



Review article

Update on local allergic rhinitis



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ABSTRACT

We here provide an update on the literature regarding local allergic rhinitis (LAR). In reviewing LAR, we have included an updated definition, classifications, mechanisms, comorbidities, and recommendations for diagnosis and treatment for LAR, as well as the defined research areas for future evidence-based studies. LAR is a localised nasal allergic response in the absence of systemic atopy characterised by local production of specific IgE (sIgE) antibodies, a TH2 pattern of mucosal cell infiltration during natural exposure to aeroallergens, and a positive nasal allergen provocation test response, with the release of inflammatory mediators. The localised allergic response of LAR is an important topic for the study of allergies. This review provides an update on the current knowledge of LAR.

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1. Introduction

In local allergic rhinitis (LAR), positive response to a nasal allergen provocation test (NAPT) and local specific IgE (sIgE) production occur [1]. LAR is seen in patients with rhinitis. In LAR and allergic rhinitis (AR) patients, symptoms of conjunctivitis and/or asthma and polysensitisation can be detected [2]. Symptoms suggestive of AR and negative skin prick test (SPT) and serum IgE are considered as LAR. During exposure to aeroallergens, local sIgE is detected in nasal secretions. Positive NAPT with local eosinophil cationic protein, and sIgE occur in LAR [3].

In Rondón et al. [1], Challenge of LAR patients with different

allergens to which subjects were already sensitised, but not with increasing concentrations. NAPT with multiple aeroallergens in LAR patients and non-allergic rhinitis (NAR) showed that several aeroallergen administration did not produce false-positive responses. Moreover, nasal priming effect, an increase in the reactivity of the nasal mucosa after repeated exposures to inhalant allergens to which the subject was previously sensitised [4], did not occur.

2. Definition

LAR is defined as a localised nasal allergic response and absence of systemic atopy. Specific IgE antibodies are produced locally. A TH2 pattern of mucosal cell infiltration during natural exposure to aeroallergens, and a positive nasal allergen provocation test response, release of inflammatory mediators such as tryptase and eosinophil cationic protein are detected. House dust mites (HDM), grass and olive pollens are responsible. For diagnosis, positive skin prick test or sIgE antibody detection are not needed. To identify the culprit allergen(s), NAPT is needed. In certain cases, local sIgE is detected in conjunctivitis and/or asthma patients. Whether LAR patients may have systemic atopy is not known exactly [5].

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3. Classification

Patients with NAR are considered non-allergic because SPT of them is negative and serum sIgE is absent. Furthermore, in these patients, local production of sIgE is detected [6–9]. LAR is proposed as a new etiological classification for rhinitis [10,11]. The classifications of AR, including AR (with systemic atopy) and LAR (without systemic atopy) [5,10,11], are shown in Table 1.

4. Epidemiological studies

LAR affects 25.7% of patients with rhinitis. More than 47% of these patients were previously diagnosed as NAR [12]. When SPT is negative and sIgE is undetectable, LAR might be present (47–62.5%). They may have perennial [6,13] or seasonal [7,14] symptoms. They may have been diagnosed as IR or NARES. LAR may be more frequent in some regions due to the levels of aeroallergens and exposure to them. Temperature, humidity and air pollution may influence LAR. Grass and olive pollen and HDM are important [5–9,13,14]. Occupational allergens, moulds and animal dander are also included. In Carney et al. [13] reported that 1 of 13 LAR patients responded to NAPT with a dog and cat allergenic extract mixture.

5. Mechanisms of Lar

5.1. Local production of sIgE and inflammatory mediators

Pathophysiology of LAR is understood totally; however, for local production of IgE, several underlying possible mechanisms have been reported. For example, nasal B cells express epsilon-germline gene transcripts and mRNA for IgE epsilon heavy chain [15]. When IgE results are negative, a T_H2 inflammatory pattern and increased IgE^+ B cells, mast cells, and eosinophils were detected via in situ hybridisation [16]. Nasal T_H2 IgE-mediated inflammation was confirmed by cytometric evaluations of nasal lavage fluid. Mast cells, basophils, eosinophils, $CD3^+$ T cells, and $CD4^+$ T cells increased when exposed to grass pollen compared to AR [7]. It was also detected in mite-induced perennial LAR [9]. In asymptomatic atopy, there is no symptoms and positive IgE tests. There is no local IgE production in nasal mucosa. In LAR, there are clinical symptoms and negative results of IgE [17].

Rondón et al. [6,7] detected nasal sIgE in NAR patients. They showed presence of nasal sIgE in LAR. Perennial and seasonal symptoms after aeroallergen exposure are 22% and 35% respectively. Possible reasons for not detecting sIgE maybe non-specific

protease activity stimulation of HDMs on airway innate immune cells. Powe et al. [18] showed free light chains (FLCs) in tissue and nasal secretions in AR and NAR patients. They may mediate hypersensitive immune responses involving mast cells.

5.2. T_H2 nasal inflammatory pattern

Inflammatory and neurogenic mechanisms and mucosal permeability changes are proposed for IR [10]. A T_H2 inflammatory pattern and mast cells, eosinophils, IgE^+ B cells [16], and T cells [19] increase have been found. Heterogeneity of NAR can be said and LAR is diagnosed in non-atopic subjects. In IR or vasomotor rhinitis, neurogenic mechanisms are present [6,7,16,19–21].

Inflammatory response, mediated by nasal T_H2 IgE has confirmed LAR [6,7]. Leukocyte–lymphocyte phenotype is similar in LAR and AR in flow cytometry. During natural aeroallergen exposure, mast cells, basophils, eosinophils, $CD3^+$ and $CD4^+$ T cells increase [6,7]. In these studies, more than 70% of patients with NAR and LAR showed NARES criteria such as nasal eosinophils >20%. In increase $CD8^+$ T-cells in AR and reduced antigen-presenting cells in IR were reported by Powe et al. [19]. In this study, NAPT was not performed and sIgE was not determined.

5.3. Positive NAPT responses

In different studies, IR diagnosis was changed to LAR in more than 47% of patients. They had positive NAPT responses and acoustic rhinometry [6–9,14] and anterior rhinomanometry [13] were also performed showing objective parameters. sIgE was detected in nasal secretions [6–9,13,14].

In LAR patients who had grass pollen sensitisation, sIgE local production and inflammatory mediators were detected after NAPT [8]. After nasal stimulation, mast cell and eosinophil activation; and IgE production were shown. Moreover, eosinophil cationic protein and tryptase were released in nasal secretions. There is correlation between tryptase release pattern and nasal itching and sneezing. Tryptase levels were higher at 15 min and 1 h after challenge compared baseline [8]. Positive NAPT responses to *Dermatophagoides pteronyssinus* were also detected in perennial LAR [9]. Nasal sIgE increased progressively 1–24-h after NAPT [8,9]. After nasal challenge, sIgE is secreted rapidly.

6. Clinical characteristics and comorbidities of Lar

In LAR patients, there are nasal symptoms of rhinorrhea, itching, sneezing and obstruction similar to AR. There are also ocular symptoms; and oral antihistamines and nasal corticosteroids can be recommended to these patients [6–8]. In LAR patients, the symptoms maybe intermittent or persistent, seasonal or perennial [6,7,27]. Severity of the symptoms maybe mild, moderate, or severe. There is also conjunctivitis and bronchial asthma symptoms [6–8]. According to the Rondón et al. [12], the main comorbidities of the LAR are conjunctivitis (51.1%) and asthma (18.8%). The most relevant allergen is *D. pteronyssinus* (51.1%). During the follow-up of the patients, rhinitis got worse (26.2%) after 5 years. New conjunctivitis and asthma symptoms are also detected. Atopy is present as 6.81% in LAR patients by SPT and/or serum sIgE.

In Rondón et al.'s study [2], LAR (25.7%), AR (63.1%) and NAR (11.2%) were diagnosed in the patients. For LAR and AR, they were non-smoking women, they have severe, persistent perennial rhinitis. Most of them have additional comorbidities of conjunctivitis and asthma. LAR onset was in childhood (36%). Aeroallergen polysensitisation was present in 37.3% of LAR patients by NAPT-M detected. *D. pteronyssinus* was detected in 60% of the LAR patients.

Table 1
Classification of allergic rhinitis with systemic atopy and without systemic atopy (local allergic rhinitis)^a.

Allergic rhinitis		
Allergic rhinitis (with systemic atopy)	Classical classification	1. Time of exposure to aeroallergen or aeroallergens: perennial, seasonal, and occupational
	ARIA classification (10)	1. Duration of symptoms: persistent and intermittent 2. Severity of symptoms: mild, moderate, and severe
Local allergic rhinitis (without systemic atopy)	Classical classification	1. Time of exposure to aeroallergen or aeroallergens: perennial, seasonal, and occupational
	ARIA classification (10)	1. Duration of symptoms: persistent and intermittent 2. Severity of symptoms: mild, moderate, and severe

^a Adopted from Refs. [5,10,11].

6.1. Local IgE production associated with nasal polyps

Nasal polyposis is known as chronic inflammatory process of the nasal and sinus mucosa. *Staphylococcus aureus* may induce the polyclonal IgE antibody synthesis against superantigens from *S. aureus* [22] and environmental allergens [23] in nasal polyp tissue. In LAR, the specific antibodies to aeroallergens are correlated with specific activation of B cells, mast cells, and eosinophils.

6.2. Local IgE production associated with asthma

B cells undergo IgE heavy chain class-switch recombination [24]. Interleukin (IL)-4 and IL-5 mRNA expression increase in lung tissue in asthmatic patients who are atopic and non-atopic [25]. There is positive response to bronchial challenge by *D. Pteronyssinus* [26].

7. Diagnosis

In the absence of systemic atopy, the detection of nasal sIgE, a positive NAPT response confirm LAR diagnosis. sIgE is determined in nasal lavage fluid during natural exposure or after NAPT [6,7]. Single aeroallergen (NAPT-S) is important diagnostic tool [6,7,13,14]. Its sensitivity is higher than nasal sIgE, tryptase, or eosinophil cationic protein level determination [6–9]. NAPT with multiple aeroallergens, the sequential application of several aeroallergens in one session, showed 100% concordance with the gold standard NAPT-S [1].

Patients have perennial or seasonal symptoms. Inferior and middle turbinates are seen as congested (boggy) and blue-grey. The reason for this appearance is excessive watery secretions and

increased vascularity [27,28]. A diagnostic algorithm for LAR is shown in Fig. 1 [2].

8. Tests for Lar

LAR was diagnosed by negative SPT and serum and a positive NPT [2]. The onset of the disease was in the childhood (in 1/3 patients). The major sensitising aeroallergen was HDM (60%). As proposed by Rondón, NPT, introduced by Marcucci and Sensi [29], detects IgE in nasal mucosa; is one method to diagnose LAR. NPT and nasal IgE positivity to *Alternaria* was detected in 70% of the LAR patients. SPT positivity ratio was 27% [30]. Polysensitisation to aeroallergens may occur in LAR and it may be detected by multiple NPTs [1].

Detection of local sIgE in nasal secretions during natural exposure to aeroallergens and a positive nasal allergen provocation test with local production of tryptase, eosinophil cationic protein, and sIgE are useful for detecting patients with LAR [3]. Local sIgE and inflammatory mediators (IL-1, IL-8, tumour necrosis factor [TNF], eosinophil cationic protein, and tryptase) are measured by appropriate sampling method to avoid false-negative results due to dilutional effects [31]. Active involvement of eosinophils and basophils, and T- and B-lymphocyte profiling has pointed to a localised CD4⁺ Th2-IgE-mediated cellular immunopathogenesis in Flow cytometry [6].

9. Treatment

Topical nasal corticosteroids and oral antihistamines are used for LAR treatment [6,7]. The effects of immunotherapy in LAR patients was investigated by Rondón et al. [32]. The LAR patients were sensitised to grass pollen. Preseasonal grass-specific subcutaneous

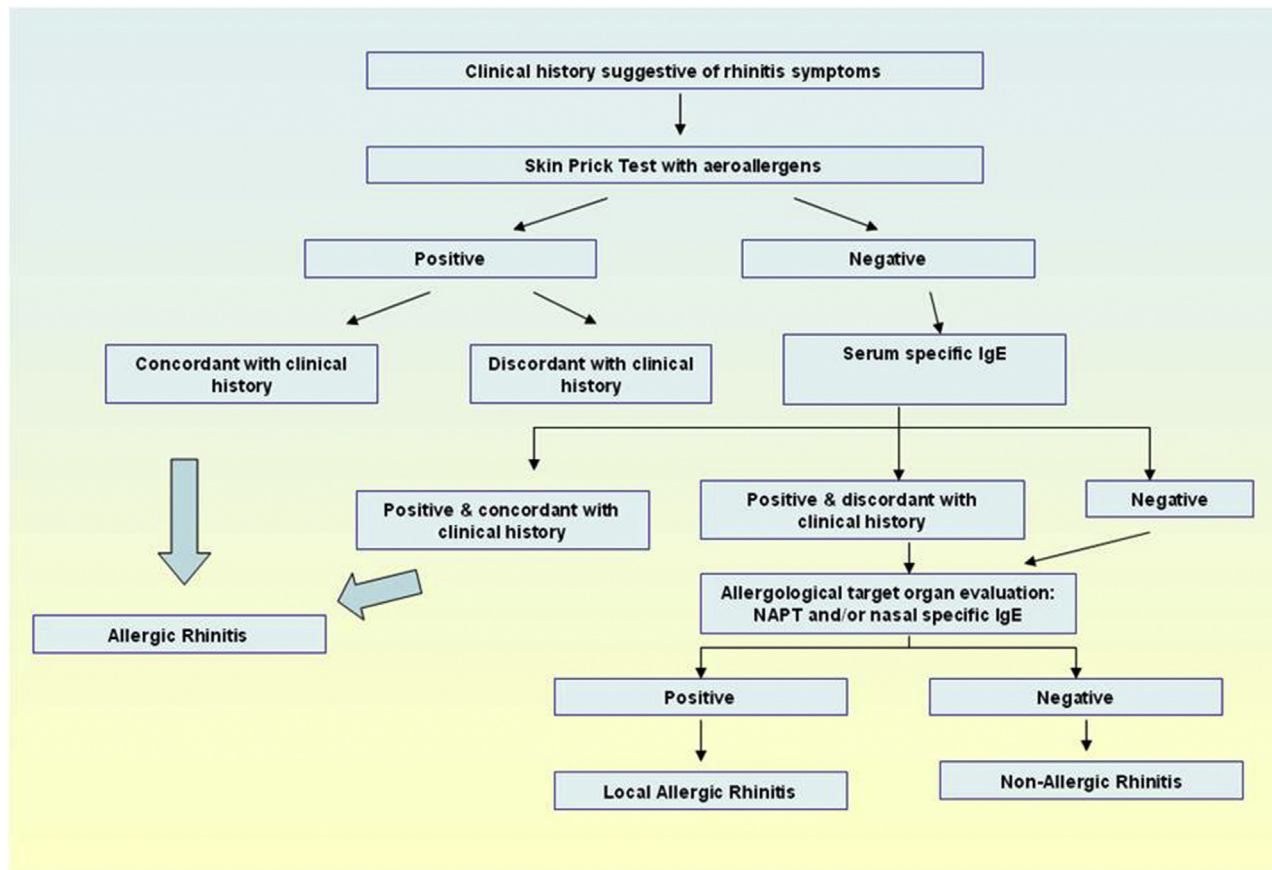


Fig. 1. Diagnostic algorithm for local allergic rhinitis. Prepared using Rondón et al., 2012 (2).

immunotherapy (SCIT) for 6 months and rescue medication in the spring (SCIT group); and rescue medication alone (control group) were given. SCIT reduced symptoms in LAR patients.

Topical corticosteroids are effective for congestion, rhinorrhoea, sneezing, post-nasal discharge [33]. Antihistamines suppress symptoms arising from IgE-dependent, as well as IgE-independent, mast-cell activation [33]. IgE is an independent sensitiser of mast cells and basophils; and monoclonal anti-IgE antibodies may cause bronchial hyperresponsiveness [34].

9.1. Avoidance

Avoidance of triggers (strong odours, perfumes, soaps, paint; and air pollutants, smoke fumes, tobacco smoke) is recommended [35,36].

9.2. Antihistamines

Intranasal antihistamines have significant effect on nasal congestion [37]. However they are generally less effective than intranasal corticosteroids for the treatment of AR [37].

Diphenhydramine, hydroxyzine, and clemastine are first-generation antihistamines. They have sedative effects (drowsiness and/or performance impairment) [38–40]. They are associated with impaired learning and school performance in children [41,42] and driving impairment [43–48]; and work impairment [35,40] in adults. When they are used with alcohol, sedatives, hypnotics, or antidepressant medication, performance impairment from antihistamines may have been enhanced [38,40]. Second-generation antihistamines have less or no tendency to cause these effects [37]. In this group, there are fexofenadine, loratadine, and desloratadine. They do not cause sedation at the recommended doses, loratadine and desloratadine may cause sedation at doses exceeding the recommended dose, and cetirizine and intranasal azelastine may cause sedation at recommended doses [37].

Efficacy of intranasal antihistamines is equal to [49] or superior to [50–52] oral second-generation antihistamines. Combination therapy with intranasal corticosteroids may provide added benefit [53]. Azelastine and olopatadine are approved for the treatment of seasonal AR. They improve congestion, rhinorrhea, sneezing, and nasal pruritus [51,52].

Oral H1-antihistamines undergo hepatic metabolism via the cytochrome P450 system and are prone to drug interactions [54]. Terfenadine, astemizole, and high doses of diphenhydramine also have arrhythmogenic actions [55,56]. Intranasal H1-antihistamines reduce itching, sneezing, runny nose, and nasal congestion [57–59].

9.3. Intranasal steroids

Intranasal corticosteroids may be useful for the treatment of some forms of NAR [38]. Local side effects of nasal irritation and bleeding are observed minimally. High drug concentrations can be achieved at receptor sites in the nasal mucosa with a minimal risk of systemic adverse effects [60–62]. Intranasal glucocorticosteroid is first-line treatment if nasal congestion is present [63–65]. Nasal antihistamines are more efficacious than intranasal corticosteroids [66,67].

Conflict of interest

Author **Niyazi Altıntoprak** declares that he has no conflict of interest.

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