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Local Allergic Rhinitis: Lights and Shadows of a Mysterious Entity

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Abstract
Local allergic rhinitis (LAR) is, to date, a debated and complex entity, still orphan of global consideration and a multicentric approach. LAR does not seem to find a proper positioning in the classic classifications and phenotypes of chronic rhinitis, and its pathophysiology relies specifically on the presence of local IgE. These patients in fact have a suggestive clinical history of allergic rhinitis in the presence of negative skin prick tests and serum IgE tests for the suspect allergen. Nasal allergen challenge, assessment of local IgE, basophil activation test (BAT), and nasal cytology are, at the moment, the most used tests in the diagnostic approach to the disease, despite their limitations. Considering that the correct interpretation of diagnostic tests and their clinical relevance is fundamental in the assessment of the right diagnosis and the subsequent therapy, we propose a new diagnostic approach that encompasses all of these methodologies and suggest that several pragmatic randomized control trials as well as prospective, multicentric studies directed at the long-term follow-up of LAR be carried out to further investigate this debated entity.

Introduction

Rhinitis is a very common disease characterized by at least one symptom between nasal congestion, rhinorrhea, sneezing, and itching [1]. Rhinitis can be divided at least in three major endotypes: infectious, allergic, and nonallergic [2]. Several phenotypes have also been proposed (senile, gustatory, occupational, hormonal, drug induced). When all possible causes of rhinitis are excluded, the term "idiopathic rhinitis" is often used [2].

Allergic rhinitis (AR) has an estimated prevalence of 10–30% among adults and about 40% among children [1]; it is classically characterized by sneezing, aqueous rhinorrhea, nasal congestion, and itching. The diagnosis is made through the combination of clinical evaluation

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(presence of typical symptoms, exclusion of other causes of rhinitis) and diagnostic tests aimed to address the presence of specific immunoglobulin E (IgE) directed against allergens (SPTs and/or assessment of serum-specific IgEs) [3].

The correct interpretation of diagnostic tests and their clinical relevance is fundamental to assess the correct diagnosis and the subsequent therapy. Nasal endoscopy can help to exclude other pathologies, as chronic rhinosinusitis (with or without nasal polyposis) or infections [3].

Nonallergic rhinitis (NAR) can be classified according to its inflammatory phenotypes (with prevalence of eosinophils, mast cells, and/or neutrophils), that can be studied through a variety of tests, including nasal cytology [4], even though efforts are ongoing to standardize this methodology [5]. Moreover, some NAR phenotypes are sustained by neurogenic inflammation [3]. Things can get even more complicated as it is not infrequent to observe "mixed" rhinitis, with overlapping allergic and nonallergic mechanisms, making it difficult to identify the right diagnosis and to prescribe the appropriate treatment [6].

In this context, another clinical entity has emerged in the last 40 years: local allergic rhinitis (LAR). The story of LAR can be traced back to 1975, when Huggins et al. [7] studied a group of patients with typical symptoms of AR to house dust mites (HDM) but with negative skin-prick tests (SPTs) and serum IgE. They hypothesized that these patients could produce only local IgE and proved their intuition performing nasal allergen challenge (NAC) and measuring local specific IgE against HDM. Since then, other researchers, especially the group led by Rondón et al. [8], investigated this newly discovered type of rhinitis. In 2003, Powe et al. [9] coined the term "entopy," defined as the possibility to develop a local allergic inflammation without the evolution in a systemic, atopic response. The fact that a limited number of studies has been carried out in this field, often using not fully standardized diagnostic methods, has pointed some shadows on LAR. In this review, we aim at summarizing the pathophysiological, diagnostic, and therapeutic aspects of LAR and to point out the principal and most fascinating aspects as well as critical points of this clinical entity.

Epidemiology

LAR is considered an underdiagnosed phenomenon due to the lack of large population studies. In fact, its real prevalence seems to be widely debated in existing literature. Some studies suggested that LAR prevalence ranges from 50 to 75% in the nonatopic population that has nasal symptoms suggestive of atopy [10]. The majority of these patients, rather than by sex and age-groups, seems to be discriminated by geographic location. For example, a study by Reitsma et al. [11] suggested that Mediterranean areas (Portugal, Spain, Italy, or Greece) showed a higher prevalence of the disease when compared to Northern Europe, while other studies conducted in Asian countries reported a lower prevalence with respect to Western areas [10]. These discrepancies may be due to distinct environmental and genetic backgrounds [12]; however, it should be acknowledged that a wide array of diagnostic methods have been used to evaluate LAR across different studies [10], and this possibly lead to confounding results.

LAR patients, like in AR, often report bronchial symptoms suggestive of asthma [13]. In a study by Rondón et al. [14], it was reported that in the LAR patients examined, the incidence of asthma increased from 18.8% to 24.4% at 5 years and 30.7% at 10 years.

Concerning the most involved allergens, again similarly to AR, *Dermatophagoides pteronyssinus* (*D. pteronyssinus*), *Dermatophagoides farinae*, and other HDM seem to be a prevalent trigger in LAR, determining perennial symptoms. Grass pollen and *Alternaria alternata* (and less frequently other seasonal allergens such as olive tree pollen) have been linked instead to seasonal LAR [10, 12] which, to the best knowledge of the authors, is a largely unrecognized entity in itself [10].

The coexistence of AR and LAR is possible and has been described both in children and in adults [15, 16]. This phenotype was first described by Eguiluz-Gracia et al. [15] who proposed the term dual allergic rhinitis to define it. Their study pointed out that most patients with perennial rhinitis symptoms, but positive SPT for seasonal allergens only, display NAC positivity for both seasonal and perennial allergens.

Pathogenesis

Classically, the development of IgE-secreting plasma cells by class switch recombination (CSR) is believed to occur in lymphoid tissues (regional lymph nodes and spleen) [17]; however, local CSR in the nasal and bronchial mucosa in asthmatic and nonasthmatic patients has been demonstrated [18]. CSR with subsequent IgE production requires IL-4 and IL-13 (first signal) and CD-40 ligand (second signal), which binds to CD-40 on the surface of B cells and allows CRS to continue. CD-40 ligand

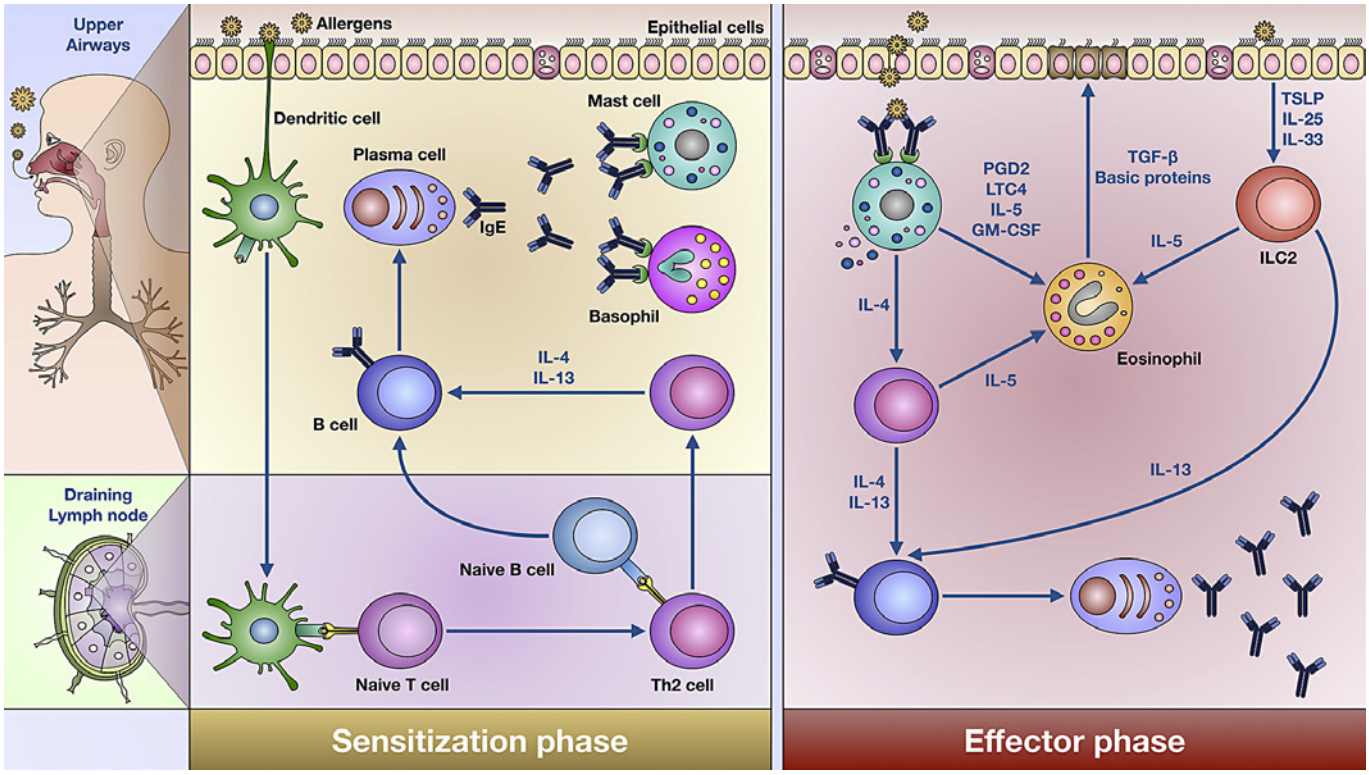

Fig. 1. Pathophysiological mechanisms involved in local IgE production at nasal mucosal level.

is expressed by T-helper 2 (Th2) activated cells and mast cells [19, 20]. Pawankar et al. [21] demonstrated that antigen-activated nasal mast cells secrete greater levels of IL-4 and IL-13 with respect to antigen-activated nasal T lymphocytes, leading to an increased synthesis of IgE.

As both signals necessary to CSR are present in the mucosa, it seems reasonable to assume that this process may also occur locally. It is also not a surprise to know that IgE + B cells have been found in nasal mucosa biopsies of nonatopic individuals, even if they were not directed against specific allergens, as it occurs in atopic patients with AR [22]. Local IgE production against allergens in nasal secretions has been demonstrated also in healthy subjects [23]. Figure 1 summarizes the most probable pathophysiological mechanisms involved in LAR.

FcεRI receptors have an extremely high affinity for IgEs [24]; thus, it is likely that free IgEs are detected only once all FcεRI receptors are saturated. In AR, locally produced IgEs, after occupying all FcεRI receptors on resident effector cells (giving positive NAC results), enter the systemic circulation where binding to basophil FcεRI receptors occurs (resulting in basophil activation test positivity) [25]. Free IgEs eventually extravasate into tissues, binding to receptors on peripheral effector cells [26] (bringing about SPT positivity). As a result, free IgEs are found in biological fluids only when all FcεRI receptors are saturated [27]. On the other hand, IgE production seems insufficient to reach peripheral tissues and secretions in LAR patients [28]. This might be the reason why in these individuals SPTs are negative, free IgEs are undetectable in serum and are absent or low in nasal secretions, whereas NAC, and usually also basophil activation test (BAT), is positive.

Diagnosis

The diagnosis of LAR is mainly based on suggestive clinical history of AR, associated with a positive NAC, when SPT and serum IgE tests are negative for the suspect allergen, in the absence of systemic atopy [28–32]. Several studies have demonstrated that more than half of patients previously diagnosed with "idiopathic rhinitis" were labelled as affected by LAR through positive NAC responses based on both subjective and objective param-

eters [31, 33–35], nasal secretion of IgE, and inflammatory mediators [30, 31, 36].

Nasal Allergen Challenge

The scope of NAC is to reproduce an allergic reaction in the nose after the exposure to one or more selected allergens in standardized and controlled conditions. This test is particularly useful in the discrimination of allergic forms of rhinitis from NAR. The symptoms elicited can be evaluated subjectively, using symptom scores and grading scales, as well as objectively, by means of proper tools [37]. A complete nasal examination should be carried out prior to the test, including exterior evaluation as well as an anterior rhinoscopy and nasal endoscopy [38] to observe the baseline condition of the mucosa [39].

The test should be performed under standardized room conditions to avoid environmental variations [38]. Dosing regimens and methods of allergen application have so far changed consistently. The most acceptable techniques involve aqueous allergen extract delivered by means of syringe, bottle dropper, micropipette, or pump action sprays, each with its own advantages and drawbacks [39]. Reproducibility and simplicity are obviously cardinal requirements in any dosing technique.

The response is evaluated subjectively and objectively. Subjective methods include visual analogue scales (VAS), Likert scale (a type of questionnaire providing a set of answers ranging between two extremes), Lebel score, and/or Linder score. Objective methods to assess nasal patency include peak nasal inspiratory flow, acoustic rhinometry, active anterior rhinomanometry, and 4-phase rhinomanometry [38]. Objective and subjective evaluations should then be contextualized and interpreted to establish the outcome of the test. To avoid repetitive NAC procedures, a multiple-nasal allergen provocation test (NAPT-M), using sequential allergens in a single session, has been proposed and validated [40]. The NAC can be divided in three steps, which include measurements at baseline, a control challenge and the allergen challenge, reassessing nasal patency, and ventilation after each one.

Control solutions should be prepared with the same dilutants used for allergen preparations because some of these dilutants contain substances that may react with the mucosa in patients with hyperreactivity to unspecific stimuli, bringing about test positivity with the control solution [38]. This phenomenon might occur in all rhinitis types and, although yet poorly understood, it is thought to be due to an exaggerated neurogenic and inflammatory immune response [41]. Positivity in response to the control solution may require that the test be halted and repeated after a few days [38].

In the past, NAC procedures were quite heterogeneous, and criteria to define positivity were not standardized. For example, there were inhomogeneities in allergenic extracts, timing, dosages, outcomes for positivity, cut-off points, and doctors' interpretation [37]. However, in recent years a significant effort to standardize the procedure has been made, and a consensus protocol has been proposed [38]. A throwback of NAC consists in the fact that it is not easily implementable in clinical practice as it requires well-trained personnel and it is time-consuming [30, 31, 42].

Assessment of Local IgE

Rondón et al. [30] reported that in a study they detected a significant increase in nasal IgE levels in response to grass pollen at 1, 6, and 24 h after NAC in 30% of their LAR patients, proposing the existence of a persistent local synthesis of nasal IgE that rapidly enhances after exposure of the nasal mucosa to aeroallergens in patients with LAR. Currently, several validated methods are used in the detection and quantification of serum IgE; the most frequently used assays are the immunoassay capture test (ImmunoCAP) and microarray-based technologies (i.e., immunosolid-phase allergen chip technology, ISAC; Allergy Explorer, ALEX) [43, 44]. However even though both ImmunoCAP and microarray-based assays can be applied to nasal secretions, they have been standardized only in the quantification of serum IgE.

Furthermore, possible pitfalls may arise even earlier in the diagnostic process. The collection of IgE samples from the nasal mucosa can be quantified by means of many diagnostic methods, both invasive and noninvasive, such as cotton swabs [45], sinus packs [46], mucosal scrapping or brush biopsy [47], and nasal lavage [48, 49]. The heterogeneity of these approaches may undoubtedly account for the poor sensitivity of local IgE detection in patients with positive NAC.

In a study by Rondón et al. [34], 32 patients with IR were examined for specific nasal IgE and underwent NAC. In 62.5% of these patients, NAC was positive; however, only 35% of these patients showed nasal-specific IgE to the same allergens. In another study by the same group [33], 50 patients with persistent NAR underwent NAC to *D. pteronyssinus* and were examined for nasal-specific IgE to *D. pteronyssinus*. Of these patients, 54% showed a positive NAC, with only 22% of these reflecting the presence of nasal-specific IgE to *D. pteronyssinus*. Furthermore, in another study by Fuiano et al. [50] 56 children

suffering from rhinitis in periods consistent with *Alternaria* spore presence were evaluated with SPT and NAC to *Alternaria* and presence of nasal IgE; concomitant positivity of NAC and nasal IgE was observed only in 69.6% of the patients. Also, in LAR studies [30, 31] where patients underwent similar diagnostic processes the same pattern emerged. A recent study [51] was directly aimed at exploring the diagnostic performance of nasal-specific IgE to *D. pteronyssinus* in order to try to predict the outcome of NAC in patients with NAR. They concluded that the test had low specificity and sensitivity as 48% of patients with rhinitis without atopy had nasal-specific IgE, but only 28% had a positive NAC. Interestingly, in the rhinitis with the allergy group, 84% of patients had nasal-specific IgE and 80% a positive NAC, while in the control group, even though NAC was thoroughly negative, 27.8% of patients still showed nasal-specific IgE to *D. pteronyssinus*.

Overall, this evident discrepancy between nasal-specific IgE and positive NAC may be related to the dilution effect in nasal lavage or other possible limitations connected to the various methods of collection of nasal secretions [30, 31, 33, 34, 52]. Furthermore, even though key inflammatory cells and mediators may appear localized, a more critical approach on the matter may suggest that these findings could also be explained by pre-switched IgE + B cells migrating into nasal mucosa from distant lymphoid tissues, therefore prompting the need of more insight on the issue [53, 54].

Basophil Activation Test

BAT is a functional assay that uses flow cytometry to measure the expression of activation markers on the surface of basophils following allergen or anti-IgE stimulation. Due to its potential to replicate type I hypersensitivity reactions in vitro, it allows to diagnose and assess prognosis of allergic diseases [55].

BAT can be implied in the detection of LAR as basophils from peripheral blood may be sensitized to allergens responsible for LAR [56]. A study on 16 LAR patients with positive NAC for HDM suggested that BAT has a sensitivity that approximates 50% and a specificity of 93% [57]. Similarly, a study on 12 subjects with LAR and *Olea europaea* sensitization showed that the BAT had a specificity of 91.7% and a sensitivity of 66% when whole pollen extract was used [58]. Sensitivity dropped to 33% when the pollen's major allergen, *Ole e 1*, was used [58]. This occurrence has been hypothesized to be due to a possible spillover of locally synthesized IgE in the circulation, where basophils may act as primary effectors [26]. These preliminary results in the utilization of a functional test like BAT in the detection of LAR patients seem to underline a primitive difficulty in the correct orientation toward a LAR diagnosis or highlight an insufficient standardization of this methodology [59].

Nasal Cytology

Nasal cytology consists of the microscopic examination of surface cells of the nasal mucosa collected via a sterile swab from the inferior turbinate. A May-Grunwald-Giemsa staining method is then used to identify the array of normal cells and inflammatory cells, as well as bacteria and fungi, when present [4]. Nasal cytology has highlighted a complex and heterogeneous landscape of NAR [4]. However, LAR does not seem to find a proper positioning in these classifications [60] because its pathogenetic aspect, consisting of local production of IgE and eosinophilia [61], tends to be confounded with an inflammatory feature, such as the one found in NAR with eosinophilia syndrome [60].

Phothijindakul et al. [61] developed a diagnostic algorithm for the diagnosis of LAR in confirmed NAR patients. The algorithm proposes the use of nasal cytology as a pivotal discriminator before the utilization of NAC due to its simplicity and contained costs. However, NAC still needs to be considered in patients with positive nasal eosinophilia in order to confirm the diagnosis.

In another study by Gelardi et al. [23], AR and NAR patients underwent nasal cytology, and the latter group showed greater eosinophilia. While these results may not be surprising due to the presence of minimal persistent inflammation in AR [62], it becomes evident that eosinophilia in NAR has to be further investigated and that a single-method approach may result lacking in terms of both sensitivity and specificity.

Nasal cytology is cost effective and easily repeatable, although so far it has been criticized for its lack of standardization. Efforts have been done to establish methodical landmarks [4], but further studies should investigate whether this promising methodology can provide a reliable endotyping of rhinitis patients, thus aiding therapeutical decisions.

Treatment, Follow-Up, and Natural History of LAR

Management of LAR relies heavily on a correct diagnostic differentiation from NAR. LAR patients have in fact been shown to benefit from the same treatment as AR patients. Several studies [42, 63, 64] concur that allergen

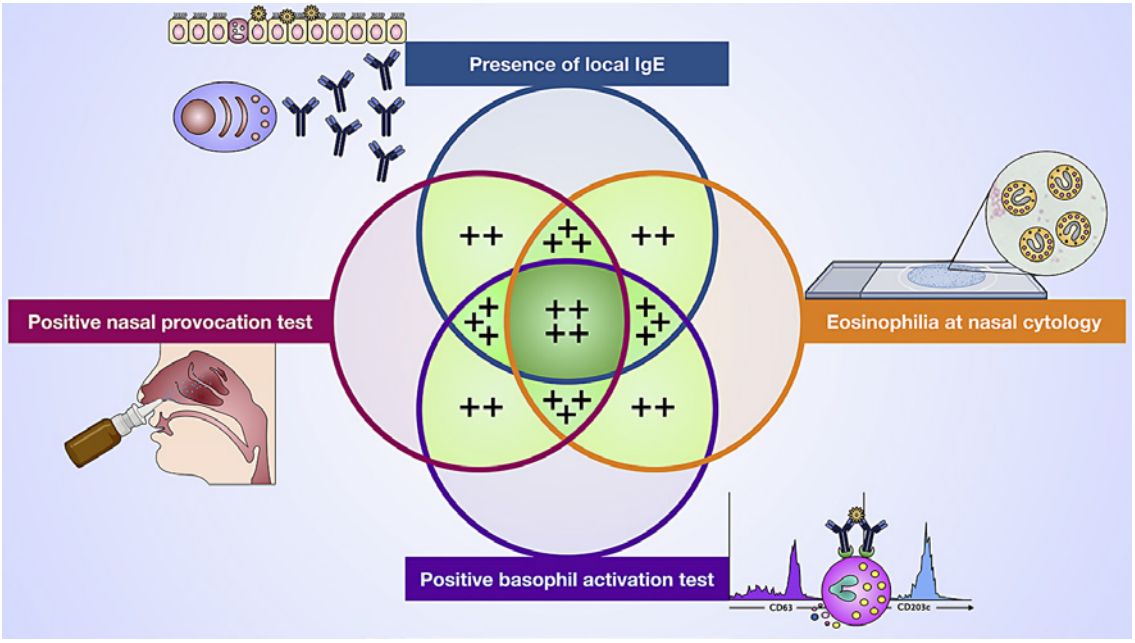

Fig. 2. Proposed multi-tool diagnostic approach to LAR.

avoidance measures and a pharmacological treatment consisting of intranasal corticosteroids, as well as oral and intranasal antihistamines, and allergen immunotherapy (AIT) can be used to treat efficiently patients with LAR. Although it is reasonable to expect a good response to antihistamines and intranasal corticosteroids, studies that demonstrate the efficacy of these therapies in LAR patients are lacking.

AIT seems to be the only treatment able to modify the natural course of the disease, as it has been shown to reduce symptoms as well as medication use [42], especially when LAR patients showed persistent, moderate to severe nasal symptomatology with conjunctivitis and/or asthma, which impacted their quality of life [63]. An example is a study carried out in patients with LAR and sensitivity to grass pollen [65]. It demonstrated that grass allergen-specific subcutaneous immunotherapy has led to an increased tolerance to the allergen and amelioration of symptoms as well as a reduction in use of rescue medication and increase in days free of treatment, when compared to patients using rescue medication alone. In another study by Bozek et al. [66], it was found that AIT can be effective and safe in the treatment of LAR with confirmed birch allergen IgE reaction, determined by a reduction in combined symptom and medication score, symptom score, and medication score after the allotted 3 years of treatment versus placebo. In general, however, further scientific evidence on the long-term effectiveness of AIT in LAR patients is still needed [65, 67] including its effect on prevention of asthma onset. This could be of particular significance in affecting the course of the disease. Arasi et al. [56] postulated that AIT could be started in children with LAR, as well as in children with AR, to alter its possible progression to overt AR with systemic IgE.

There are few studies regarding the natural course of LAR and whether it may evolve into classical allergic rhinitis. Rondón et al. [29] investigated the natural disease course in 194 LAR patients over a 10-year period. The study revealed that 6.8% of the LAR population experienced de novo systemic sensitization to aeroallergens (detected by SPT and/or serum-specific IgE). Surprisingly, the degree of atopy development was not particularly different from the one of controls (4.5% of controls), although they reported a significant increase in the number of patients needing emergency assistance due to severe symptoms of rhinitis and/or conjunctivitis and asthma attacks, as well as number of visits. Patients' subjective evaluation of their symptomatology also showed a significant reduction in health perception related to rhinitis and worsening of the disease.

Conclusion

Independently to the clinical label, a category of patients with symptoms suggestive of AR with negative SPT and serum IgE has been reported. These patients are approached differently and are ultimately treated according to whether or not the local allergic component is deemed to be contributory to their overall clinical picture of chronic rhinitis.

LAR is, to date, a debated and complex entity still orphan of global consideration and a multicentric approach. Moreover, we recognize that several aspects of LAR require a critical approach, not only under the diagnostic point of view but also concerning its pathophysiology. On this regard, the detection of local IgE is one of the most prominent diagnostic methods used so far in the diagnosis of LAR; however, it is paramount to explore further why some individuals produce only local IgE, if they are indeed produced locally and do not originate elsewhere and if those findings are actually clinically relevant. Furthermore, another point worthy of further insight concerns LAR patients that underwent AIT as it could be interesting to investigate the immunomodulatory effects to better understand the pathophysiological mechanisms behind LAR itself.

Considering that all diagnostic techniques have evident limitations and, in some cases, lack standardization, we propose an alternative approach with multiple tools to increase the probability of correctly diagnosing this entity (shown in Fig. 2). This approach consists in determining the probability of a diagnosis of LAR utilizing the compound sensitivity of all the current proposed diagnostic methods: the higher is the number of positive tests, the higher is the probability of correctly identifying the disease. Eguiluz-Gracia et al. [68] recently developed a diagnostic algorithm that allows for an accurate identification of LAR patients, considering skin prick tests and NAC as the most helpful diagnostic modalities for this purpose. We are in line with this approach, but we also support the use of nasal cytology and local IgE detection, particularly for controversial cases. The four proposed diagnostic tools measure different aspects of LAR: nasal cytology assesses the presence of local inflammation (that is crucial for the pathogenesis of LAR); the presence of local specific IgE confirms the local sensitization to a given airborne allergen; BAT positivity confirms that the exposure to that given allergen is functionally associated with an activation of effector cells (e.g., the basophils); and NAC assesses the elicitation of consistent symptoms after allergen exposure, which reflects nasal hyperreactivity. Based on the assumption that the single measurement cannot definitively clarify the diagnosis, the use of all four tests could increase the sensitivity and specificity in diagnosing LAR. Our proposed diagnostic algorithm, in order to be implemented in clinical practice, requires further studies in order to assess the sensitivity and diagnostic specificity of the proposed composite approach. In conclusion, it would be useful to prompt several pragmatic randomized control trials in the hope of acquiring new insight on LAR as well as prospective multicentric studies directed at the long-term follow-up of LAR patients in a real-life setting to explore the natural history of the disease.

Conflict of Interest Statement

Enrico Heffler reports participation to advisory boards and personal fees from AstraZeneca, Sanofi, GSK, Novartis, Circassia, Nestlè Purina, Boheringer Ingheleim, and Valeas, outside the submitted work; Giulio Melone, Veronica Giorgis, Marina Di Pino, Corrado Pelaia, Emanuele Nappi, Giovanni Paoletti, Massimo Landi, and Matteo Gelardi have no conflicts of interest to declare.

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Author Contributions

Enrico Heffler, Massimo Landi, Matteo Gelardi, and Giovanni Paoletti contributed to the conception of the review article and to draft and revise the article. Giulio Melone, Veronica Giorgis, Marina Di Pino, Emanuele Nappi, and Corrado Pelaia contributed to draft and revise the article. All the authors approved the final version of the article. The accuracy of any part of the article was appropriately investigated and resolved in agreement with all the authors.

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