

Local Allergic Rhinitis



Paloma Campo, MD, PhD^a, María Salas, MD, PhD^a,
Natalia Blanca-López, MD, PhD^b, Carmen Rondón, MD, PhD^{a,*}

KEYWORDS

- Local allergic rhinitis • Asthma • Nasal allergen provocation test • Local IgE
- Natural evolution • Allergen immunotherapy

KEY POINTS

- Local allergic rhinitis (LAR) is a rhinitis phenotype defined by a nasal allergic response in patients with negative skin prick test and nondetectable serum specific immunoglobulin E (sIgE) antibodies.
- Patients from different countries, ethnic groups, and ages may be affected. Impairment of quality of life and association with conjunctivitis and asthma are frequent.
- Diagnosis is based on clinical history, the demonstration of a positive response to nasal allergen provocation test and/or the detection of nasal sIgE. A positive basophil activation test may support the diagnosis.
- Allergen immunotherapy is a clinically effective immune-modifying treatment for LAR.

DEFINITION OF LOCAL ALLERGIC RHINITIS

Local allergic rhinitis (LAR) is a clinical entity characterized by symptoms suggestive of allergic rhinitis (AR) owing to a localized allergic response in the nasal mucosa in the absence of systemic atopy assessed by conventional diagnostic tests such as skin prick test or determination of specific immunoglobulin E (sIgE) in serum.^{1–17}

UNDERLYING IMMUNE MECHANISMS

A better understanding of the underlying immune mechanisms is essential for developing diagnostic methods and targeted therapies. The immune characteristics of LAR (**Fig. 1**) include:

- Nasal T-helper 2 cell allergic inflammation^{4–6,18,19}
- Positive response to nasal allergen provocation test (NAPT)^{3,5,11,20}
- Nasal production of sIgE^{5,6,8,9,18,19} and inflammatory mediators^{8,21,22}
- Allergen-specific basophil activation^{23,24}
- No detectable sIgE antibodies in serum^{16,17}

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^a Regional University Hospital of Malaga, Plaza Hospital Civil s/n pabellon 6, Málaga 29009, Spain; ^b Allergy Service, Hospital Infanta Leonor, Gran Vía del Este, 80, Madrid 28031, Spain

* Corresponding author. Allergy Unit, Hospital Civil, pabellon 6, Plaza del Hospital Civil, Málaga 29009, Spain.

E-mail address: carmenrs61@gmail.com

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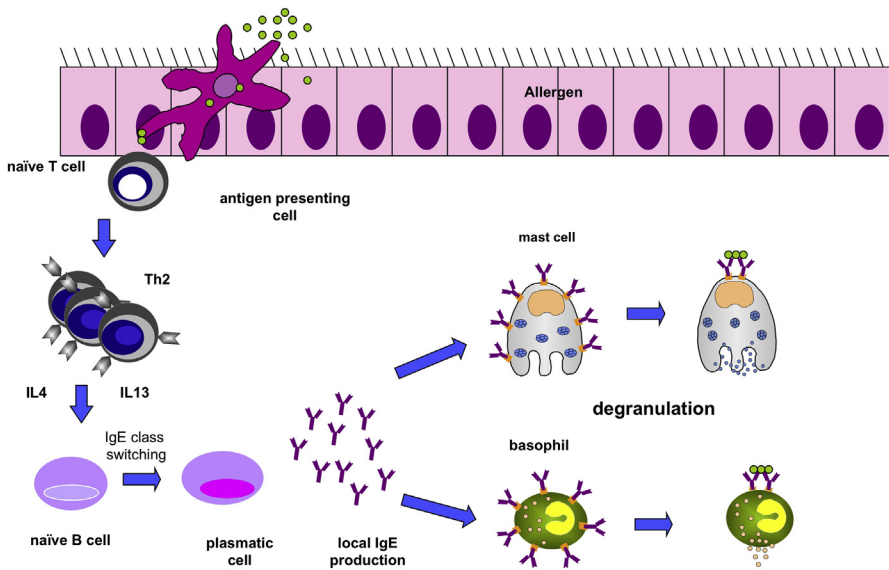


Fig. 1. Local allergic immune response. IgE, immunoglobulin E; IL, interleukin; Th2, T-helper 2 cell. (Adapted from Rondón C, Fernandez F, Canto G, et al. Local allergic rhinitis: concept, clinical manifestations, and diagnostic approach. *J Investig Allergol Clin Immunol* 2010;20:366.)

T-helper 2 Cell Nasal Immunologic Response

Natural exposure to aeroallergens induces a nasal T-helper 2 cell inflammatory response in LAR with increased eosinophils, basophils, mast cells, CD3⁺, and CD4⁺ T cells.^{5,6} T cells may play a role in eosinophil recruitment and IgE production.

Positive Response to the Nasal Allergen Provocation Test

NAPT studies have helped to increase our understanding of the pathophysiology of LAR,¹³ confirming the characteristic immediate/early and late phases of the allergic response in LAR patients.^{21,22} The response to NAPT has been confirmed objectively by acoustic rhinometry,^{5,6,8,20–22} anterior rhinomanometry,³ and by nasal secretion of sIgE^{5,6,8,9,21,22} and inflammatory mediators^{5,6,8,21,22} as well as subjectively by nasal and ocular symptoms.^{3,5,6,20–22}

In LAR, aeroallergen exposure induces local sIgE production, mast cells, and eosinophil activation with nasal secretion of tryptase and eosinophil cationic protein (ECP).^{21,22} The maximum secretion of tryptase occurs 15 minutes after NAPT, returning to baseline at 6 hours (immediate responders), or 24 hours (dual responders). Nasal secretion of ECP is long lasting, increasing progressively from 15 minutes to 24 hours.^{21,22} A recent study showed that 83% of LAR subjects sensitized to *Olea europaea* pollen responded to NAPT with nOle e 1, demonstrating that purified allergens can also induce an allergic response with secretion of ECP potentially acting as a confirmatory biomarker of this inflammatory response.²⁴

Local Specific Immunoglobulin E Production

Mechanistic studies have shown nasal production of sIgE in AR^{25–28} and LAR.^{2,5,6,8,9,19,21,22} The local production of sIgE in target organs may explain why

some atopic subjects develop rhinitis, and others asthma, conjunctivitis, and/or eczema alone or in combination.²⁹ Conversely the absence of local sIgE could explain why up to 50% of the population, who demonstrate positive skin prick test/serum sIgE, have no clinical manifestations of allergy.²⁹

Since the first detection of nasal sIgE in nonatopic rhinitis patients by Huggins and Brostoff in 1975,² several studies have confirmed the presence of nasal sIgE in LAR patients after natural exposure,^{5,6} after controlled exposure to aeroallergens by NAPT,^{8,9,21,22} as well as during periods of nonexposure to aeroallergens.^{21,22}

Cellular studies have confirmed the expression of epsilon germline gene transcripts and messenger RNA for the epsilon heavy chain of IgE in nasal mucosal B cells.²⁶ In addition, the localization of free light chains of IgE in tissue and nasal secretions of patients with AR and with NAR suggests that they could mediate immune responses involving mast cells.^{30,31}

Basophil Activation

Recent studies have shown that local sIgE production with binding to the high-affinity receptor for IgE of basophils could take place without detectable circulating sIgE in LAR patients sensitized to dust mites and pollens.^{23,24} Furthermore, wortmanin experiments demonstrated that the activation of basophils is IgE mediated.²³ These findings suggest that, after local IgE production, basophils might be the first cells for sIgE leaked from the target organ to the circulation.

CLINICAL FEATURES AND EPIDEMIOLOGIC DATA

Clinical Features of Local Allergic Rhinitis

Studies performed in well-phenotyped rhinitis patients have shown that some clinical features are similar between AR and LAR. However, several clinical-demographic features may be useful for identifying LAR patients among those subjects with rhinitis symptoms and absence of atopy^{11–13} (**Box 1**).

Epidemiologic Studies

There are several epidemiologic studies for LAR (**Table 1**). Early reports studying small populations showed frequencies of 47% of LAR sensitized to betula²⁰ and 62% to *Dermatophagoides pteronyssinus*³ among adult patients previously labeled as NAR. A recent study performed in children with rhinitis detected positive nasal sIgE to *Alternaria*.³² Another study of 219 elderly subjects with rhinitis (65–89 years of age) revealed that 21% of patients had LAR, 40.2% had AR, and 38.8% had NAR diagnosed by NAPT.⁸

In a recent prospective study of 428 rhinitis subjects in Spain, we found a LAR prevalence of 25.7%¹¹ diagnosed by NAPT. Two independent studies in different geographic areas with high allergenic load (grass pollen and house dust mites) revealed a frequency of 61% and 72%, respectively,^{33,34} using NAPT. Taken together, these studies show that LAR is common in several populations, and in children and adults.^{7–10,20,35} However, larger population studies using established LAR diagnosis protocols are required to fully determine its prevalence and incidence.

COMORBIDITIES AND LOCAL ALLERGIC RESPIRATORY DISEASE

As with AR, LAR frequently presents with other diseases such as asthma and conjunctivitis.^{11–13}

Box 1**Clinical-demographic features for identifying LAR***Clinical Similarities Between LAR and AR*

- Nasal pruritus, watery rhinorrhea, and sneezing are the most common clinical features
- Association with conjunctivitis
- Accompanied by lower airway symptoms
- Mostly moderate to severe symptoms
- Not limited to adults: 36% of subjects develop it in childhood
- Tendency to worsen over time

Differential Characteristics of LAR Compared with NAR

- Significantly younger
- Nonsmokers
- More likely female
- Family history of atopy
- More severe symptoms

Abbreviations: AR, allergic rhinitis; LAR, local allergic rhinitis; NAR, nonallergic rhinitis.

Data from Refs.^{11–13}

Local Immunoglobulin E in Lower Airways

More than 30% of subjects with LAR also report asthmatic symptoms.^{11,12,36} IgE may play an important role in nonatopic asthma, and may be produced locally as in the nasal mucosa of LAR subjects.³⁷ Several studies have demonstrated the local synthesis of IgE in the bronchial mucosa of atopic and nonatopic asthmatics, with increased expression of the IgE epsilon heavy chain germ line and mature gene transcripts (epsilon chain messenger RNA) and local IgE class switching.^{38,39} There is also a similar cellular infiltrate in bronchial mucosa in both atopic and nonatopic asthmatics, with a similar increase in cytokines and their receptors such as interleukin-4, -5, and -13.^{40,41} However, the possible role of allergens in the bronchial symptoms of LAR patients requires further clarification. Researchers have demonstrated the presence of *D pteronyssinus* sIgE in the sputum of nonatopic asthmatics after bronchial allergen challenge, even though subjects did not respond clinically to the allergen,⁴² and have also demonstrated a correlation with periostin.⁴³ Pillai and colleagues⁴⁴ have also found elevated levels of total IgE in tissues of both atopic and nonatopic patients, but only demonstrated allergen sIgE in atopic subjects. Preliminary results obtained by our group revealed positive bronchial responses to *D pteronyssinus* demonstrated by bronchial allergen provocation test in 8 of 16 subjects with LAR, with increased eosinophils and ECP in induced sputum, providing more evidence for a possible equivalent to LAR in the lower airways.⁴⁵

Conjunctivitis and Local Immunoglobulin E

Ocular symptoms are often found in LAR patients.^{11–13} The existence of an ocular local allergic response has been demonstrated through specific conjunctival provocation tests and determination of sIgE in ocular secretions.^{46,47} In some cases, the ocular allergic response was demonstrated in patients clinically suggestive of LAR.⁴⁷ Investigators have reported a lack of correlation between serum sIgE and ocular allergy, suggesting that the sIgE detected in the eye is most likely produced locally.⁴⁸

Table 1
Epidemiologic studies for LAR

Author, Year	Country	Study Groups	Group Age	Allergens	Positive NAPT Response, n (%)
Carney et al, ³ 2002	UK/ Australia	21 IR (perennial)	Adults	DP/DF Cats/Dogs Grass	13/21 (61.9)
Wedback et al, ²⁰ 2005	Sweden	15 IR (seasonal)	Adults	Birch Timothy	7/15 (46.7)
Rondon et al, ⁵ 2007	Spain	50 IR (perennial)	Adults	DP	27/50 (54)
Rondon et al, ⁶ 2008	Spain	32 IR (seasonal)	Adults	Grass Olive	21/32 (65.6)
Fuiano et al, ³² 2012	Italy	36 IR (perennial)	Children (4–18 y)	Alternaria	25/36 (69.4)
Cruz Niesvaara et al, ³³ 2012	Spain	30 IR (perennial)	Adults	DP	19/30 (63.3)
Rondon et al, ¹¹ 2012	Spain	158 IR (seasonal/ perennial)	Adults	DP Alternaria Grass Olive Cat Dog	110/158 (69.6)
Cheng et al, ¹⁰ 2013	China	147 IR (perennial)	Adults	DF	12/147 (8.1)
Chang et al, ⁷ 2014	Korea	62 IR	Adults	DP	22/62 (35.5)
Bozek et al, ⁸ 2015	Poland	131 IR (perennial)	Adults >65 y	DP Phleum Molds Trees Cat	46/131 (35.1)
Klimek et al, ⁹ 2015	Germany	2 IR (perennial)	Adults	Alternaria	2 (case report)
Adinoff et al, ⁶³ 2015	USA	30 IR (seasonal/ perennial)	Adults/ children	Trees Weeds Timothy grass Cat	11/30 (36.7)
Jang et al, ⁶⁴ 2015	Korea	110 IR (perennial)	Adults	DP	12/110 (10.9)
Buntarickpornpan et al, ⁶⁵ 2015	Thailand	25 IR (perennial)	Children (8–18 y)	DP	0/25 (0)
Refaat et al, ⁶⁶ 2015	Egypt	40 IR	Adults	DP	25/40 (62.5)
Blanca-López, ³⁴ 2016	Spain	61 IR (seasonal)	Adults/ Children	Phleum	37/61 (61)

Abbreviations: DP, *Dermatophagoides pteronyssinus*; IR, idiopathic rhinitis; LAR, local allergic rhinitis; NAPT, nasal allergen provocation test.

Data from Refs.^{3,5–11,20,32–34,63–66}

NATURAL HISTORY AND RISK FACTORS

The characterization of LAR has generated important clinical questions as to whether it develops into AR with systemic atopy, or is a risk factor for asthma.³⁶ The results of the first longitudinal study revealed that LAR is a well-differentiated disease with a similar low rate of conversion to AR as for healthy controls (6.25% vs 5.2%) after 5 years of evolution.¹² This study periodically evaluated a cohort of 149 LAR patients and 130 controls using questionnaires, skin tests, serum sIgE, lung function, and NAPTs.¹² LAR patients worsened over time, with impairment in quality of life, an increase in rhinitis persistence and severity, the use of emergency assistance, and new associations with conjunctivitis and asthma.

Previously, a retrospective study had detected a 24% conversion rate from NAR to AR, indirectly suggesting that a long-term conversion from LAR to AR might be possible⁴⁹; however, this study did not differentiate between NAR and LAR patients.

In 2015, a retrospective study performed in 19 LAR patients reevaluated by skin prick test or intracutaneous testing reported a 21% long-term conversion rate from LAR to AR after more than 7 years of evolution.⁵⁰ This figure was very close to the 17% conversion rate detected in 7930 healthy subjects evaluated in the region where the study was conducted.⁵¹ However, the retrospective design, lack of healthy controls, surveillance bias, small number of patients included, and great variability in patient age and time interval between evaluations must be considered when interpreting the results.⁵² It will be interesting to compare these results with our 10-year longitudinal follow-up study in LAR subjects, which will be completed in the next 2 years.

Diagnostic Test and Differential Diagnosis

The diagnosis of LAR must always be considered for patients with symptoms of AR but no evidence of systemic atopy as measured by conventional methods (skin testing/serum sIgE).^{1,16,17,36} By conducting a detailed clinical history, a thorough nasal exploration (anterior rhinoscopy/endoscopy) and/or imaging (CT scan), a differential diagnosis can be established (**Box 2**). The prototype LAR patient is a young female nonsmoker with family history of atopy and clear symptoms of AR.^{11,12} However, to confirm a diagnosis of LAR it is necessary to perform a specific allergological evaluation^{1,16,17,36} (**Fig. 2**).

The diagnosis of LAR starts with the demonstration of an allergen-specific nasal response by means of NAPT and/or sIgE in nasal secretions or tissue.^{5,6,11–13,16,36} NAPT is considered the gold standard for AR and LAR diagnosis,^{11,16,36,53,54} with a higher sensitivity than allergen-sIgE measurement in nasal secretions.^{13,21,36} NAPT with multiple allergens may be useful as an initial screening method for LAR and NAR.⁵⁴ The presence of nasal sIgE has been demonstrated in nasal biopsies,²⁵ but in clinical practice noninvasive methods for diagnosis are recommended.^{13,36} However, the measurement of sIgE in nasal secretions can vary depending on the technique used. Although highly specific, sensitivity is rather low when measured by nasal lavage, ranging from 22% to 40%,^{5,6,21,22} most likely owing to dilutional effects. Other techniques such as the direct application to the ostium of a cellulose device coupled to the allergen,³² nasal brushing⁵⁵ and sinus packs or filter disks⁵⁶ used in AR need to be tested in LAR subjects.

The basophil activation test has proved to be useful for LAR diagnosis. In patients with LAR to *D pteronyssinus*, it has a sensitivity of 50% with greater than 90% specificity.²³ For patients with LAR to *O europaea*, the sensitivity is 66% with greater than 90% specificity.²⁴ Therefore, basophil activation test can be a useful adjunctive tool to diagnose LAR to inhalant allergens.

Box 2**Differential diagnosis of local allergic rhinitis**

- Nasal polyposis
- Chronic rhinosinusitis
- Known causes of nonallergic rhinitis
 - Drug-related
 - Hormonal
 - Systemic diseases
 - Cystic fibrosis
 - Primary ciliary dyskinesia
 - Granulomatosis
 - Sarcoidosis
 - Amyloidosis
 - Atrophic rhinitis
 - Occupational (irritant)
- Anatomic alterations
 - Septal deviation
 - Turbinate hypertrophy
 - Adenoidal hypertrophy
 - Cerebrospinal fluid leaking

Data from Refs.^{1,11,12,17,36}

Establishing the correct diagnosis of LAR will allow for the identification of the allergen(s) that trigger the allergic response and the administration of a specific treatment.^{13,16,36} This diagnostic approach should also be applied to workers with nasal respiratory symptoms clearly related to occupational exposure but who have negative immunologic tests, especially for high molecular weight agents.³⁷

THERAPEUTICS OPTIONS

Given the clinical-immunologic similarities between AR and LAR, it is reasonable to think that these patients will benefit from the same therapeutic approaches.^{13,16,36} This includes education, allergen avoidance measures, pharmacologic treatment with intranasal corticosteroids, oral and intranasal antihistamines, and allergen immunotherapy (AIT).⁵⁷ Information based on the clinical evolution of LAR patients shows a similar response in terms of symptomatic relief and disease control with oral antihistamines and intranasal corticosteroids.^{5,6,12}

AIT has the ability to modify the natural course of AR, increasing immunologic tolerance, and reducing the clinical symptoms and the use of medication.^{58,59} The most relevant question is how beneficial AIT may be in LAR patients, and which immunologic effects it may produce. According to ARIA guidelines, AIT is indicated in children and adults with moderate to severe, persistent or intermittent AR and/or allergic asthma,^{57,58,60} so the question is this: Should LAR be considered a new indication for AIT?

An observational study with grass pollen¹⁴ and a double-blind, placebo-controlled clinical trial with *D pteronyssinus* subcutaneous immunotherapy¹⁵ have demonstrated the clinical and immunologic effect of AIT in LAR. The former study was conducted in a group of LAR patients sensitized to grass pollen.¹⁴ It showed that grass pollen subcutaneous immunotherapy induces a significant improvement in nasal tolerance to NAPT, and clinical symptoms in response to the natural exposure to the allergen, with reduced use of rescue medication.¹⁴ These findings have been recently confirmed in a 2 years

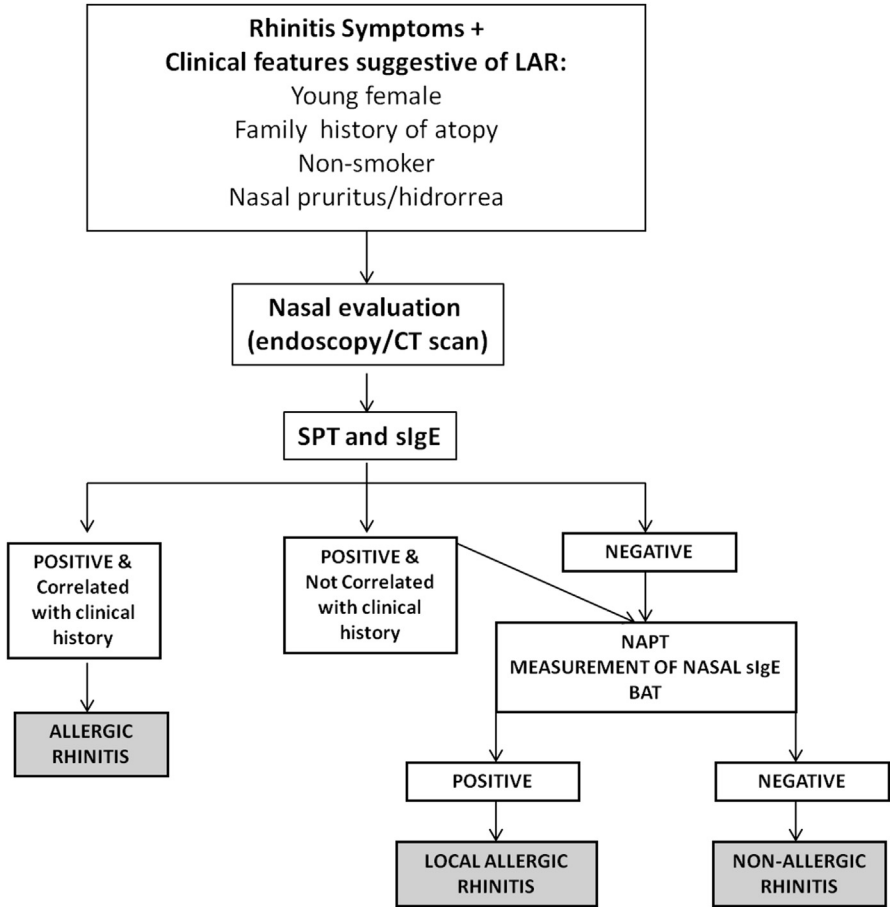


Fig. 2. Diagnostic approach in local allergic rhinitis (LAR). BAT, basophil activation test; CT, computed tomography; NAPT, nasal allergen provocation test; sIgE, specific immunoglobulin E; SPT, skin prick test. (Adapted from Rondón C, Fernández F, Canto G, et al. Local allergic rhinitis: concept, clinical manifestations, and diagnostic approach. *J Investig Allergol Clin Immunol* 2010;20:368.)

phase II randomized double-blind, placebo-controlled clinical trial with *D pteronyssinus* subcutaneous immunotherapy.¹⁵ In this study, AIT had a short-term and sustained clinical effect reducing symptom and medication scores, and increasing the number of medication-free days¹⁵ as occurs with AR.^{61,62} The immunologic effects were demonstrated by the production of allergen sIgG4 and a decrease in serum sIgE with a significant improvement in nasal allergen tolerance. At the end of the study, two-thirds of patients treated with AIT tolerated a concentration of Der p1 10 times higher by NAPT than basal concentration, and NAPT was negative in 50% of patients.¹⁵ These results support the indication for AIT in LAR.

FUTURE CONSIDERATIONS AND SUMMARY

LAR constitutes an interesting model of allergic inflammation localized in the target organ. Despite recent achievements in the investigation of this disease, there remain

many unanswered questions. Future research will focus on the study of the patho-physiologic mechanisms of LAR, elucidation of lower airway and ocular responses, AIT studies with different allergens, the improvement of sIgE detection in nasal secretion and the further development of reproducible in vitro tests that can be performed readily in the clinical setting.

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