



Prevalence and clinical characteristics of local allergic rhinitis to house dust mites

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Purpose of review

Local allergic rhinitis (LAR) is a recently classified subtype of rhinitis defined by a nasal allergic response in patients without systemic evidence of atopy. Recent studies have reported the prevalence, clinical course, culprit allergens, diagnostic methods and treatment outcomes of LAR. The purpose of this review is to summarize the most relevant and updated scientific evidence for LAR, especially focusing on its prevalence and clinical characteristics.

Recent findings

LAR is found in a significant proportion (3.7–61.9%) of patients previously diagnosed with nonallergic rhinitis, but the prevalence may differ among ethnic groups and countries. Common allergens of LAR are similar to those of allergic rhinitis, in which house dust mites are the most common cause, followed by grass pollen, tree pollen, weed pollen and animal dander confirmed by provocation tests. Although the nasal provocation test to a single allergen is considered the gold standard method, the detection of allergen-specific IgE and other inflammatory mediators from nasal secretions and the basophil activation test can assist in the diagnosis of LAR. Conjunctivitis and asthma are the most common comorbid conditions, and the occurrence rate of asthma increases over period. However, the conversion rate to allergic rhinitis was not significantly different between LAR and healthy controls.

Summary

LAR is a well-differentiated entity of rhinitis, which should be considered in patients with persistent and severe symptoms without any systemic evidence of atopy. Further research is needed to investigate the long-term outcome, and geographic and ethnic differences of LAR.

Keywords

diagnosis, allergen, local allergic rhinitis, prevalence, morbidity

INTRODUCTION

Rhinitis is defined as an inflammatory disease of the nasal mucosa which is characterized by rhinorrhea, itching, sneezing and nasal obstruction. Traditionally, rhinitis can be classified as allergic rhinitis and nonallergic rhinitis (NAR) based on clinical manifestations and allergic sensitization to common allergens [1]. Recent evidence showed another class of rhinitis -- local allergic rhinitis (LAR) -- which is confined to nasal mucosal allergic immune response in the absence of systemic atopy [2].

The first concept of LAR was introduced after allergen-specific IgE was found in the nose without any evidence of systemic sensitization detectable by the skin prick test (SPT) or serum-specific IgE assays [3]. This phenomenon was called entopy [4]. Even before the introduction of the concept of LAR, Carney *et al.* [5] found that a subgroup of NAR shows nasal airway responses similar to those seen in allergic rhinitis, when subjected to allergen nasal provocation, and

Powe *et al.* [6] found nasal mucosal inflammatory infiltrate similar to that seen in allergic rhinitis containing IgE-positive cells, mast cells and eosinophils.

In 2007, a positive response to the nasal provocation test (NPT) and the detection of nasal-specific IgE to *Dermatophagoides pteronyssinus* were demonstrated and these patients were diagnosed with a new entity of rhinitis, LAR, by a Spanish group [2]. That study indicated that a positive response to NPT

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Curr Opin Allergy Clin Immunol 2018, 18:10–15

DOI:10.1097/ACI.0000000000000413

KEY POINTS

- LAR which shows a positive response to NPT and the local production of IgE antibodies without systemic IgE detection is a condition that should be considered in patients with NAR.
- The prevalence of LAR varies according to ethnics and regions, and these differences might be attributed to the difference in patients' exposed environment and genetic conditions.
- NPT is considered the gold standard method to diagnose LAR. Other techniques such as IgE detection in nose and BAT may help the diagnosis.
- LAR has severe symptoms than allergic rhinitis with conjunctivitis and asthma as the most common comorbid conditions.
- After 10-year follow-up study, the conversion rate to allergic rhinitis was not significantly different between LAR and healthy controls.

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PREVALENCE

There is a major question of how many patients have LAR in those previously diagnosed with NAR. In 2002, Carney *et al.* [5] challenged 23 idiopathic rhinitis patients with house dust mites (HDMs), cat/dog and a grass pollen mixture, and then found positive responses in 61.9%. They also reported that HDMs were the most prevalent allergen (85%), followed by cat/dog and a grass pollen mixture, and that they used a different criterion for the diagnosis of LAR -- changes in nasal resistance as measured using rhinometry, without evaluating the visual analogue scale (VAS), after one spray of 100 μ l of each allergen. Another study reported that 54% of the NAR patients showed a positive NPT to *D. pteronyssinus* when evaluating both symptom scores and changes in acoustic rhinometry results according to a gradual increase of allergen concentration [2]. However, the results do not represent global prevalence. The prevalence of LAR caused by *Dermatophagoides farinae* was reported to be 8.2% in Chinese patients [7], and that caused by *D. pteronyssinus* or *D. farinae* was found to be 10.9 or 4.5% in Korean patients, respectively [8,9]. Although the concentrations used were different between studies, the prevalence of LAR is higher in Western countries than in Asian countries. Moreover, the prevalence of LAR in children showed similar geographic results.

LAR was diagnosed in 52.5% of patients aged 12–18 years who were previously diagnosed with NAR to grass, birch or *Artemisia* pollens in Poland [10], but the prevalence of LAR to *D. pteronyssinus* was found to be 3.7% in children aged 8–18 years in Thailand [11]. These differences might be attributed to the difference in patients' exposed environment and genetic conditions.

Although HDMs are the most prevalent causative allergens of allergic rhinitis and LAR, other inhalant allergens can also be causative allergens of LAR. Grass pollen induced positive NPT responses in 62.5% of idiopathic rhinitis patients, and *Olea europea* induced positive responses in 12.5% [12]. Moreover, Bozek *et al.* [13[■]] measured nasal-specific IgE levels and performed NPT with various common allergens on elderly rhinitis patients. They showed that 21% of the patients were diagnosed with LAR, and reported the frequency of causative allergens in 46 patients with LAR as follows: as assessed by NPT, birch (19.6%), alder (10.9%), hazel (95.7%), Phleum (23.9%), *Artemisia* (6.5%), *Cladosporium* (4.3%), *Alternaria* (43.5%), cat (4.3%) and mite (63.0%); and as assessed by nasal IgE measurement, birch (19.6%), alder (10.9%), hazel (17.4%), Phleum (13.0%), *Artemisia* (6.5%), *Cladosporium* (4.3%), *Alternaria* (39.1%), cat (4.3%) and mite (56.5%). Table 1 [5,2,7–12,13[■],14] summarizes the prevalence and causative allergens of LAR.

Collectively, in LAR and allergic rhinitis, the prevalence of LAR varies according to ethnics and regions, although causative allergens were similar. Further well-designed studies are needed to confirm these results.

MECHANISMS FOR LOCAL ALLERGIC RHINITIS

Although the reasons why allergen-specific IgE is undetectable in blood are not obvious, the pathogenesis of LAR is similar to that of typical allergic rhinitis. The epsilon germ-line gene was expressed in nasal B cells and mRNA for interleukin (IL)-4 chain detected in the nasal tissues of both hay fever patients and normal controls [15]. Powe *et al.* [16] found IgE free light chains in nasal tissue and secretion from allergic rhinitis and NAR patients. In addition, nasal Th2-mediated inflammation was confirmed by cytometric evaluation of nasal lavage fluid from NAR patients after allergen challenge: increases in mast cells, basophils, eosinophils, CD3⁺ T cells and CD4⁺ T cells when exposed to grass pollen [12]. Moreover, leukocyte–lymphocyte phenotypes, as measured by flow cytometry, were similar between allergic rhinitis and NAR patients [2], whereas there were no IgE-positive cells or local

Table 1. Prevalence of local allergic rhinitis

Study	Study design (number of patients)	Allergens (method)	Definition of positive NPT	Prevalence of LAR (each allergen)	Nation, age (range)
Carney <i>et al.</i> [5]	IR 23, AR to perennial aeroallergens 8, NC 8	DP/DF, cat/dog, grass pollen mix Excluded NH Single-dose challenge Spray 100 µl of each allergen	Rhinometry: >50% increase nasal resistance VAS: χ	61.9% (13/21 IR patients) DP/DF: 84.6% (11/13) Cat/dog: 7.7% (1/13) Grass: 15.4% (2/13)	UK, NA
Rondon <i>et al.</i> [2]	NAR 50, AR to DP 30, NC 30	DP Excluded NH Multiple doses challenge Spray two puffs (0.05 ml) of each dose	Rhinometry: >30% decrease nasal volume and VAS: >30% increase total score	54.0% (27/50 NAR patients)	Spain, 18–70
Rondon <i>et al.</i> [12]	Rhinitis 147 (seasonal IR 32, AR to pollen 35, AR to HDM 30, NC 50)	Grass and <i>Olea europea</i> (outside in pollen season) Excluded NH Multiple doses challenge Spray two puffs (0.05 ml) of each dose	Rhinometry: >30% decrease nasal volume and VAS: >30% increase total score	Grass: 62.5% (20/32 seasonal IR patients) <i>Olea europea</i> : 15.6% (5/32 seasonal IR patients)	Spain, 18–70
Rondon <i>et al.</i> [14]	Rhinitis 428 (NAR 42, AR to aeroallergens 270, LAR to aeroallergens 110), NC 25	Multiple aeroallergens (DP, <i>Alternaria alternate</i> , <i>Olea europea</i> , grass pollen, dog and cat epithelia) Excluded NH Single-dose consecutive challenge Spray two puffs (100 ml) at 15-min intervals	Rhinometry: >30% decrease nasal volume and VAS: >30% increase total score	25.7% (110/428 rhinitis patients)	Spain, 14–68
Cheng <i>et al.</i> [7]	NAR 147, NC 20	DF Excluded NH Multiple doses challenge Filter paper for 10 min of each dose	Rhinometry: >30% decrease nasal volume and VAS: >30% increase total score	8.2% (12/147 NAR patients)	China, 9–78
Jang and Kim [8]	Rhinitis 262 (NAR 110, AR to DP 152)	DP Excluded NH Single-dose challenge Spray (~50 µl)	Rhinometry: >29% decrease nasal volume (regardless of VAS)	10.9% (12/110 NAR patients)	South Korea, 11–69
Jung <i>et al.</i> [9]	Rhinitis 150 (NAR 75, AR to DF 69, LAR to DF 6)	DF Excluded NH and subclinical AR Single-dose challenge Spray (40–50 µl)	Rhinometry: χ VAS: >6.5 increase total score with ≥ 2 increase nasal obstruction score	4.0% (6/150 rhinitis patients)	South Korea, 6–78
Buntarickpornpan <i>et al.</i> [11]	NAR 54, AR 2	DP Excluded NH Multiple doses challenge Spray two puffs (0.125 ml each) of each dose	Rhinometry: >25% decrease nasal volume/>40% decrease nasal airflow (regardless of VAS) or VAS: >5 increase total score with >20% decrease nasal airflow	3.7% (2/54 NAR patients)	Thailand, 8–18
Krajewska-Wojtyś <i>et al.</i> [10]	NAR 101, AR to aeroallergens 115	Common aeroallergens Excluded NH Single-dose challenge Spray 100 µl of each allergen	Rhinometry: $\geq 30\%$ decrease nasal volume and VAS: $\geq 30\%$ increase total score	52.5% (53/101 NAR patients)	Poland, 12–18
Bozek <i>et al.</i> [13 ^a]	Rhinitis 219 (NAR 85, AR to aeroallergens 85, LAR to aeroallergens 46)	Common aeroallergens Excluded NH Single-dose challenge Spray of each allergen	Rhinometry: >30% decrease nasal volume and VAS: >30% increase total score	21.0% (46/219 Rhinitis patients) DP: 63% (29/46) Phleum: 23.9% (11/46) Alternaria: 43.5% (20/46) Birch: 19.6% (9/46) Alder: 10.9% (5/46) Hazel: 95.7% (44/46) Artemisia: 6.5% (3/46) Cladosporium: 4.3% (2/46) Cat: 4.3% (2/46)	Poland, 65–85

χ , not measured; AR, allergic rhinitis; DF, *Dermatophagoides farinae*; DP, *Dermatophagoides pteronyssinus*; HDM, house dust mite; IR, idiopathic rhinitis; LAR, local allergic rhinitis; NA, not analyzed; NAR, nonallergic rhinitis; NCs, normal controls; NH, nonspecific nasal hyperactivity; NPT, nasal provocation test; VASs, visual analogue scale for nasal symptoms.

IgE production in the nasal mucosa of asymptomatic atopic controls.

A previous study explained the reason for the absence of systemic allergic responses in LAR by

comparing immunologic properties of nasal secretions and blood between allergic rhinitis and LAR [17]. The level of IL-10 in blood was significantly higher in LAR than in allergic rhinitis, and the levels of IL-13, IL-5,

IL-10 and transforming growth factor-beta (TGF- β) in the nasal secretions were also higher in LAR than in allergic rhinitis. Although that study evaluated a relatively small number of study samples and did not explain elevations in Th2 cytokines in LAR compared to allergic rhinitis, it advocated that the prominent immunomodulatory properties of LAR could lead to no systemic allergic responses. Further studies are needed to elucidate exact mechanisms for LAR.

DIAGNOSIS OF LOCAL ALLERGIC RHINITIS

The diagnosis of LAR must be considered in patients without systemic allergic responses to allergen exposure. Detailed medical history and physical examination of nasal mucosa cannot provide a clue to discriminating between LAR and NAR, although longer disease duration, younger women, non-smoker and severe and persistent symptoms are the key features of LAR in several studies [9,14].

It is necessary to optimize diagnostic tools to diagnose LAR because a large number of patients with LAR can be misdiagnosed as NAR. NPT is a widely used diagnostic method in patients with negative results in SPT or serum-specific IgE measurement, and its sensitivity and specificity showed relatively high compared to other methods, such as detection of nasal allergen-specific IgE, tryptase or eosinophil cationic protein [8,18,19]. A positive response to NPT was determined based on both an increase in the VAS scores and a decrease in nasal volume by acoustic rhinometry. Standardized study protocols and accepted diagnostic criteria vary among individual studies. Many studies used an increase in total VAS scores by more than 30% and a decrease in nasal volume measured by acoustic rhinometry at 2–6 cm by more than 30% from baseline as diagnostic criteria [2,20], whereas some studies used other criteria, including a change in total nasal symptom score (>6.5) and a change in total nasal volume ($>27.6\%$) [8]. Moreover, rhinometry is often impractical and has limited value in patients who have nasal diseases, such as chronic sinusitis or nasal septal deviation, which are common comorbid conditions in rhinitis patients. A recent study used only a change in VAS scores from baseline after NPT for *D. farinae* to diagnose LAR [9]. NPT is considered the gold standard method to diagnose LAR in patients; however, standardized protocol, method and interpretation are necessary to establish clear criteria and to perform further studies on LAR patient.

Local synthesis of IgE in the nasal mucosa was the first step to developing LAR. Powe *et al.* [4] detected allergen-specific antibodies in nasal tissue from 30% of the NAR patients, although nasal

biopsy is an invasive and impractical procedure. Since the first detection of local IgE to *D. pteronyssinus* in nasal tissue in 1975 [3], many investigators have attempted to develop easy and effective methods for collecting secretions from the nose. Nasal saline lavage has been widely used to detect allergen-specific IgE antibodies and other mediators during or after NPT. However, this procedure was not feasible without patient cooperation and showed a low sensitivity of 22–40% due to dilution effect [2,12]. Allergen-coupled cellulose derivative use, nasal scraping, microsuction, aspiration and filter disk use can be alternative methods [21]. Recently, nasal packs have been used to detect nasal-specific IgE to *D. farinae* after NPT [22]. This method is noninvasive and reproducible [23], but the standardized protocol for the interpretation of positive results is required to apply in the diagnosis of LAR.

Target organ mucosa is the primary site producing allergen-specific IgE antibody. If a large amount of IgE secretes into systemic circulation, we can detect it in the blood by the conventional technique. However, if it is not sufficient, the basophil activation test (BAT) can be another option to evaluate the presence of allergen-specific IgE in effector cells. Gomez *et al.* [24] reported that 50% of the LAR patients who were diagnosed by NPT showed positivity to HDM allergen challenge, and that BAT had excellent positive (89%) and negative predictive values (62%). The usefulness of BAT was reevaluated using olive tree pollen. The sensitivity of BAT was 66.6% to *Olea europaea*, even 33% to a component allergen, nOle e 1 [25]. Collectively, this test has higher sensitivity than diagnostic methods for detecting nasal allergen-specific IgE antibody and is less time-consuming than NPT.

TREATMENT OF LOCAL ALLERGIC RHINITIS

On the basis of similarity of pathologic mechanisms between allergic rhinitis and LAR, it is reasonable to apply the same therapeutic strategy. Oral antihistamines and intranasal corticosteroids are the most frequently prescribed drugs, but their therapeutic efficacy was not sufficient for LAR patients because a worsening of rhinitis is detected, with an increase in symptom severity during a follow-up period. The use of oral antihistamines in LAR patients significantly increased after 5 years of follow-up [26].

Allergen immunotherapy (AIT) is the only disease-modifying treatment option in allergic diseases like allergic rhinitis. On the basis of immunologic characteristics of LAR, an earlier pilot study was undertaken in adult LAR patients sensitive to grass pollen [27]. Ten patients were treated with preseasonal subcutaneous

immunotherapy using grass pollen extracts for 6 months and another 10 patients received rescue medication only. The AIT group showed a significant improvement in nasal tolerance showing a higher threshold concentration in NPT to grass pollens 6 months after AIT compared to the only-rescue medication group. AIT also improved symptom scores and rescue medication scores (up to 45%) compared to the rescue medication-only group, without significant adverse effects.

A large randomized, double-blind, placebo-controlled study was conducted to investigate the effectiveness of AIT for 24 months in 36 LAR patients sensitive to *D. pteronyssinus* [28[¶]]. Subcutaneous immunotherapy to *D. pteronyssinus* significantly reduced total symptom medication scores and increased medication-free days compared to the placebo-treated group, after which 50% of the LAR patients showed negativity in NPT to *D. pteronyssinus* and serum-specific IgG4 level was elevated 12 months after AIT. AIT could be a safe and effective treatment for LAR and might be a new indication for AIT. However, the long-term benefit and the effect of different routes of AIT should be evaluated in future studies.

NATURAL HISTORY OF LOCAL ALLERGIC RHINITIS

Ten years have passed since this subtype was named LAR. Although several questions are answered regarding prevalence, diagnostic methods and so on, there are still unsolved questions regarding the prognosis or natural history of LAR.

Recently, a 10-year follow-up study was conducted by a Spanish group [29^{¶¶}]. A total of 176 patients with LAR were evaluated in terms of clinical progression, immunologic tests and NPT to allergens with 115 age-matched and sex-matched healthy controls. The majority of LAR patients had persistent perennial rhinitis with moderate severity at the time of diagnosis. After a 10-year follow-up, the clinical severity of LAR worsened with frequent emergency department visits and impaired quality of life. Conjunctivitis and asthma were the most common comorbidities at diagnosis; interestingly, the incidence of asthma increased from 18.8 to 30.7% and the average value of FEV1 dropped from 94.1 to 89.1% predicted after 10 years. Another study reported considerable changes in their sensitization status and tolerance [30]. The proportion of polysensitization rose from 36.4 to 52%, and tolerable allergen concentration in NPT fell for *D. pteronyssinus*, *Alternaria*, grass and olive pollens after 10 years compared to baseline. Nonetheless, the occurrence rate of allergic rhinitis was not significantly different

between LAR (9.7%) and healthy controls (7.8%) at the completion of the study. In contrast, there was an opposite report to the progression from LAR to allergic rhinitis determined by allergen skin test. They demonstrated that negative skin test responses were converted into positive results in 40% of LAR patients during 1–27 years of follow-up period in their observation study [30]. However, relatively smaller sample size, a retrospective design and a long time to conversion of LAR to allergic rhinitis might be weak points of that study.

Taken together, LAR is a clearly defined clinical entity with worsening symptoms and higher association with asthma over time. The clinical features need to be verified in long-term future studies.

CONCLUSION

LAR is a well-defined disease entity which should be considered in patients with persistent and severe symptoms without any systemic evidence of atopy. Although there has been much progress in the study of prevalence, diagnostic modalities and treatment responses, further research is needed to clarify the long-term disease course as well as geographic and ethnic differences.

Acknowledgements

None.

Financial support and sponsorship

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number: HI16C0992).

Conflicts of interest

There are no conflicts of interest.

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