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Local allergic rhinitis – a narrative review

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Abstract. – This narrative review aims to provide an up-to-date definition of local allergic rhinitis (LAR), its classification, mechanisms, comorbidities, recommendations for diagnosis and treatment, and define needs in this area. Both 'PubMed' and 'Science Direct' literature was reviewed systematically, and a manual search for studies not previously encountered in the databases was also carried out. Published studies were identified in PubMed covering the period from 1947 to 2022. The following keyword search strategy was used: (local allergic rhinitis* OR entopy* OR local Immunoglobulin E * OR nasal specific Immunoglobulin E). LAR involves Type 2 nasal inflammation with local IgE and cannot be diagnosed by systemic methods, such as skin prick or blood IgE tests. A nasal allergen challenge is necessary for diagnosis. LAR can respond to usual AR treatments, including allergen specific immunotherapy (AIT). LAR is a novel entity that requires additional investigation in terms of prevalence, proper diagnosis, treatment, and prognosis. The target outcomes and possible benefits of this review are to achieve a consensus for the study and diagnosis of LAR and increase interest in this area.

Key Words:
Atopy, Classification, Comorbidities, Local Allergic Rhinitis (LAR), Local IgE production, mechanisms, Rhinitis, Specific Immunoglobulin E (IgE), Nasal provocation test (NPT).

Introduction

Tissue IgE has been demonstrated in many organs[1-5]. The first evidence for local allergic rhinitis (LAR) came in 1975 when Huggins and Brostoff[6] demonstrated the existence of a positive response to nasal allergen provocation tests and the detection of *Dermatophagoides pteronyssinus*, specific IgE antibodies in nasal secretions of rhinitis patients with negative skin prick-tests and no detectable serum-specific IgE.

Subsequent studies[7-18] have confirmed the existence of a localized nasal allergic response in non-atopic rhinitis patients in what is now known as LAR[11] or entopy[17].

Definition

LAR involves typical AR symptoms without evidence of systemic IgE[8,19,20].

Type 2 inflammation in the nasal mucosa allows local IgE production and response to allergen provocation[8-12,19-21].

A positive nasal allergen provocation test is the gold standard for diagnosing LAR[7,8,19] due to the limitations of detecting locally specific IgE.

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Questions

The identification of LAR among non-atopic subjects with nasal symptoms has generated important questions for clinicians and researchers[19]:

1. What is the correct diagnosis of LAR, and what are the diagnostic restrictions?
2. What is the prevalence of LAR?
3. What influence do environmental factors have?
4. Are the underlying mechanisms different for LAR and allergic rhinitis (AR)?
5. Is there local IgE production beyond the nose involving lower airways and ocular mucosa?
6. What is the natural history of LAR? Is LAR a precursor of systemic atopy, or does it represent an independent and well-defined entity?
7. Is allergen sensitization the same in LAR as in AR?
8. How does LAR management differ from that of AR?

Literature Search

Both PubMed and ScienceDirect literature was reviewed systematically, and a manual search for studies not previously encountered in the databases was also carried out.

All the authors reviewed the findings to reach an informal consensus.

Published studies were identified in PubMed covering the period from 1947 to 2022. The following keyword search strategy was used: (local allergic rhinitis* OR entopy* OR local Immunoglobulin E* OR nasal specific Immunoglobulin E). All reference citations from selected papers within the 1947-2022 time frame that had not otherwise been identified in the initial search were reviewed, and relevant papers were added.

Classification

Patients with non-allergic rhinitis were previously considered non-allergic because they had negative skin prick test responses and non-detectable serum-specific IgE. However, some of these subjects react to an allergen with nasal symptoms, are positive for nasal allergen challenge, and have mucosal IgE[9-12]. This suggests that they are suffering from what is now termed Local Allergic rhinitis (LAR)[21,22]. A diagnostic algorithm for LAR is shown in Figure 1.

Epidemiology

The prevalence of LAR in Europe, as well as other populations, is unknown as there has been no systematic investigation. Studies[9,10,13,14,23,24]

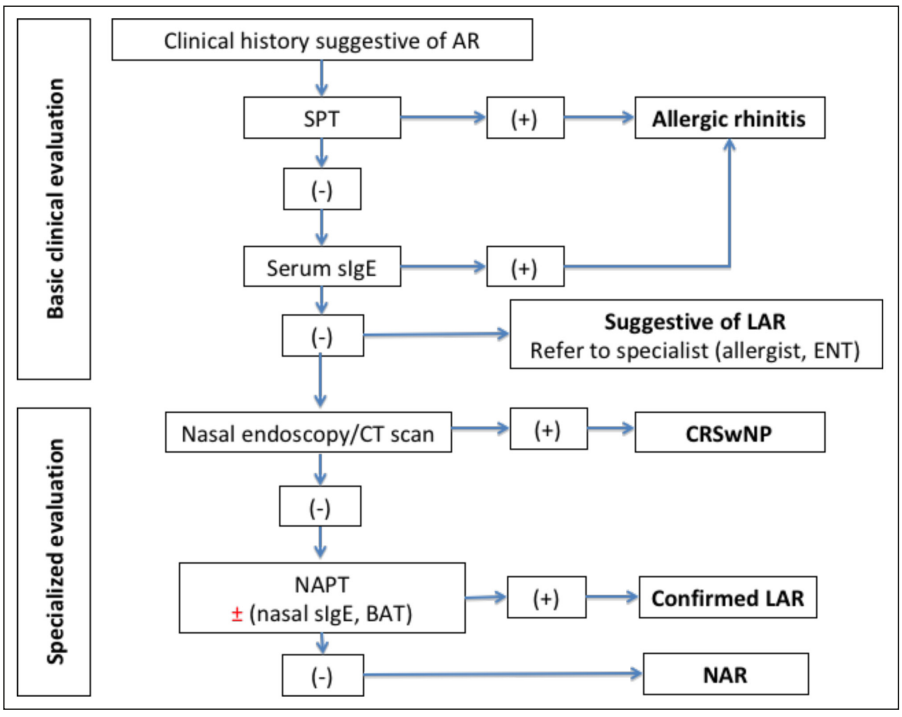

Figure 1. Diagnostic algorithm for Local Allergic Rhinitis (LAR). CRSwNP: Chronic rhinosinusitis with nasal polyposis; NAPT: Nasal allergen provocation tests; NAR: Non-allergic rhinitis; SPT: Skin prick test

evaluating individuals with rhinitis have shown that LAR is an under-/mis-diagnosed disease that may affect between 10-47% of patients previously classified as non-allergic rhinitis and may involve 25.7% of rhinitis patients referred to an allergy clinic[8]. LAR has been found[25,26] in rhinitis patients from different countries, ethnic groups, and ages. Its prevalence may be higher in the Mediterranean than in Nordic countries (Portugal, Spain, Italy, and Greece). House-dust mite-sensitive LAR was lower (<20%) in Asian than in Western countries[27].

In 1975, Huggins and Brostoff[6] studied a group of 14 patients with clinical histories strongly suggestive of allergic rhinitis to *Dermatophagoides pteronyssinus*, but with negative skin prick tests and serum-specific IgE. These patients were proven to be clinically allergic using nasal allergen provocation test and nasal detection of specific IgE against *Dermatophagoides pteronyssinus*. In 2002, Carney et al[13] performed weekly bilateral nasal challenges with different aeroallergens in 21 patients with idiopathic rhinitis. They observed a 62% positive response rate to nasal allergen provocation test, mainly to house dust mites. In 2005, Wedback et al[14] evaluated 17 patients with seasonal non-allergic rhinitis detecting a 47% positive response rate to nasal allergen provocation test with birch pollen.

In 2007, Rondón et al[9] evaluated a group of 50 patients with idiopathic perennial rhinitis during natural exposure to house dust mites and after bilateral nasal allergen provocation test with *Dermatophagoides pteronyssinus*, detecting a positive response to nasal challenge in 54% of cases. In 2008, the same group[10] performed a nasal allergen provocation test with grass and olive pollen in 32 patients with idiopathic seasonal rhinitis and observed a 62.5% positive response to the nasal allergen provocation test.

Fuiano et al[23] reported positive responses to nasal allergen provocation test with Alternaria in 30 out of 36 children (83.3%) with perennial rhinitis and negative skin prick tests.

More recently, in a large study[8] carried out in a South of Spain population evaluating more than 3,000 rhinitis patients, 25.7% of cases were shown to have LAR, and the onset of the disease in childhood in 36% of subjects was noted, indicating that this entity is not limited to adults and extends to ages as low as eight years.

Although the evidence for LAR is clear, more extensive population studies in children and adults using consensus procedures for detecting LAR are needed to determine the true prevalence and incidence of this allergic rhinitis.

Natural History

Determining whether LAR represents the initial phase in the natural progression of AR accompanied by systemic atopy or constitutes a distinct and consistent entity is a question that requires examination through prospective studies.

A study[28] of the development of LAR patients over five years revealed a 26.2% deterioration of rhinitis, an increase in symptom duration and intensity, and novel connections with conjunctivitis and asthma. After five years, individuals with LAR (6.8%) and healthy controls (4.5%) had similar rates of atopy[28]. This study will continue for ten years, and further patients will be included.

Allergens and Environmental Factors

The influence of environmental factors in developing LAR is unknown, but high levels of allergen exposure may predispose to LAR[29,30].

A few highly prevalent aeroallergens have been identified[7,9,11-13,19,21,28] as etiological antigens in LAR. These have included both perennial (house dust mites, molds, animal dander) and seasonal inhalant allergens (grass and olive pollen). Pet allergens are less often associated with LAR[8,13,19]. Further epidemiological studies are needed.

LAR Mechanisms

Local production of specific IgE is equally important in AR and LAR. In AR, local IgE production has been extensively described and is probably the initial phase of the disorder[31]. The nasal mucosa produces at least a large part of the specific IgE in allergic rhinitis patients.

Bachert[32] showed that the same IgE specificities were found in nasal secretions as in the corresponding serum of grass pollen and house dust mite allergic subjects.

In KleinJan et al's study[33], significantly more IgE-positive B-cells and IgE-positive plasma cells were found in the nasal mucosa of allergic patients than in that of non-allergic controls; specific IgE was found to be produced locally in the nasal mucosa in patients with seasonal allergic rhinitis and perennial allergic rhinitis, but not in non-allergic controls.

In LAR, allergen-specific nasal IgE has been found[6,9-13] after environmental allergen exposure and following provocation tests.

As with AR, kinetic studies[34-36] in LAR patients after nasal allergen provocation tests with grass pollen[11] and *Dermatophagoides pteronyssinus*[12] have revealed not only local IgE production but also immediate activation of mast cells and eosinophils with the nasal release of characteristic pro-inflammatory mediators: tryptase and eosinophil cationic protein. The presence of nasal-specific IgE in patients with LAR during periods of non-exposure to house dust mites and grass pollen and the rapid and progressive increase from 1 to 24 hours after nasal allergen provocation test, demonstrates persistent local production of IgE, which rapidly increases after relevant allergen stimulation in the nasal mucosa[11,12].

These findings suggest that the presence of specific IgE in the nasal mucosa of patients with rhinitis is better correlated with the appearance of clinical allergy than skin prick test or serum-specific IgE. The absence of nasal-specific IgE might explain the absence of symptoms in individuals with asymptomatic systemic sensitization (false positive skin prick test to allergens in the absence of clinical allergy)[36].

Several possible mechanisms underlying the local production of IgE have been reported[37,38]. B cells express epsilon germline gene transcripts and mRNA for the heavy epsilon chain of IgE in the nasal mucosa[37]. In patients with negative skin tests, an *in-situ* hybridization detected a Th2 inflammatory pattern (with an increased number of IgE+ B cells, mast cells, and eosinophils)[38]. The possible role of follicular lymphoid cells, noted by Powe et al[15], remains to be determined.

It is not known whether there are differentiating factors in the local synthesis of IgE in patients with AR and LAR.

Positive Nasal Allergen Provocation Test Responses

Studies[9-12,14] have demonstrated that up to 47% of patients given a previous diagnosis of non-allergic rhinitis actually had LAR with positive nasal allergen provocation test responses assessed by clinical symptoms plus objective parameters measured by acoustic rhinometry, anterior rhinomanometry[15], and/or nasal secretion with specific IgE and inflammatory mediators[9-14] (see Table I).

Following allergen provocation, the kinetics of tryptase in nasal secretions showed[11] a strong correlation with nasal itching and sneezing. Immediate responders had significantly higher levels of tryptase at 15 minutes and 1 hour after the test compared with baseline values, whereas dual responders showed[11] significantly increased levels from 15 minutes to 6 hours. These results were confirmed in patients with perennial LAR with positive nasal allergen provocation test responses to *Dermatophagoides pteronyssinus*[12]. Local IgE increased following allergen provocation in two studies[11,12].

Differential Diagnosis

Patients with non-allergic rhinitis should be recognized from those with LAR. Non-allergic rhinitis (NAR) is characterized by symptomatic nasal mucosal inflammation with at least two nasal symptoms (such as nasal obstruction, rhinorrhea, sneezing, and/or itchy nose), no clinical evidence of endonasal infection, and no systemic indicators of sensitization to inhalant allergens[39]. NAR encompasses a wide range of conditions[40], some life-threatening, and needs accurate investigation and sub-diagnosis. NAR subjects usually do not report symptom exacerbation in response to exposure to known allergens[24].

Chronic rhinosinusitis with nasal polyposis is a chronic inflammatory condition of the nasal and sinus mucosa that may involve very high local levels of total and polyclonal specific IgE and must be distinguished from LAR by nasal endoscopy and/or a CT sinus scan[41,42].

Staphylococcus aureus has been shown[43,44] to change airway illness by triggering the creation of polyclonal IgE antibodies against its superantigens and various environmental allergens in nasal polyp tissue. IgE probably plays a key role in chronic rhinosinusitis with nasal polyposis, as revealed by the clinical effectiveness of anti-IgE treatment[45]. This differs from LAR in being polyclonal and at higher levels in the mucosa[46].

Local IgE in Other Allergic-Type Diseases

Asthma is Connected with Local Immunoglobulin E Production

There is evidence that atopic and non-atopic asthma overlap. Several studies[47-49] have found an increase in the frequency of B lymphocytes undergoing IgE heavy chain class-switch recombination[47], as well as an increase in the production of interleukin (IL)-4 and IL-5 mRNA in lung tissue from both atopic and non-atopic asthmatic

Table I. Nasal provocation test in non-atopic patients with rhinitis symptoms.

Study	Allergens	Study patients	Positive Nasal allergen provocation test in patients	Controls	Positive Nasal allergen provocation test in controls	Nasal allergen provocation test protocol and evaluation
Carney et al[13] 2002	*Dermatophagoides pteronyssinus/ Dermatophagoides farinae* mix; cat/dog mix; grass pollen	21 persistent idiopathic rhinitis	62%	8 Allergic Rhinitis (*Dermatophagoides pteronyssinus/ Dermatophagoides farinae*, cat/dog, or grass) 8 healthy control	100% 0%	Protocol: Nasal allergen provocation test -S Evaluation: symptoms + Allergic Rhinitis
Wedbäck et al[14] 2005	birch pollen timothy pollen	15 seasonal idiopathic rhinitis 13 perennial idiopathic rhinitis	47% 39%	19 Allergic Rhinitis	100%	Protocol: Nasal allergen provocation test -S Evaluation: symptoms + Allergic Rhinitis
Rondón et al[9] 2007	*Dermatophagoides pteronyssinus*	50 persistent idiopathic rhinitis	54%	30 Allergic Rhinitis to *Dermatophagoides pteronyssinus* 20 Allergic Rhinitis to pollens 30 healthy controls	100% 0% 0%	Protocol: Nasal allergen provocation test -S Evaluation: symptoms + Allergic Rhinitis
Rondón et a[l10] 2008	grass pollen olive pollen	32 seasonal idiopathic hinitis	66%	35 Allergic Rhinitis (grass or olive) 30 Allergic Rhinitis to *Dermatophagoides pteronyssinus* 50 healthy control	100% 0% 0%	Protocol: Nasal allergen provocation test -S Evaluation: symptoms + Allergic Rhinitis
Rondón et al[11] 2009	grass pollen	22 Local Allergic Rhinitis (grass)	100%	30 healthy control	0%	Protocol: Nasal allergen provocation test -S Evaluation: symptoms + Allergic Rhinitis, + nasal specific Immunoglobulin E, tryptase and eosinophilic cationic protein
López et al[12] 2010	*Dermatophagoides pteronyssinus*	36 Local Allergic Rhinitis (DP)	100%	50 healthy control	0%	Protocol: Nasal allergen provocation test -S Evaluation: symptoms + Allergic Rhinitis, + nasal specific Immunoglobulin E, tryptase and eosinophilic cationic protein

Table continued

Table I *(continued)*. Nasal provocation test in non-atopic patients with rhinitis symptoms.

Study	Allergens	Study patients	Positive Nasal allergen provocation test in patients	Controls	Positive Nasal allergen provocation test in controls	Nasal allergen provocation test protocol and evaluation
Fuiano et al[23] 2011	*Alternaria*	36 idiopathic rhinitis	83.3%	20 Allergic Rhinitis (*Alternaria*)	75%	Protocol: Nasal allergen provocation test -S Evaluation: Symptoms + nasal specific Immunoglobulin E
Rondón et al[7] 2011	*Dermatophagoides pteronyssinus* *Alternaria* grass pollen olive pollen	25 Local Allergic Rhinitis	100%	25 Non-allergic Rhinitis	0%	Protocol : Nasal allergen provocation test -M Evaluation: symptoms + Allergic Rhinitis
Rondón et al[8] 2012	*Dermatophagoides pteronyssinus* *Alternaria* grass pollen olive pollen dog epithelia	158 idiopathic rhinitis	69.6%	270 Allergic Rhinitis (*Dermatophagoides pteronyssinus, Alternaria,* grass, olive and dog)	100%	Protocol : Nasal allergen provocation test -M Evaluation: symptoms + Allergic Rhinitis

patients[48] and response to anti-IgE in some non-atopic asthmatics[49]. Dust mite-specific IgE antibodies have been found[50] in intrinsic asthma. In LAR subjects, bronchial challenge test with *Dermatophagoides pteronyssinus* resulted in a rise in sputum eosinophils and basophils[51]. This suggests a LAR-like situation in some asthmatics, as does a response to anti-IgE[49].

However, severe asthma is more associated with chronic rhinosinusitis (CRS), rather than AR or LAR, and local polyclonal IgE, provoked by *Staph. Aureus* is more likely[52].

It is possible that there are two mechanisms for local IgE synthesis in the lower airway: allergen-stimulated and *S. aureus*-induced.

Local IgE in the Conjunctivae

Conjunctivitis is also frequent in LAR patients[8,11,12]. Specific conjunctival provocation tests and the determination of specific IgE in conjunctival secretions[53-56] have demonstrated an allergic reaction resulting from the interaction of an allergen and the immunological system in the ocular mucosa; in some of these cases, symptoms suggestive of LAR were reported[56]. According to Hoffmann-Sommergruber et al[56], serum IgE does not correlate with ocular allergy, and tear IgE is most likely created locally rather than being exuded from serum. It has been proposed[56] that the presence of IgE in tear fluid is due to an enhanced rate of IgE synthesis from plasma cells in the eye. The presence of local allergic conjunctivitis (LAC) is a possibility for allergic conjunctivitis (AC) phenotype[57].

LAR Diagnosis

To identify individuals with LAR, a complete clinical history of symptoms is required. These symptoms are similar to AR (nasal itching, sneezing, rhinorrhea, and nasal congestion/obstruction, frequently coupled with ocular symptoms), worsening with relevant allergen exposure, and responding to nasal corticosteroids and oral/local antihistamines[9-11] (in contrast to non-allergic rhinitis, where an excellent therapeutic response to nasal corticosteroids and oral/local antihistamines occurs in a limited number of cases).

As with AR patients, LAR patients can have both persistent and intermittent symptoms, as well as perpetual or seasonal ones[9,10,14], and their intensity can be characterized as mild, moderate, or severe. The most common clinical profile of a LAR patient is a nonsmoker with moderate-seve-

re, chronic perennial rhinitis, typically coupled with conjunctivitis and asthma[8-11]. Atopy in the family and the development of nose symptoms in childhood are common aspects described by LAR and AR patients.

A detailed clinical history suggestive of allergen exacerbation, plus the demonstration of a nasal allergic response to aeroallergens *via* nasal allergen provocation test (NPT) or the detection of nasal-specific IgE can be used to make the diagnosis of LAR[8,19].

Chronic rhinosinusitis with/without nasal polyps should be excluded.

Nasal eosinophilia on nasal cytology is a useful screening tool for LAR, but because of its limited specificity, an NPT is required to confirm LAR[58].

The diagnosis of LAR has become difficult for practitioners because of the lack of availability of NPTs and nasal detection of specific IgE (Table II). In Figure 1, a diagnostic approach for the diagnosis of LAR is suggested.

This allergological diagnostic method should be expanded to individuals who have respiratory symptoms that are directly connected to their occupational activities[59].

Confirmed Diagnosis of LAR

Another supplementary in vitro test that may aid in the diagnosis of LAR utilizing a nasal challenge is a basophil activation test. However, despite the fact that more than half of LAR and AR patients test positive in basophil activation test (BAT), a negative result does not rule out the diagnosis of LAR[57,60].

Nasal Detection of Specific Immunoglobulin E

The gold standard for establishing the presence of specific IgE in diagnosing LAR is to measure total and specific IgE in nasal biopsies. During nasal surgery, nasal tissue can be taken, processed, and homogenized for IgE measurement by ImmunoCap[46,61,62]. However, because this approach is intrusive and requires a laboratory expert, it is not a viable diagnostic tool for regular clinical practice.

Various other approaches have been employed to detect nasal IgE in LAR, with various degrees of success. Local sIgE levels in nasal discharge are a valid and efficient diagnostic tool for LAR[63].

Nasal lavage aids the detection of nasal-specific IgE in LAR patients[9,10] as well as after nasal allergen provocation tests[6,11,12]. Although it has a high specificity[6,9-12], its sensitivity ranges from 22 to 40%[9,10]. Possible explanations include nasal lavage's dilution impact, the absence of any occult allergen(s), and the existence of another immunologic mechanism, such as the possibility of non-specific protease activity stimulation by house dust mite on airway innate immune cells.

An allergen-coupled cellulose derivative inserted in a two-hole applicator strip, coated with a permeable membrane, and positioned in the upper posterior tract of the internal nasal ostium is an alternative noninvasive approach for detecting nasal-specific IgE[23,64]. Because no inflammatory protein dilution occurs, newer polyurethane foam sample procedures have been demonstrated[65] to be superior to nasal lavage. Gevaert et al[45] measured mediators and IgE in nasal secretions using surgical swabs; the approach has been utilized in therapy trials in chronic rhinosinusitis with nasal polyposis for over a decade[66,67]. Recent studies[68,69] reveal that specific IgE for house dust mite and grass pollen allergens may be identified in allergic rhinitis patients' nasal secretions using surgical swabs and filter discs. All of these approaches can be viable solutions, but they need to be further tested in LAR.

A mucosal brush biopsy of the inferior turbinate is an invasive approach for detecting nasal-specific IgE that Reisacher et al[74] recently evaluated in 20 idiopathic rhinitis patients. However, because the study did not include a healthy control group, the procedure's sensitivity and specificity cannot be assessed.

Table II. Diagnostic limitations of different tests for local allergic rhinitis (LAR).

Tests	Limitations
Skin prick tests	Quality of extracts, regional relevance of extracts, cross reactivity, interference with drugs, variability of technique/training
Serum IgE	Cost, cross reactivity, relevance for local inflammation
Nasal tissue IgE	Invasive, processing, no standard values
Nasal secretion IgE	Standard methods, dilution, variability of technique/training
Nasal allergen provocation tests	Quality of extracts, regional relevance of extracts, cross reactivity, interference with drugs, variability of technique/training, nasal hyper reactivity, false positive/false negative
Basophil activation test	Sensitivity and specificity, cost

Developing a noninvasive in vitro test with high sensitivity and specificity for identifying nasal-specific IgE would be a significant step forward in the diagnosis and screening of LAR.

Provocation Test for Nasal Allergens

The nasal allergen provocation test is often regarded as the gold standard for verifying LAR diagnosis[9-12]. It mimics the allergic reaction that occurs after natural allergen exposure, indicating the existence of local allergen-specific IgE and allergen participation in symptom production. Objective measurements, such as acoustic rhinometry[9-12,14] or anterior rhinomanometry[13], are used to evaluate nasal blockage; they are safe, sensitive, specific, and reliable diagnostic tests in LAR.

This procedure is time-consuming, may take many sessions for each patient, and is only used in a few places since it requires well-trained workers. A recent design for a novel protocol for multiple allergen nasal allergy provocation testing in a single session, utilizing numerous allergens sequentially, has simplified the procedure without compromising the test's sensitivity, specificity, and repeatability[7]. This suggested technique may be useful in screening LAR since it allows for the elimination of non-allergic rhinitis patients in a single session while still discovering clinically meaningful polysensitization in LAR patients[7].

An alternative approach to generating a larger volume of data effectively would be to expose suspected LAR subjects, plus controls, in an allergen challenge chamber[70].

Treatment

The ability to distinguish between LAR and non-allergic rhinitis is critical since non-allergic rhinitis requires different treatments. However, patients with LAR have reported[9,10] positive responses to treatments used for AR, such as topical nasal corticosteroids and oral antihistamines.

Individuals with LAR might also benefit from allergen-specific immunotherapy. A pilot observational study conducted by Rondón et al[71] in 20 patients with LAR sensitized to grass pollen revealed that a 6-month course of pre-seasonal subcutaneous allergen immunotherapy induced an increase in tolerance to the aeroallergen, a reduction in symptoms, and rescue medication, and an increase in the number of days free of treatment in the immunotherapy group compared to the rescue medication group[71]. The 36 adult individuals with LAR were randomized to receive placebo or active allergen immunotherapy (Pangramin PLUS, ALK, *Dermatophagoides pteronyssinus* extract) for 24 months in the first phase II placebo-controlled clinical study[72] in local allergic rhinitis. Subcutaneous allergen immunotherapy with *Dermatophagoides pteronyssinus* was found to be a useful and safe treatment in LAR patients, exhibiting clinical improvements in symptom-medication ratings and tolerance to nasal allergen provocation tests as compared to placebo.

Eguiluz-Gracia et al[60] introduced a therapeutic approach for various allergic rhinitis phenotypes[73] that is also relevant for individuals with LAR. The EUFOREA Allergic Rhinitis guidelines[74,75], designed for both adults and children, are also applicable to LAR patients.

Conclusions

LAR is a novel entity that requires additional investigation in terms of prevalence, proper diagnosis, treatment, and prognosis. LAR involves type 2 nasal inflammation with local IgE and cannot be diagnosed by systemic methods, such as skin prick or blood IgE[76] tests. A nasal allergen challenge is necessary for diagnosis. LAR can respond to usual AR treatments, including allergen-specific immunotherapy (AIT). The target outcomes and possible benefits of this review are to achieve a consensus for the study and diagnosis of LAR and increase interest in this area.

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Conflict of Interest

The authors declare that they do not have any conflict of interest with this paper.

Authors' Contributions

The authors contributed equally to the planning, literature survey, and writing of the manuscript.

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Ethics Approval
Since the article is a narrative review, the Ethics Committee approval is not applicable.

Informed Consent
Not applicable, due to the design of the study.

Availability of Data and Materials
All data for this review are presented in this paper.

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