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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Local allergic rhinitis – a big challenge in clinical practice

Rajica Stošović[1,2], Vesna Tomić-Spirić[1,2]

[1]University Clinical Center of Serbia, Clinic for Allergology and Immunology, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia

SUMMARY
Local allergic rhinitis is a new rhinitis phenotype characterized by symptoms similar to allergic rhinitis, in non-atopic patients with a positive nasal allergen provocation test (NAPT). The disease is diagnosed in over 25% of non-atopic patients with rhinitis, marked as non-atopic rhinitis. It most often has perennial and severe symptoms and a progressive course. It is often associated with conjunctivitis and/or asthma. It is necessary to consider local allergic rhinitis in patients with non-atopic rhinitis. The gold standard for diagnosis is a positive NAPT. Pharmacological therapy fails to stop the natural progression and development of comorbidities. Allergen immunotherapy reduces the symptoms, consumption of medicines and increases the tolerance to allergens responsible for local allergic rhinitis. New studies are needed to confirm the curative effects and evaluate the preventive effects of allergen immunotherapy.
Keywords: local allergic rhinitis; diagnosis; therapy

INTRODUCTION

Local allergic rhinitis (LAR) is a new rhinitis phenotype, defined and introduced into clinical practice by Campo et al. [1] and Rondon et al. at the end of the previous decade [2–4]. The base of LAR is a localized allergic reaction limited to the nasal mucosa, in the absence of systemic atopy. Patients have seasonal or perennial symptoms similar to allergic rhinitis (AR), without signs of atopy. To date, researchers have elucidated the etiology, underlying mechanisms, clinical features, and provided guidelines for the diagnosis and treatment. Most commonly, LAR has severe symptoms and progressive course, and is often associated with other inflammatory diseases, such as conjunctivitis and/or asthma. The continuous progression of the disease and poor response to pharmacological therapy significantly decrease the quality of life of these patients [5, 6, 7]. Considering that chronic rhinitis affects more than 30% of the population, of whom at least a quarter are patients with LAR, it is clear that this disease represents a huge financial burden on the health system. The characteristics of LAR impose the need for recognition, timely diagnosis, and effective treatment [8].

RHINITIS CLASSIFICATION

Rhinitis has been traditionally classified as infectious, non-infectious, and mixed rhinitis. This traditional classification of rhinitis is based on etiological criteria [8]. Non-infectious rhinitis is the most frequent chronic rhinitis, which divides into AR and non-allergic rhinitis (NAR). This division is also etiological and relies on the atopy characteristics: the presence of a positive skin prick test and/or allergen-specific IgE in serum. NAR is characterized by symptoms of chronic rhinitis, a negative skin prick test, and the absence of allergen-specific IgE in serum. NAR forms a heterogeneous group, divided into several phenotypes. The most important phenotypes with known etiology are drug-induced rhinitis, hormonal imbalance-induced rhinitis, occupational, gustatory, and rhinitis in the elderly. NAR of unknown etiology includes rhinitis with eosinophilia syndrome and idiopathic rhinitis. AR is a unique phenotype, which has characteristic symptoms and positive signs of atopy: skin prick test and/or allergen-specific IgE in serum. By isolating LAR, the traditional dichotomous division of non-infectious rhinitis has been "demolished." The recognition of this new phenotype of rhinitis, which does not have any sign of atopy, enabled its separation from NAR, where it was unjustifiably classified. In the new classification of non-infectious rhinitis, LAR is labeled as new AR phenotype and it is added to a group of AR, together with atopy AR. This change is of great importance. It allows patients with LAR to be recognized and treated more efficiently [8–11].

LOCAL ALLERGIC RHINITIS DEFINITION

LAR is a new and distinct rhinitis phenotype characterized by symptoms of AR, in patients with a negative skin prick test and the absence

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Correspondence to:
Rajica STOŠOVIĆ
Olge Alkalaj 2/4
11050 Belgrade, Serbia
rajicastosovic@gmail.com

of serum-specific IgE directed to inhalant allergens, but with a positive nasal allergen provocation test (NAPT) [1, 2, 3]. Therefore, these patients do not have indicators of atopy [5]. The main cause of disease is allergic response to inhalant allergens restricted to the nasal mucosa. This is also called "entopia," which distinguishes these patients from patients with AR and atopy [10, 11, 12, 13].

EPIDEMIOLOGY

Non-infectious rhinitis is a global health problem, with a frequency exceeding 30% of the general population and of great medical, economic, and social importance [14]. Until LAR was recognized, it was estimated that approximately half of these patients had NAR, based on the absence of signs of atopy. With the knowledge that LAR also does not have signs of atopy, because it was not distinguished from NAR, these two groups of rhinitis were marked as non-atopic rhinitis. This has attracted a great deal of researchers' attention. Over the past decade, numerous epidemiological and clinical studies have indicated a high incidence of LAR in patients with non-atopic rhinitis, in the range of 50–75% [15]. Some studies indicate greater representation in the Mediterranean than in Northern Europe or in some Asian countries [16, 17, 18]. The most recent systemic and meta-analysis of selected studies indicates that the incidence of LAR in adults with non-atopic rhinitis is about 25%. The incidence is higher if positive NAPT is not the only criteria for diagnosis, but there are also symptoms suggestive of AR [19]. The prevalence in the elderly is estimated at 21% [20]. Despite this knowledge, there is an opinion that LAR is underdiagnosed, i.e., that a large number of these patients remain unrecognized [15, 20].

PATHOPHYSIOLOGY

The first evidence of exclusively local production of specific IgE in the nasal mucosa in individuals with non-atopic rhinitis was documented in 1975. In the nasal secretion of patients with symptoms of AR and negative outcome of allergic tests, Hugins and Brostof were the first to detect specific IgE directed to dust mites *Dermatophagoides pteronyssinus* [21]. Later, at the beginning of the 21st century, the infiltrates of IgE-positive cells in the nasal mucosa was also detected in individuals with atopic and non-atopic rhinitis [22]. Following the isolation of LAR, a new term "entopia" was introduced to highlight the basic feature of the new rhinitis phenotype, exclusively the local synthesis of specific IgE in the nasal mucosa [12].

The underlying pathophysiological mechanism of LAR is anaphylactic hypersensitivity, mediated by helper T lymphocytes, cytokine phenotype 2, and allergen-specific IgE directed to common inhaled allergens. A direct consequence of the allergic response, triggered by environmental allergens, is the development of type 2 inflammation, restricted to the nasal mucosa [23, 24, 25]. After natural exposure to allergens from the external environment or after NAPT, there is a transient increase in tryptase concentration and a progressive increase in the concentration of specific IgE, the number of eosinophils and the eosinophil cationic protein in the nasal secretion. The allergic inflammation thus originated has all the features of eosinophilic inflammation and a similar cell phenotype to that of AR. Allergic inflammation in both cases is characterized by a high content of eosinophils, basophils, mast cells and helper lymphocytes T, cytokine phenotype 2 [23, 26].

In subjects with AR, local synthesis of specific IgEs, after exposure to environmental allergens, is potent, rapid and results in complete sensitization of nasal mucosal effector cells. Specific IgEs bind to their high-affinity receptors on a number of resident effector cells (mast cells, eosinophils, T and B lymphocytes) with Fc fragment. However, a large portion of locally synthesized specific IgE remains free, enters the systemic circulation, and sensitizes circulating basophils and subsequently other resident cells, such as skin mast cells and other cells. After the saturation of high-affinity receptors on the resident cells of numerous tissues and organs, a free fraction of specific IgE appears in the serum [14, 27].

Unlike AR, there is no direct evidence that the same process occurs in patients with LAR. In these individuals, it is assumed that locally synthesized specific IgEs, after saturation of the high-affinity receptors on resident cells of the nasal mucosa, enter the systemic circulation only to a small extent. The systemic fraction of specific IgE sensitizes circulating basophils but no other resident cells, nor does it appear as a free fraction in serum. In support of this assumption is the positive outcome of a basophil activation test and a positive response to allergen immunotherapy (AIT) in patients with LAR [28, 29, 30].

Despite pathogenetic similarities, the precise pathophysiological mechanisms and role of specific IgEs in LAR are still insufficiently known. It remains unclear why most patients with symptoms of AR develop systemic sensitization (atopy), while a far smaller number develop only a local allergic response [31].

CLINICAL CHARACTERISTICS

LAR is an isolated, independent, and well characterized rhinitis phenotype. The most commonly affected individuals are young adults, in whom disease has a chronic course with a tendency to worsen. Patients most often have perennial, moderately severe to severe rhinitis that is difficult to control [14–18]. Dust mites and molds are major causes [32]. One of the main features of this rhinitis phenotype is its independence. In a large study by Rondon et al. [7], a 10-year follow-up of over 190 adolescents and adult subjects with LAR recorded a low conversion rate to atopic AR. This conversion rate did not differ from the general population. This confirmed the independence of this phenotype with evidence that LAR is not an initial stage in the development of atopic AR. Regardless of the age at which it occurs, it always has a progressive course that leads to a continual exacerbation of the disease. The exacerbation is manifested by the following: worsening of symptoms with extension of

their duration and a greater need for medication, a decrease in the tolerance threshold for allergen exposure, the emergence of new local sensitizations and comorbidities, most commonly conjunctivitis and asthma. The most intense period of exacerbation is the first five years of the disease [7]. An inevitable consequence of such a clinical course is a decrease in the quality of life of these patients. A typical patient with LAR is a younger non-smoker, who has perennial rhinitis, often associated with symptoms of conjunctivitis and asthma. Compared to patients with NAR, these patients are significantly younger, with more severe symptoms and a positive family history of atopy [15].

LOCAL ALLERGIC RHINITIS AND ASTMA

Some studies by Spanish authors indicate that LAR is a risk factor for asthma in non- atopic individuals [33, 34]. These patients often have symptoms associated with the lower respiratory tract indicating asthma. It is estimated that 20–47% of patients report typical asthma symptoms, while half of patients have a positive methacholine test and a confirmed diagnosis of asthma. The association of LAR with asthma has been observed at the outset of the disease, and this association has steadily increased over time, with a tendency to exacerbate asthma symptoms and pulmonary function [7, 34]. This conclusion is also indicated by the results of a large and to date the only long-term, 10-year follow-up study of patients with LAR. In this study, less than 19% of patients with associated asthma symptoms were registered at the onset of the disease; after 10 years, the incidence increased to over 30%. The fastest and the highest rate of progression to asthma was during the first five-year period of the disease. There was also a significant increase in emergency room interventions, physician visits, and impaired pulmonary function. This study confirms the natural, progressive course of LAR and its association with asthma [7]. The nature of this close association has been the subject of intense research in recent years. Recent studies show that as many as 28% of patients with LAR, due to hypersensitivity to dust mites and confirmed asthma, have a positive outcome of specific bronchoprovocation test with *Dermatophagoides pteronyssinus*, followed by worsening asthma and increased non-specific bronchial hyperreactivity. Analysis after the test showed a significant increase in the number of eosinophils, monocytes, and the concentration of eosinophilic cationic protein in induced sputum, but not in peripheral blood. The cell content did not differ from that in allergic asthma. This finding indicates that the development of eosinophilic inflammation in the bronchial mucosa is the basis of asthma, in patients with LAR [34]. This is a direct confirmation of the existence of allergic asthma in persons with non-atopic constitution. The results of this study reinforce the earlier findings of local synthesis of specific IgE in bronchial mucosa, as well as the increase in IgE concentration in induced sputum after a specific bronchoprovocation test in patients with non-atopic asthma [33, 34]. These studies confirm that etiology of asthma in patients with LAR is a localized allergic inflammation of the bronchial mucosa. For these reasons, asthma in these patients has been called local allergic asthma, in an effort to isolate a new phenotype of allergic asthma in individuals with non-atopic constitution [34]. These findings further confirm the concept of united airway diseases, by unequivocal evidence of the pathophysiological connection between LAR and local allergic asthma [35–39].

LOCAL ALLERGIC RHINITIS AND CONJUNCTIVITIS

Patients with LAR often experience itching in the eyes, redness, and increased tearing. Eye symptoms are more common in patients with local sensitization to various pollen species than in those with local sensitization to household dust mites. In these patients, the presence of IgE in tears was demonstrated, which prompted a group of Japanese researchers to suggest a new term – local allergic conjunctivitis. A large number of mast cells, T and B lymphocytes, are present in the epithelium of the conjunctiva, and in allergic conjunctivitis there are resident B cells that synthesize specific IgE that sensitizes mast cells in the conjunctiva. However, it is still unclear whether ocular symptoms in LAR are due to local sensitization of the conjunctiva or activation of the naso-ocular reflex, after exposure of the nasal mucosa to inhaled allergens [40].

DUAL ALLERGIC RHINITIS

Following the discovery of LAR, its association with AR and coexistence in the same atopic person was observed. This phenotype is called dual allergic rhinitis. It is characterized by the presence of symptoms of AR, that are consequence of both local sensitization of the nasal mucosa i.e., entopic to certain allergens and systemic sensitization, i.e., atopy to other inhalation allergens. The number of these patients in clinical practice is not negligible, and trials are yet to define this latest rhinitis phenotype more closely [41, 42].

LOCAL ALLERGIC RHINITIS IN CHILDREN

A significant number of adolescents and adults with LAR associate their first symptoms with childhood. For these reasons, a number of studies indicate the need to include LAR in a differential diagnosis in children with chronic rhinitis. This remark is justified by the systematic analysis of several studies on over 250 pediatric patients with suspected LAR with a prevalence of positive NAPT of 16.1% [15]. Recent studies conducted on nearly 400 pediatric patients, some of whom with multiple NAPT, confirm LAR in a wide range of 37–67% of children. The highest incidence is in western countries, with the often-associated atopic dermatitis and conjunctivitis as the most common comorbidities. The evolution and clinical characteristics of LAR in children are still under investigation [43, 44, 45].

DIAGNOSIS

LAR should always be considered in patients with symptoms of AR, but without evidence of atopy. Recognition and early diagnosis are crucial for the timely introduction of therapy, symptom control, and comorbidity prevention. Diagnostic procedure involves a detailed patient history and examination, tests to prove atopy and allergic response of the nasal mucosa, provident their correlation with natural allergen exposure and exclusion of other potential causes of rhinitis [1, 3, 5, 9–12]. The history and examination of patients suspected to LAR is characterized by the symptoms and the look of patient that are characteristic of AR. However, these patients do not have a positive skin prick test nor specific serum IgE to common inhaled allergens. When there is doubt, other causes of rhinitis should be ruled out. The gold standard for the diagnosis of LAR is NAPT with selected allergen (or allergens) suspected to be responsible for the onset of the symptoms. People with a negative outcome of NAPT definitely have NAR. A positive outcome of NAPT indicates that the allergen that triggers allergic inflammation in the nostril mucosa under laboratory conditions is responsible for the symptoms of the disease. The connection of symptoms in positive NAPT with natural exposure to the same allergens clearly confirms that the given allergen is responsible for LAR [1, 5, 25, 41, 44, 46]. NAPT is characterized by high sensitivity, specificity, and reproducibility. The performance of this test should be entrusted to trained personnel in specialized institutions using standardized protocols. Under these conditions, performing NAPT is safe and reliable [43, 46]. In recent years, protocols have been developed to perform two or more NAPT at a single visit to a diagnostic unit, thus shortening diagnosis [7, 40]. Testing concentration of specific IgE in the nasal secretion and a basophil activation test were also developed. However, the low sensitivity of these assays and poor reproducibility still precludes their routine application [5, 44].

THERAPY

Contemporary therapy of LAR is based on well-known strategies for treating AR, relying on the immune and clinical similarities of these two phenotypes [1, 5, 47, 48]. Considering that avoiding causative allergens is difficult to implement in practice and that there are no official recommendations for AIT, treatment relies on patient education and pharmacological therapy. The goal of therapy is to control the symptoms and prevent disease progression.

To date, there are no studies evaluating the efficacy of leading controllers, oral antihistamines, and intranasal corticosteroids in LAR. Experience indicates a similar short-term effectiveness of these drugs in the control of AR and LAR [5, 9, 13]. However, more recent studies, with long-term monitoring of the effectiveness of pharmacological therapy, show different results. In patients with LAR, in a 10-year period, there was a significantly increased need for oral and intraocular antihistamines with a progressive increase in the use of intranasal and oral corticosteroids. At the same time, there was a worsening of symptoms, decreased tolerance to allergens responsible for the symptoms, and development of associated asthma symptoms. The results of a long-term trial show that pharmacological therapy, however, fails to control the symptoms and stop the natural progression of LAR, exacerbation, and development of comorbidities, primarily asthma [1, 8].

The similarity between LAR and AR phenotype and the proven efficacy of AIT in AR, have led researchers to apply AIT in LAR. Regardless of the absence of official recommendations, AIT was chosen as the best choice to the naturally progressive course of LAR. The experience is based on a total of four studies evaluating the short-term, clinical, and immunological effects of subcutaneous immunotherapy (SCIT) in LAR. All four studies were conducted using standardized allergen extracts, one observational and three randomized, double-blind, placebo-controlled studies, on a total of 140 subjects [2, 27, 28, 29].

The first study and the first official administration of AIT in LAR, was published by Rondon et al. [27] in 2011. They conducted an open-label, observational study, in patients with moderately severe seasonal LAR due to grass pollen hypersensitivity. In this study, they demonstrated that SCIT with a grass pollen mixture in the preseason protocol (six months), has beneficial clinical and immunological effects. Subjects who underwent SCIT had significantly fewer symptoms and lower drug consumption compared to the pre-SCIT season. These patients also achieved a significantly greater number of medication-free days than the control group, treated only with pharmacological therapy. During SCIT, patients significantly increased the tolerance of the nasal mucosa to the grass pollen. Clinical effects were accompanied by a significant increase in serum-specific immunoglobulin G4 (IgG4) concentration [27]. Although these results were impressive, the value of the study significantly diminishes its experimental design. For this reason, the same group of authors subsequently published two randomized, controlled studies, focusing on the clinical and immunological effects of SCIT in seasonal and perennial LAR. The results of these studies show that the two-year of SCIT with allergenic extract *Phleum pratense* in seasonal and *Dermatophagoides pteronyssinus* in perennial LAR also had beneficial clinical and immunological effects. Subjects receiving SCIT significantly reduced the combined symptom drug score, with significant increase of medication-free days and nasal mucosal tolerance to grass pollen and *Dermatophagoides pteronyssinus*. After the SCIT termination, as much as 50% of the treated patients tolerated maximum concentrations of allergens in laboratory conditions when performing NAPT. Beneficial clinical effects have been confirmed by improving the quality of life of these patients. The overall clinical effects of SCIT were also accompanied by a significant increase in specific IgG4 concentration in the serum [2, 28]. Similar effects of SCIT in LAR were confirmed in the randomized clinical study by Bozek et al. [29].

CONCLUSION

The rejection of the traditional conception of equalization of the allergic etiology of rhinitis with atopy changed the understanding and approach to patients with non-atopic rhinitis. The outcome of this change is LAR, the discovery of which was undoubtedly a major step forward in allergology at the beginning of the 21st century. Unfortunately, due to the low availability of NAPT in clinical practice, many cases remain unrecognized. It is necessary to include NAPT in the diagnostic algorithm of chronic rhinitis as soon as possible, as well as to better equip diagnostic units of airway allergic diseases. The disease has a progressive course, tends to worsen, cause the comorbidities and poor response to pharmacological therapy. The experience gained with AIT is positive and encouraging. Therefore, there is optimism that this causal therapy has the ability to slow and/or stop the progressive course of LAR and facilitate the disease control. New studies are needed to confirm existing curative effects and to evaluate the long-term preventive effects of AIT. LAR remains a major challenge for all physicians dealing with allergic airway diseases.

Conflict of interest: None declared.

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Локални алергијски ринитис – велики изазов у клиничкој пракси

Рајица Стошовић[1,2], Весна Томић-Спирић[1,2]

[1]Универзитетски клинички центар Србије, Клиника за алергологију и имунологију, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија

САЖЕТАК

Локални алергијски ринитис је нови фенотип ринитиса који се одликује симптомима сличним алергијском ринитису, без показатеља атопије али са позитивним специфичним ринопровокационим тестом. Болест се дијагностикује код преко 25% неатопијских пацијената са ринитисом, названим неатопијски ринитис. Најчешће има перенијалне и изражене симптоме и прогресиван ток. Често је удружен са конјуктивитисом и/или астмом. Локални алергијски ринитис треба обавезно размотрити код особа са неатопијским ринитисом. Фармаколошка терапија не успева да заустави прогресију и развој коморбидитета. Алергенска имунотерапија умањује симптоме, потрошњу лекова и повећава толеранцију на алергене одговорне за локални алергијски ринитис. Потребне су нове студије које ће потврдити постојеће и проценити превентивне ефекте алергенске имунотерапије.

Кључне речи: локални алергијски ринитис; дијагноза; терапија