Chapter

Local Allergic Rhinitis: An Old Story but a New Entity

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Abstract

Local allergic rhinitis (LAR) is a novel concept defining clinical allergic rhinitis with no evidence of systemic sensitization to aeroallergens. In this unique condition, the allergic response is confined to the nasal mucosa and can be demonstrated using different methods such as the immunoglobulin-E (IgE) level in the nasal secretions, nasal provocation test (NPT), or basophil activation test (BAT) with specific allergens or more sophisticated molecular diagnostic techniques. Furthermore, local allergic rhinitis can be relieved by interventions used to treat systemic allergic conditions such as antihistamines or anti-IgE monoclonal antibodies. Last but not least, several small studies demonstrated the efficacy of allergen immunotherapy for ameliorating LAR symptoms. In this chapter we reviewed old data and new concepts regarding clinical manifestation, plausible mechanisms, and treatments of LAR. The long-standing question whether LAR is an integral part of the "atopic spectrum" or it is a single-organ immune-mediated disease, is yet to be determined.

Keywords: allergic rhinitis, local allergic rhinitis, mite, rhinitis, immunotherapy

1. Definition of local allergic rhinitis

Local allergic rhinitis (LAR) is defined by symptoms suggestive of allergic rhinitis (AR), but with no detected sensitivity to an allergen using common allergy testing, while allergen-specific immunoglobulin-E (IgE) in the nasal mucosa can be detected.

2. Background

The first report of local production of IgE in the nasal mucosa was documented in 1975 among patients with typical symptoms of allergic rhinitis and negative allergy evaluation (i.e., negative skin prick tests (SPT) or serum-specific IgE (sIgE)). In this early report, specific IgE antibodies to *Dermatophagoides pteronyssinus* (house dust mite) had been detected in the nasal secretions of patients [1]. Later on, several methods to detect IgE in nasal secretions were evaluated, but only in 1989 a direct measuring technique was established [2]. This was tracked in

2010, by defining the concept *entopy* as opposed to atopy. Although still somewhat controversial, *entopy* addresses local production of IgE in the nasal and respiratory mucosa, while atopy is characterized by serum-specific IgE and positive skin reaction [3, 4]. In recent years advances in documentation of nasal IgE production among patients with typical symptoms of allergic rhinitis substantiated the entity of LAR, which is now accepted and relevant worldwide.

3. Prevalence

The prevalence of LAR is uncertain and was long considered a rare disorder. In recent years, with the improvement of diagnostic methods, new and surprising data has emerged. In 2012 Rondon et al. reported a prevalence of 25.7% of LAR among a group of 428 adult patients with chronic rhinitis. In the same cohort, 63.1% were diagnosed with AR and 11.2% with non-allergic rhinitis (NAR). The most frequently causative allergen in both LAR and AR was *D. pteronyssinus* (*house dust mite*) [4]. Similar ratio between LAR and AR was reported by Bozek et al. among 219 elderly patients (mean age 65.8 years). The prevalence of LAR was 21% and that of AR was 40.2%, and *again D. pteronyssinus* was found to be the major culprit allergen [5]. However, this data was obtained in selected populations of patients with chronic rhinitis, while the prevalence of LAR in the general population is yet to be established.

4. Diagnosis of LAR

As mentioned above, LAR has to be considered in the differential diagnosis of AR, when no evidence of systemic atopy is present. The evaluation of a patient suspected to have LAR should include a detailed clinical history, typically resembling AR, as well as assessment of comorbidities, such as ocular, skin, and bronchial symptoms. This may enable further evaluation for systemic atopy or a filter for patients with non-allergic rhinitis (NAR; see **Table 1**). A detailed physical examination includes inspection of the nasal cavity via nasal endoscopy, and for some patients, a CT scan may be required to exclude other causes of chronic rhinitis. This should be followed by tests to verify sensitization to aeroallergens, either skin prick tests (SPT) or serum-specific IgE. It has been suggested that when there is a high index of suspicion of allergy and no reaction to SPT, intradermal skin tests to common aeroallergens may be considered. In the absence of evidence for systemic sensitization, one must prove local rhino-mucosa hyper-reactivity to aeroallergens in order to diagnose LAR [6, 7] (**Figure 1**). Three methods can be used to diagnose LAR:

1. *Nasal allergen provocation test* (*NAPT*) is considered the gold standard for LAR diagnosis. NAPT consists of eliciting a local nasal allergic response by exposure to allergens. A response is characterized by rhinorrhea, itching, sneezing, edema of the nasal mucosa, and increased airflow resistance following exposure of the nasal mucosa to a specific allergen. NAPT has the potential to differentiate between allergic (both AR and LAR) and the non-allergic rhinitis (NAR) or healthy controls. Furthermore, among allergic patients it could differentiate between clinically relevant and nonrelevant allergen sensitizations. NAPT could be done with single allergen or with multiple aeroallergens in one session [8]. In another study 60% of LAR patients responded immediately to nasal allergen provocation test (NAPT) with a specific allergen demonstrating

nasal symptoms, elevated tryptase (mast cell activation marker), and eosinophil cationic protein (ECP marker of eosinophil activation) [9, 10]. Notably, this method may highlight a subgroup of patients that suffers from both local and systemic sensitizations, namely, the "dual allergic rhinitis (DAR)" patient. For instance, a DAR patient may suffer from perennial symptoms, but his allergy testing will demonstrate sensitivity only to seasonal allergens, whereas his NAPT study will be positive to perennial allergens.

NAPT is a sensitive and specific technique, although it requires special training and is time-consuming [8]. Furthermore, it has some pitfalls. Nasal challenge with saline prior to NAPT is recommended to rule out non-specific nasal hyper-reactivity, which may induce a false-positive result. Having said that, there is yet lack of standardization regarding allergenic extract, dose, timing, and outcome definitions of NAPT [9].

2. *sIgE in the nasal secretions* is determined in nasal lavage fluid (e.g., after natural exposure), after NAPT, or following mucosal brushing [10]. Notably, sIgE could also be measured in nasal biopsies for more accurate results, but in the clinical practice, noninvasive methods might be preferable. The measurement of sIgE in nasal secretions is dependent on the technique used. Thus, although positive results are highly specific (>90%), sensitivity is rather low utilizing nasal lavage, ranging from 22 to 40%, most likely owing to dilution effect [7, 9]. Hence, when the lavage results are negative and there is a high index of suspicion, it is recommended to perform a more invasive procedure, as specified earlier.

3. *Basophil activation test* (*BAT*): Peripheral basophils are key cells in allergic responses and are involved in immediate IgE-mediated reactions. Their primary role is to degranulate pro-inflammatory mediators following stimulation and activation by allergens. Basophil activation can be measured by flow

- Chronic rhinosinusitis
    - With nasal polyposis (CRSWNP)
    - Without nasal polyposis (CRSW/ONP)
- Non-allergic rhinitis
    - Drug-related
    - Hormonal
    - Related to systemic diseases:
        1. Genetic disease: cystic fibrosis, primary ciliary dyskinesia
        2. Autoimmune/inflammatory diseases: granulomatosis, relapsing polychondritis, sarcoidosis
        3. Amyloidosis
        4. Malignancy related
    - Atrophic rhinitis
    - Occupational rhinitis (irritant)
    - Rhinitis medicamentosa
    - Anatomic defects:
        1. Local: Septal deviation, turbinate hypertrophy, adenoid hypertrophy (nonatopic variant)
        2. Nonlocal: Cerebrospinal fluid leaking

Table 1.
Differential diagnosis of allergic and local allergic rhinitis.

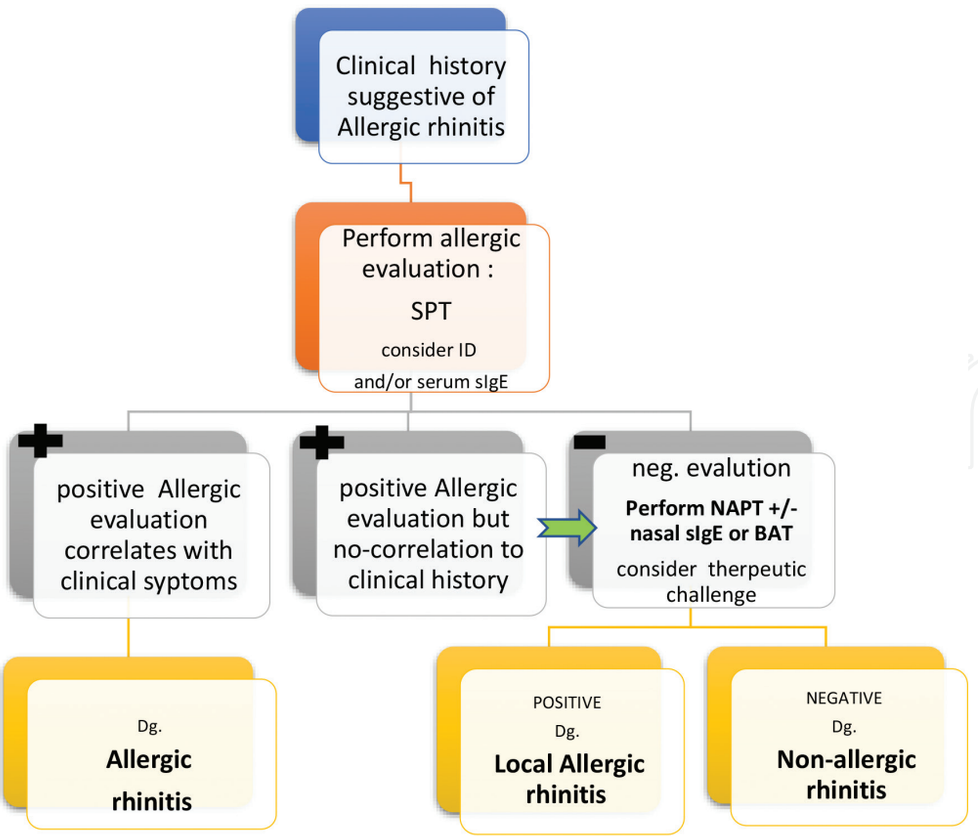

Figure 1.
Allergic rhinitis diagnostic algorithm. SPT, skin prick test; ID, intradermal skin tests; sIgE, specific IgE; NAPT, nasal provocation test; BAT, basophil activation test.

cytometry in which surface activation markers such as CD63 are quantified. The BAT is a flow cytometry-based assay performed on patient's peripheral blood, where the expression of these activation markers is measured following stimulation with allergen. BAT have been extensively studied and validated for in vitro diagnosis of sensitization to inhalant and food allergens, Hymenoptera venom, and several drug hypersensitivities [11]. The first evidence of specific basophil activation in peripheral blood from patients with LAR was reported in 2013 by Gome et al. [12], in which it was demonstrated for the first time that the activation of basophils in LAR patients was mediated by specific IgE to *D. pteronyssinus*. BAT was linked with 50% sensitivity and >90% specificity, which may be superior to the current data on sIgE in nasal lavage (e.g., specificity of 22%). In another study of patients with LAR to *Olea europaea*, BAT sensitivity was 66% with >90% specificity [7].

In summary, BAT has a medium-grade sensitivity and a high specificity for the diagnosis of local sIgE, which may outperform other methods for sIgE detection. It is less time-consuming; however, it is performer dependent compared to NAPT.

5. The pathophysiology of LAR

The pathogenesis of allergic rhinitis (AR) is well established. It is a Th2-mediated disease which involves mast cell activation, recruitment of eosinophils, basophils and T cells expressing Th2 cytokines, and secretion of interleukin as

IL-4, IL-13, IL-5, and others. The pathophysiology of LAR is less well established, and the question why the majority of allergic patients exhibit systemic sensitization (atopy) while some develop only local responses (entopy) is yet to be answered. Nonetheless, it has been suggested that the natural history of allergy is composed of multiple steps leading eventually to atopy. In a recent review, Dullaers et al. [13] suggested that the first step to atopy takes place in the nasal mucosa, where allergen-specific IgE is produced. The authors further hypothesized that some subjects lack spillover of these mucosal-produced allergen-specific IgEs into the circulation. In another study, the detection of allergen-specific IgE on the surfaces of peripheral basophils from patients with LAR eluded to the idea that the second step to atopy is on the surface of peripheral basophils and other target immune cells, followed by the third and final step which is the detection of serum-specific IgE and skin mast cell sensitization [12]. Thus, differences between LAR and AR may explain different stages of sensitization to allergen. For example, it was demonstrated that following nasal provocation of patients allergic to olive, the ECP levels in nasal lavage were significantly higher in both AR and LAR patients than in controls, while basophil activation test (BAT) was higher only in the LAR group, which potentially represents an earlier step in sensitization, associated more closely with LAR [14].

In contrast, similarities between AR and LAR pathophysiology were observed while evaluating the immunologic responses to therapy and particularly to immunotherapy. Namely, alike AR patients a significant increase of serum-specific IgG4 antibodies is observed following allergen immunotherapy among LAR patients. This not only substantiates the IgE-mediated mechanism of disease but also the notion that LAR may be the prodrome of AR [15]. Last but not least, allergen-specific IgEs to various allergens in the nasal scrapings from patients with AR, non-allergic rhinitis (NAR), and healthy controls were reported to be 86.7, 33.3, and 50%, respectively. Thus, although a wide difference between allergic and non-allergic patients was documented, a relatively high percent of IgE production was observed among controls [16]. One may suggest that healthy controls were sensitized but developed spontaneous tolerance, e.g., "a backward step" following the first, second, or third stage of atopy.

6. Local allergic rhinitis and comorbidity

AR is an essential part of the "atopic march" [17] and thereby associated with comorbidities, such as asthma, atopic dermatitis, food allergies eosinophilic esophagitis, allergic conjunctivitis, chronic rhinosinusitis with nasal polyposis (CRSwNP), and more [18]. The association of these comorbidities with local allergic rhinitis (LAR) was less explored [19], although bronchial symptoms have been reported in patients with LAR [20] and any chronic rhinitis is a risk factor for poorly controlled asthma with recurrent hospital visits [19]. Recently, self-reported bronchial symptoms, suggestive of asthma, were reported in over 30% of patients with LAR, suggesting a new asthma phenotype, "local allergic asthma" [21, 22]. As in classical allergic rhinitis, conjunctival symptoms were also associated with LAR. It was shown that patients with LAR experience ocular symptoms during nasal exacerbations due to allergen exposure or during in vitro nasal provocation tests [20]. In one study, this was the most prevalent comorbidity associated with LAR [23]. In a recent study by Rondon et al. [19], a 10-year follow-up of 176 LAR patients entailed other comorbidities, such as food allergy and drug hypersensitivity, which were documented only in few patients.

7. Treatment of LAR

In daily practice NAPT, BAT, or other specific tests are rarely performed. Hence, performing a therapeutic trial with antihistamines may be beneficial for diagnosis of LAR. Early and substantial response to antihistamine further supports an allergic histamine-driven mechanism. In the same line of thought, treatment with nasal corticosteroid spray may be clinically beneficial, but will not enable to differentiate causes of chronic rhinitis. Most LAR patients are currently treated similarly to AR patients, and according to the allergic rhinitis and its impact on asthma (ARIA) guidelines. This is done by using personal and environmental education, allergen avoidance measures and non-specific pharmacologic modalities, such as, intranasal corticosteroids, and oral and intranasal antihistamines [7–10]. Having said that, such non-specific therapy for LAR will ameliorate symptoms but alike AR will not change the natural progression of disease.

Immunotherapy is a common therapeutic modality for moderate to severe unresponsive AR. Allergen immunotherapy is based on gradual exposure to a culprit allergen via subcutaneous or sublingual exposure. This will eventually result in "induced tolerance" to the targeted allergen and amelioration of the allergic response. Allergen immunotherapy is highly effective and safe and confers long-term clinical benefit in adequately selected patients. Furthermore, it is the only etiological treatment for AR and asthma which conveys disease-modifying effect that can actually change the natural course of the disease [8, 9]. Thus, although LAR is by definition a local rather than systemic disease, few studies provide evidence for clinical benefit of allergen immunotherapy among LAR patients. These studies demonstrated a significant symptom improvement, an increase in the number of medication free days, and a beneficial effect on ocular symptoms, asthma control, and quality of life compared to placebo, as well as tolerance induction defined by an increase in allergen-specific IgG4 [6–8, 10].

8. Conclusions

In the last decade, growing evidence indicates that nasal reactivity to aeroallergens can occur in the absence of evidence of systemic atopy. The published literature raised the suspicion that many patients diagnosed previously as suffering from non-allergic rhinitis actually suffer from LAR. This may be of importance as treatment options differ between non-allergic and AR/LAR diseases. Diagnosis of LAR remains a challenge, as none of the diagnostic methods suggested are optimal nor commonly available in most centers. Therefore, high index of suspicion, utilizing specific methods if accessible as well as therapeutic challenge, may enable correct and early diagnosis. This may enable specific allergen-directed interventions (e.g., allergen immunotherapy), as well as early detection and treatment of comorbidities (like asthma and conjunctivitis). In this regard, implementation of NAPT, BAT, and other methods of diagnosis, especially in referral centers, as well as long-term studies to better define the mechanisms, course, and response to therapy of LAR, is needed.

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