new nasal aeroallergen sensitization. Monosensitization was the predominant aeroallergen pattern; however, after 5 years of follow-up, the percentage of patients with polysensitization had increased, from 36.4% to 40.9%. Data are shown in Table IV.

Systemic atopy

De novo systemic atopy to aeroallergens was detected by means of SPT in 12 patients with LAR (6.8%) and by serum sIgE and SPT in 1.1% during the first 3 years of the follow-up. DP was the main systemic sensitizing aeroallergen (5.1%), followed by grass pollen (4%). Two patients developed systemic sensitization to aeroallergens not included in the NAPT at the initial evaluation (*Cupressus*, *Parietaria*, dog and cat epithelia). One of the 11 patients with LAR and with nonrespiratory allergy at the initial evaluation (Hymenoptera allergy) developed systemic sensitization to DP. In the control group, 6 subjects (5.2%) developed perennial persistent allergic rhinitis with systemic atopy, with a positive response to SPT (5.2%) and serum sIgE (3.4%). More detailed information is shown in Table V.

To evaluate the clinical importance of these systemic sensitizations, NAPT was performed in patients and controls at the fifth year of follow-up. The concentrations used in NAPT with *Cupressus*, *Parietaria*, and cat and dog extracts were: 0.3, 3, 15,

TABLE IV. Evolution of nasal and systemic allergen sensitization in patients with LAR

	At baseline, no. (%)	After 5 y, no. (%)
Sensitization pattern		
Monosensitization	112 (63.6)	104 (59.1)
Polysensitization	64 (36.4)	72 (40.9)
Positive NAPT	176 (100)	176 (100)
DP	90 (51.1)	96 (54.5)
<i>A alternata</i>	62 (35.2)	65 (36.9)
Grass pollen	58 (32.9)	59 (33.5)
<i>O europea</i> pollen	51 (29.0)	52 (29.5)
Systemic sensitization	0 (0.0)	12 (6.8)
SPT	0 (0.0)	12 (6.8)
Serum sIgE	0 (0.0)	2 (1.1)
Systemic allergen sensitization	0 (0.0)	12 (6.8)
DP	0 (0.0)	9 (5.1)
<i>A alternata</i>	0 (0.0)	2 (1.1)
Grass pollen	0 (0.0)	7 (4.0)
<i>O europea</i> pollen	0 (0.0)	4 (2.3)
Other	0 (0.0)	4 (2.3)
<i>Cupressus</i> pollen	0 (0.0)	2 (1.1)
<i>Parietaria</i> pollen	0 (0.0)	1 (0.6)
Dog epithelia	0 (0.0)	1 (0.6)
Cat epithelia	0 (0.0)	1 (0.6)

TABLE V. Development of allergic rhinitis with systemic atopy in the control group

	At baseline, no. (%)	After 5 y, no. (%)
Systemic sensitization	0 (0.0)	6 (5.2)
SPT	0 (0.0)	6 (5.2)
Serum sIgE	0 (0.0)	4 (3.4)
Allergens sensitization		
DP	0 (0.0)	4 (3.5)
Grass pollen	0 (0.0)	2 (1.7)
<i>Olea</i> pollen	0 (0.0)	1 (0.9)
Positive NAPT		
DP	0 (0.0)	4 (3.5)
Grass pollen	0 (0.0)	2 (1.7)
<i>Olea</i> pollen	0 (0.0)	1 (0.9)

and 30 HEP/mL. Total concordance (κ index = 1) between systemic sensitization and a positive response to NAPT was obtained in the LAR and control groups. No cases with a positive response to SPT or serum sIgE were observed in patients with a negative NAPT.

Patients with LAR who developed systemic atopy showed a significant association with asthma (odds ratio 14.112 [95% CI, 2.745-72.551]) and smoking habit (odds ratio 13.377 [95% CI, 2.866-62.426]) at the beginning of the study compared with patients with LAR who did not develop systemic atopy. No significant associations were found with sex, family history of atopy, time of exposure to aeroallergen, persistence or severity of nasal symptoms, other comorbidities, pattern of allergen sensitization, or worse evolution.

DISCUSSION

The aim of this study was to explore the natural history of LAR by following a large cohort of cases and healthy controls over a

long period of time to answer several important questions. We were interested in elucidating whether LAR could be the first step in the development of AR with systemic atopy or a distinct phenotype with a different natural history, and in determining whether there would be an equivalent to the atopic march in the LAR population, with an evolution toward asthma.

The results of this first, 5-year, prospective study of patients with LAR showed that the demographic and clinical profile at the onset of the disease was a young female patient who was a nonsmoker and with an urban lifestyle, with no family history of atopy, and with perennial, persistent, and moderate rhinitis, mainly associated with conjunctivitis. After 5 years, the subjects with LAR experienced worsening of the rhinitis, reflected in the assessment of both the physician and the patient, in the use of emergency assistance, and in the increased prevalence of conjunctivitis. The presence of severe rhinitis symptoms increased significantly, from 18.8% to 39.2%, after 5 years. An evolution toward asthma was present in 5.6% of the patients with LAR after 5 years of follow-up.

An important proportion of patients perceived impairment in their health (17.6%) and quality of life (40.3%) after 5 years. Analysis of these data confirmed that LAR is a relevant disease that affects the health and quality of life of adult patients in this study. One of the main outcomes of this study was the detection of *de novo* systemic atopy, evaluated by objective measures such as SPT and serum sIgE determination. SPT detected a higher proportion of systemic atopy than serum sIgE determination in the LAR and control groups,²² which confirmed that SPT was the most sensitive method for the detection of new systemic atopy in patients with LAR. After the first 5 years of follow-up, a similar rate of conversion to systemic atopy was detected in adult patients with LAR (6.25%) and healthy controls (5.2%), which suggests that LAR is an independent entity and not the first step in the development of AR with systemic atopy. Although the number of patients with LAR who converted to AR was low, the risk of developing systemic sensitization to aeroallergens was higher in patients with asthma and smoking history, and occurred in all cases within the first 2 years of the natural course of LAR.

One of the strengths of our study was the evaluation of patients with LAR and with a recent onset of the disease (≤ 2 years), which avoided the survival bias that would have excluded from the study subjects who had already developed systemic atopy in their natural evolution and which, therefore, would have underestimated the conversion or progression rate to systemic atopy. A prospective cohort study avoids some of the validity problems, such as bias in the ascertainment of exposure, but losses to follow-up and the clinical interview could introduce bias. In our study, the former was not likely because the follow-up rate was high (90.7%), and no significant demographic or clinical differences were found between the participating and the nonparticipating subjects. The possibility of a classification bias by the use of subjective data from clinical questionnaires was minimized by the employment of additional objective data (physical examination, lung function test, SPTs, determination of serum total IgE and sIgE, acoustic rhinometry, and use of medical emergency services).

Currently, no data are available on the natural history of LAR in children. In our service, the age of the population evaluated starts at 14 years because of the organization of the patient referral system, and, therefore, we did not have the opportunity to

evaluate younger subjects. Whether in these patients LAR is also prevalent, and, if so, whether it may evolve to systemic atopy is not known. Our results highlight the need to explore the natural history of LAR in children. Thirteen of our patients presented with food, drug, or Hymenoptera allergy in spite of having LAR, with only one developing *de novo* systemic sensitization to aeroallergens during the follow-up period. Although this is a low number of cases, this phenomenon requires further study by increasing the population size and follow-up period.

In conclusion, our study detected a similar rate of development of systemic atopy in patients with LAR and in healthy controls, which suggests that LAR and classic AR may be 2 independent entities. LAR is not a minor disease, and, during the first 5 years of its natural evolution, it produces a significant impairment in health and quality of life of affected patients and increases in the persistence and severity of nasal symptoms, an association with conjunctivitis, and the use of emergency assistance, mainly due to asthma attacks. Interestingly, we noted an increase of 5.6% in the incidence of asthma in patients with LAR after 5 years of follow-up compared with baseline values. However, this did not reach statistical significance. To improve the consistency of these results and to explore possible risk factors involved in the development of *de novo* systemic atopy and evolution toward asthma, we now have recruited a higher number of subjects and are currently following up these cohorts of patients with LAR and the controls over a 10-year period.

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Clinical implication: Local allergic rhinitis is a common respiratory disease that does not evolve to allergic rhinitis in most patients after a follow-up period of 5 years.

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