



Local Allergic Rhinitis Revisited

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Abstract

Purpose of Review Local allergic rhinitis (LAR) represents a diagnostic and therapeutic challenge for clinicians. Even though it affects a considerable number of chronic rhinitis patients and a significant number of articles regarding prevalence, evolution, diagnosis, and treatment have been published, the condition remains still largely unrecognized and therefore misdiagnosed and mistreated.

Recent Findings LAR is a unique form of chronic rhinitis; it is neither classical allergic rhinitis (AR) nor non-allergic rhinitis (NAR). The symptoms, duration, severity, and complications of LAR are similar to those of AR and can affect adults and children. Thus, a portion of patients diagnosed with NAR or chronic rhinitis of unknown etiology may have LAR. The relationship between LAR inflammation and systemic allergic inflammation is unclear. Patients are frequently misdiagnosed with idiopathic NAR, and distinguishing between both entities is difficult without specific diagnostic tests. Underdiagnosis of LAR has implications on the management of these patients, as they are deprived of allergen immunotherapy (AIT) that has been demonstrated to modulate the immune mechanisms underlying allergic diseases.

Summary This review aims to comprehensively summarize the current knowledge on LAR and address unmet needs in the areas of disease diagnosis and treatment.

Keywords Local allergic rhinitis · Allergic rhinitis · Nasal IgE · Nasal provocation test · Allergen immunotherapy

Introduction

Rhinitis is a general term indicating any inflammatory disease of the nasal mucosa, defined by the presence of two or more of the following symptoms: nasal discharge, sneezing, nasal itching, and congestion. According to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, rhinitis is classified as intermittent (with symptoms present for ≤ 4 days per week or for ≤ 4 consecutive weeks) or persistent (with symptoms present for > 4 days per week and for > 4 consecutive weeks), while severity is based on estimation of impaired

items such as sleep, daily activities, work and/or school performance, and troublesome behavior and is classified as mild and moderate to severe [1, 2]. Chronic rhinitis (CR) is a very common disease with an increasing incidence, especially in the Western countries, where the actual prevalence in the general population is comprised between 20 and 40% [3].

CR can be classified in allergic rhinitis (AR) and non-allergic non-infectious rhinitis often simplified as non-allergic rhinitis (NAR) [4, 5•]. AR is a relatively homogenous condition characterized by eosinophilic inflammation as a result of IgE-sensitization to seasonal or perennial aeroallergens [4]. Atopic individuals are identified by skin prick testing (SPT) or the determination of allergen-specific IgE (sIgE) in serum [6, 7]. AR patients are positive for at least one of these two diagnostic tests of atopy [4], whereas NAR individuals test negative for both [5••].

On the contrary, NAR is a highly heterogeneous group including disorders characterized by either immunological or neurogenic inflammation [5••, 8]. Up till today, the following forms of NAR have been recognized: (1) hormonal rhinitis (pregnancy, associated to menstrual cycle, hypothyroidism); (2) rhinitis of the elderly; (3) gustatory rhinitis (hot and spicy

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foods, alcohol consumption, etc.); (4) drug-induced rhinitis (nasal decongestant “rhinitis medicamentosa,” aspirin, systemic alpha- and beta-adrenergic antagonist, phosphodiesterase inhibitors, calcium channel blockers, etc.); (5) occupational non-allergic rhinitis (irritants, corrosive substances); and (6) idiopathic rhinitis (IR) [9].

A subgroup of non-atopic patients will be positive for the nasal allergen challenge [10]. Local allergic rhinitis (LAR) is characterized by a localized nasal allergic response and the absence of systemic atopy since 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 (NAPT) response, with the release of inflammatory mediators such as mast cells, eosinophils, IgE, B cells, and T cells, are detected [11].

The objective of this review is to gain a better understanding and to emphasize the key role of IgE since the underlying mechanism of LAR has not yet been fully understood, and the relevant literature reports are scarce.

Epidemiology

In the last decade evidence regarding LAR is growing, and various studies report that LAR is an underdiagnosed entity, affecting a considerable number of chronic rhinitis individuals of different countries, ethnicity, and age [12–14].

Two recent systematic reviews and meta-analysis from Hamizan et al. have shed light into LAR prevalence [15, 16]. The first one included data from 3400 patients and healthy controls reporting a 24.7% probability of a positive nasal allergen challenge (NAC) in rhinitis patients that were negative for both SPT and serum sIgE [15]. The second one included 648 non-atopic rhinitis patients which reported a 10.2% of detectable nasal sIgE among them, whereas among those with a history suggestive of allergy, the proportion increased to 19.8% [16].

It had been suggested that LAR prevalence in Mediterranean countries (Portugal, Spain, Italy, or Greece) might be higher than in Northern European countries [17]. A recent study from Poland reported similar results [18]. In terms of East versus West, studies from Asian countries do however show a lower (<20%) prevalence of LAR as compared with Western countries with house dust mite (HDM)—*Dermatophagoides pteronyssinus* (*Der p*) being the most common allergen [19–21].

Similarly, prevalence of LAR in pediatric population is higher in Western countries (range 36.7–66.6%) [22, 23] compared with Asian [24, 25]. The largest study has been performed in 121 NAR children with seasonal rhinitis in Poland, where LAR to several pollens (*Phleum* spp., *Artemisia* spp., and birch) was confirmed by NAPT in 17 (16.6%), 6 (5.9%), and 9 (8.9%) patients, respectively [26•].

History of Local IgE Production and Local Allergic Rhinitis

The concept of local IgE production is widely accepted nowadays, though it is not a new finding. In the early 1970s, the detection of ragweed-specific IgE antibodies in nasal secretions of AR patients [27] and soon after, the detection of *Der p* specific IgE antibodies of patients with negative SPTs by Huggings and Brostoff confirmed the theory [28]. Afterwards, Johansson and Deuschl introduced a nasal spray washing method to detect specific IgE in nasal secretions in 52 out of 60 patients with negative allergy tests [29]. It was not until the last decade with the introduction of “entopy” that more and more researchers focused on the local production of IgE in nasal mucosa [30].

LAR was first described by Rondón et al. [31], who showed that NAPT could detect positive cases in patients diagnosed with NAR depending on the negative results of SPTs or sIgEs [32]. Similar findings were reported in a cohort of 176 patients with LAR and 115 healthy controls (matched to age and gender). This prospective 10-year study showed that LAR is a chronic condition tending to clinical worsening and is associated with conjunctivitis and bronchial symptoms. The results showed that 9.7% of LAR patients turned into AR compared with 7.8% of healthy controls implying that LAR is an independent rhinitis phenotype [33•].

Pathophysiological Aspects

The pathophysiology underlying local production of sIgE in LAR has been a subject of interest for different groups, and a number of possible mechanisms involved in the local production of IgE have been reported. There is evidence that B cells in the nasal mucosa express epsilon germ-line gene transcripts and mRNA for the epsilon heavy chain of IgE [34]. In patients with negative skin tests, a type 2 inflammatory pattern, with increased number of IgE + B cells, mast cells, and eosinophils, was detected by in situ hybridization [35]. Localization of follicular lymphoid cells (FLCs) in tissue and nasal secretions of patients with AR and in some with NAR has been demonstrated suggesting that they could function to mediate hypersensitive immune responses involving mast cells [36].

Even though the precise chain of phenomena leading to AR have not been demonstrated in LAR, the existence of a nasal Th-2 IgE-mediated inflammatory response has been shown in patients with LAR leading to immediate activation of mast cells and eosinophils with the nasal release of characteristic pro-inflammatory mediators: tryptase and eosinophil cationic protein (ECP) [37, 38]. The presence of nasal sIgE in patients with LAR during periods of non-exposure to HDM and grass pollen and their fast and progressive increase of 24 h following NAPT demonstrates the persistent local production of the

IgE which rapidly increases after allergen stimulation in the nasal mucosa [39, 40].

Flow cytometric studies in nasal lavage fluid have demonstrated that patients with LAR and AR had a similar leukocyte-lymphocyte phenotype with increased levels of eosinophils, basophils, mast cells, CD3⁺ T cells, and CD4⁺ T cells during natural exposure to aeroallergens [10, 32]. Additionally, an increase in CD8⁺ rather than CD4⁺ T cell in patients with NAR and AR is compared with controls and reduced numbers of antigen-presenting cells in patients with idiopathic rhinitis (IR) compared with those with AR [41].

The functions of other cells within the lymphoid lineage, such as innate lymphoid cells (ILC), invariant natural killer T cells, or tissue-resident memory T cells, have not been investigated to date in LAR. Type 2 ILC (ILC2) have been related to eosinophilic nasal inflammation in humans, and they might have a role in reactivating memory T and B cells in LAR individuals [42]. Further investigation is needed to establish whether FLCs have an adjuvant or independent role in patients with IgE-mediated allergy and to elucidate the presence of FLCs in patients with LAR.

Diagnosis

The diagnosis of LAR presents a challenge for clinicians and should be based on a detailed clinical history, the demonstration of a nasal allergic response to aeroallergens by NAPT in patients with negative SPT and non-detectable serum sIgE, and the exclusion of chronic rhinosinusitis with/without nasal polyps (Fig. 1) [43, 44].

The position paper of the European Academy of Allergy and Clinical Immunology (EAACI) on the standardization of nasal allergen challenges indicates the NAPT as the gold standard for LAR diagnosis. NAPT displays the optimal sensitivity and specificity [45]. Furthermore, standardized allergen extracts should be used, the allergens should be applied bilaterally, and the measurement of the NAPT outcome should be based on both subjective (nasal-ocular symptoms) and objective (nasal patency) parameters [46]. To assess the nasal patency, several methods are acceptable: peak nasal inspiratory flow (PNIF), active anterior rhinomanometry, acoustic rhinometry, and four-phase rhinomanometry. A NAPT is considered positive if the patient experiences a very significant change in symptom score or in nasal patency. The NAPT can be also considered positive if moderate changes occur simultaneously in both parameters [45–47].

Several sampling techniques have been used to measure nasal sIgE (secretions, scraping, brushing, tissue, etc.), and even though not all of them have been applied to LAR, the sensitivity of the measurement for LAR diagnosis is considerably lower than that of NAPT (positive in 20–43% of LAR cases) even when measured after allergen provocation,

probably because of a dilution effect of nasal lavage [48, 49]. Therefore, nasal sIgE should not be recommended for routine LAR diagnosis and regarded mostly as a research tool [50, 51].

The basophil activation test (BAT) represents a validated and reproducible technique for in vitro diagnosis of sensitization to aeroallergens [52]. Studies from different groups reported that 50–53.3% of HDM-LAR patients have positive BAT responses [53]. Even so, it also should be considered as a research tool or in the first steps of a rational diagnostic approach when NAPT is not available, and more studies are needed to validate its diagnostic performance.

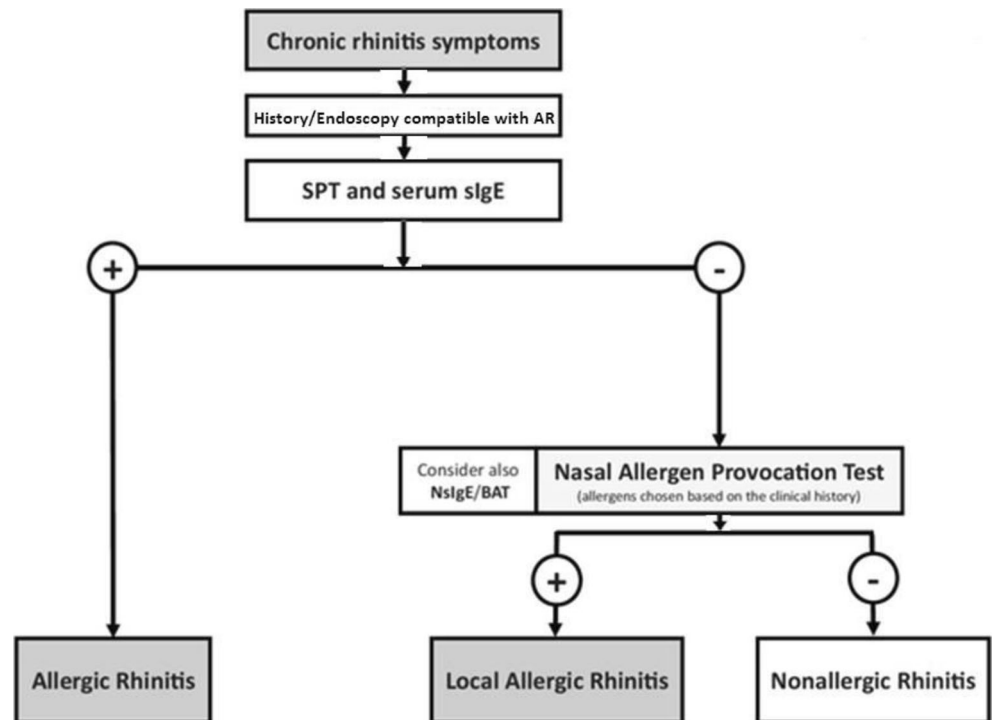
Local Allergy in Chronic Rhinosinusitis and Superantigens

Chronic rhinosinusitis (CRS) is defined as a chronic inflammation of the nasal cavity and sinuses. The disease is divided into two major subgroups based on the existence or not of nasal polyps and chronic rhinosinusitis with or without nasal polyps, respectively (CRSwNP and CRSsNP), exhibiting different pathogenic mechanisms and clinical manifestations [54, 55•, 56•]. CRS has a complex pathogenesis, including allergies, inflammation, infections, anatomic abnormalities, genetic factors, superantigens, and bacterial biofilms [57, 58].

Some researchers have suggested that local elevations in IgE might be caused by a different factor, fueling up the conversation regarding superantigens (SEs). Production of local IgE has been found to be upregulated in the lavage fluid of CRSwNP patients, without the elevation of serum IgE [59]. Even though the pathway is different compared with classical allergic inflammation, SEs appear to activate a large number of T and B cells producing local polyclonal IgE. The existence of SEA- and SEB-sIgE in nasal polyps suggests a role for SEs in the pathogenesis of CRSwNP [60]. Currently, six SE subtypes have been identified: SEA, SEB, SEC, SED, SEE, and toxic shock syndrome poison-1 (TSSP-1) [61]. In a recent study using flow cytometry, SEA-, SEB-, and TSSP-1-positive T cells were increased in the nasal polyps of CRSwNP patients [62]. Excluding superantigens, local allergic inflammation may be the main reason for the elevation of local IgE in non-allergic CRSwNP. In particular, IgE levels in local tissues increased in eosinophilic CRSwNP, with no evidence for systemic allergy or SEs [63], and similarly, local IgE levels were elevated in eosinophilic CRSwNP patients without systemic allergy but with local allergic inflammation [64]. On the other hand, another study of 31 CRSwNP patients and 13 cases of CRSsNP failed to identify SEs in cases of CRS [65].

Thus, whether elevated local IgE levels in CRSwNP patients are caused by superantigens or local allergic inflammation still remains unknown.

Fig. 1 Diagnostic algorithm for chronic rhinitis



Local Allergic Asthma

In the existing literature, there is evidence suggesting an overlap between atopic and non-atopic asthma. Certain studies have demonstrated increased numbers of B cells undergoing IgE heavy chain class-switch recombination, with an increase in *IL4* and *IL5* mRNA expression in lung tissue from both atopic and non-atopic asthmatic patients [66, 67].

These findings have led to support of the theory of an equivalent of LAR element affecting patients with asthma. The efficacy of therapy with anti-IgE in some severe non-atopic asthma patients also suggests the possible presence of local IgE although a biopsy study proved negative [68, 69]. However, the association between more severe asthma and more severe nasal disease, i.e., CRS rather than simply rhinitis, suggests that, if present, in severe asthma, the local IgE may be polyclonal and related to *S. aureus* stimulation of T cells, as in nasal polyps, rather than the lower mono- or oligoclonal levels found in LAR [70].

The frequent association between LAR and asthma suggests a local allergic response in the bronchial mucosa of these patients [71]. The results of a study detecting a clinical and inflammatory allergic response after bronchial provocation test with *Der p* in LAR-asthmatic patients support this hypothesis [72]. The presence of sIgE in nasal or bronchial secretions is not sufficient to induce an allergic response by itself, and a study conducted in non-atopic asthmatic patients has detected sIgE in induced sputum that able to bind *Der p1* and *Der p2* major allergens and to activate basophils but unable to induce an allergic response after DP-BPT [73, 74].

Overall, these data support the existence of a bronchial counterpart of LAR in some non-atopic asthma patients, highlighting the pathophysiological links between the upper and lower airways and reinforces the united airways concept. However, functional studies are needed to investigate the underlying mechanisms of the bronchial allergic response.

Local Allergic Rhinitis Treatment

Oral antihistamines and intranasal corticosteroids, alone or in an intranasal formulation of fluticasone + azelastine (MP-AzeFlu) in severe cases, are the two traditional cornerstones of AR treatment [75]. Clinical experience indicates that these drugs are similarly effective in LAR patients as compared with AR individuals. This fact is not surprising, as both entities share many clinical and pathophysiological features, including the eosinophilic nasal inflammation and the reactivity to the allergens. No study has evaluated to date the therapeutic performance of oral antihistamines or nasal steroids in LAR patients, and only recently, a cluster analysis of rhinitis endotypes found an association between LAR and histamine metabolites [76].

According to the “allergic/atopic march” hypothesis and to the “united airways disease” concept, AR can be associated to lung function test abnormalities and/or anticipate the onset of asthma [77–79]. Thus, an important aim of the therapy of AR with identifiable allergenic triggers should be also prevention of the progression to asthma or other respiratory diseases, in addition to ameliorating patient’s life quality. Such a goal may

be reached through the inclusion of allergen-specific immunotherapy (AIT) in the early treatment of AR. SIT—unlike symptomatic drugs—has been demonstrated to modulate the immune mechanisms underlying the allergic disease, and, therefore, it is the only treatment that currently could modify the natural history of allergic diseases [80].

In the last decade, four different studies have provided evidence that subcutaneous immunotherapy (SCIT) is an effective and well-tolerated treatment for LAR: one observational study of SCIT with a mixture of six grass pollens [81], and three doubled-blind placebo-controlled clinical trials (DBPCCT) of SCIT with *Der p* [82], *Phleum pratense* [83], and *Betula verrucosa* pollen [84]. The clinical effect of SCIT in LAR patients induces significant improvements in combined symptoms-medication scores, number of medication-free days, quality of life, and tolerance to higher allergen concentration in NAPT [80–85].

Conclusions

Even though the relationship between local allergic inflammation and systemic allergic inflammation is unclear, LAR is a well-differentiated clinical entity with a natural evolution toward worsening and involvement of the lower airway. LAR is an example of precision medicine, where a correct early diagnosis through NAC enables the establishment of an etiologic treatment in means of AIT, facilitating the improvement in quality of life in the years to follow and potentially preventing the development of lower airway disease.

Since the mechanism of LAR has not been fully understood and the relevant literature reports are scarce, there is an urgent need to continue studies on this topic.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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