Introduction

Local allergic rhinitis (LAR) is a localized allergic response of the nasal mucosa to aeroallergens in the absence of atopy with characteristic production of specific local immunoglobulin E antibodies in the nasal mucosa, T helper type 2 cellular infiltration response during the exposure to aeroallergens and positive results via the nasal allergic provocation test with the release of inflammatory mediators (triptase and eosinophil cationic proteins). Even though the prevalence of LAR has been and is still being investigated, a large number of patients with diagnosed non-allergic rhinitis or idiopathic rhinitis are currently classified as having LAR. The causes of LAR are most commonly house dust, dust mites, pollens and many others. Diagnosis of LAR is made using nasal allergen provocation tests when the prick test for standard inhalation allergens and the serum specific IgE analysis for aeroallergens are negative. The increasing amount of data on localized allergic response in non-atopic patients asks for many answers regarding LAR. These answers can be obtained by a study on the prevalence and incidence in children and adults, the impact of positive family atopy in the development of disease, the impact of associated diseases of the lower respiratory tract and conjunctiva, the effectiveness of drug treatment and the issue of administration of specific immunotherapy.

Key words: Rhinitis; Allergic, Seasonal; Rhinitis, Allergic, Perennial; Nasal Mucosa; Allergens; Immunoglobulin E; Prevalence; Signs and Symptoms; Diagnosis; Therapeutics

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LAR will develop a systemic atopy in the future or not and what that depends on. Further studies are necessary in order to find out the incidence of LAR and develop new diagnostic methods, therapeutic approaches and effects of immunotherapy.

In 1975, Huggins and Brostoff were the first to report the production of local IgE antibodies in the nasal mucosa of patients with allergic and non-allergic rhinitis [1–9]. This discovery preceded the development of the idea of local allergic rhinitis (LAR), as well as the state of the local allergic response of the nasal mucosa in the absence of atopy [7]. Further research in the field of LAR was conducted by a group of Spanish ear, nose and throat (ENT) allergists led by Ron- don et al. This condition is characterized by the local production of sIgE antibodies [1, 8, 9], TH2 inflammatory response [5, 7–10], the positive response to nasal allergen provocation test (NAPT) [6, 8, 9, 11] with overt symptoms and increased levels of sIgE, tryptase and eosinophil cationic protein (ECP) in nasal secretions [12, 13].

**Etiologic Classification of Rhinitis**

From the etiological point of view, non-infectious rhinitis has traditionally been classified as allergic and non-allergic and the diagnosis was based on the history of health problems, skin prick test and serum level of IgE antibodies to aeroallergens [14] (Table 1).

| Table 1. Etiologic classification of rhinosinusitis (according to Rondon et al.) |
| Tabela 1. Etiološka klasifikacija rinosinuzitisa (prema Rondon i sar.) |
| 1. Allergic rhinosinusitis/Alergijski rinosinuzitis |
| • Allergic rhinitis(rinosinusitis) (with systemic atopy)/Alergijski rinitis(rinosinusitis) (sa sistemskom atopijom) |
|   i. Classic classification/i. Klasificacija klasifikacija |
| 1. According to exposure to aeroallergen: perennial, seasonal, and occupational/Vreme ekspozicije na aeroalergen ili aeroalergene: perenialni, sezonski, i okupacioni |
|   ii. ARIA classification (14)/ii./ARIA klasifikacija (14) |
| 1. Duration of symptoms: persistent and intermittent/Dužina simptoma: perzistentni i intermitentni |
| 2. Severity of symptoms: light, moderate, severe/Težina simptoma: laki, umereni, i teški |
| • Local allergic rhinitis (rhinosinusitis) (without systemic atopy)/Lokalni alergijski rinitis(rinosinusitis) (bez sistemske atopije) |
|   i. Classic classification/i. Klasificacija klasifikacija |
| 1. According to exposition to aeroallergen: perennial, seasonal, and occupational/Vreme ekspozicije na aeroalergen ili aeroalergene: perenialni, sezonski, i okupacioni |
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| 1. Duration of symptoms: persistent and intermittent/Dužina simptoma: perzistentni i intermitentni |
| 2. Severity of symptoms: light, moderate, severe/Težina simptoma: laki, umereni, i teški |
| 2. Nonallergic rhinosinusitis/Nealergijski rinosinuzitis |
| • Infectious/Infektni |
| • Occupational (irritating)/Okupacioni (iritantni) |
| • Medicamentous/Medikamentozni |
| • Hormonal/Hormonalni |
| • Food induced/Hranom indukovan |
| • Emotional/Emocionalni |
| • Atrophic/Atrofiji |
| • GERD induced or laryngopharyngeal reflux induced rhinosinusitis (GERD - gastroesophageal reflux disease)/GERBom ili faringolaringealnim refluksom udružen rinosinusitis (GERB - gastroezofageal refluks bolest) |
| • NARES/NARES |
| • Idiopathic rhinosinusitis/Idiopatski rinosinusitis |
Allergic rhinitis (AR) is the most common form of non-infectious rhinitis [14]. However, the prevalence of non-allergic rhinitis (NAR) is unknown and a minimal effort has been made in the identification of NAR phenotypes using standard methods [14]. NAR is a heterogeneous group of disorders of nasal inflammation. Some of these disorders are caused by a visible trigger or causative agent although the cause remains undiscovered in most cases. NAR with a known cause include medical, hormonal, emotional, food-induced, atrophic, occupational/professional (irritants from the environment), rhinitis associated with Gerbe or laryngopharyngeal reflux. However, as much as 60% of non-allergic rhinitis has no detectable cause and is diagnosed as idiopathic rhinitis. According to the pathophysiological mechanism, idiopathic rhinitis is divided into two phenotypes: the one conditioned by neurogenic mechanisms and the one with inflammatory mechanisms. Knowing the type of idiopathic rhinitis is very important for the therapeutic action, namely idiopathic rhinitis caused by an imbalance of the sympathetic and parasympathetic nervous system that will not respond to topical corticosteroids, whereas the inflammatory type of idiopathic rhinitis will react. Vasomotor rhinitis, which is essentially an idiopathic rhinitis caused by neurogenic mechanism, is often mentioned in the literature. The neurogenic mechanism involves the imbalance of parasympathetic / sympathetic, hyper-reactivity of the nonadrenergic, non-cholinergic or peptidergic nervous system leading to neurogenic inflammation, hyperesthesia or dysesthesia of the central nervous system and the strong localization of nitrite oxide synthase in the smooth muscle of blood vessels of the cavernous sinus [15–19]. Non-allergic rhinitis with eosinophilia (NARES) was first described by Jacobs et al. in 1981 as a phenotypically distinct group of non-allergic rhinitis of unknown etiology with perennial nasal symptoms of profuse watery secretion, choppy sneezing attacks, itching of the nose with the recorded eosinophilia in nasal discharge with no obvious allergies (a negative skin prick test on SIA and absence of specific IgE in the serum) [20], NARES is often associated with nasal polyposis, bronchial hyper-responsiveness, non-allergic asthma and sleep apnea syndrome [21]. In the presence of aspirin intolerance with nasal polyposis and non-allergic asthma, it is diagnosed as ASA SY [22, 23]. Most authors identify NARES with idiopathic rhinitis, while some authors define it as a separate entity [24–26].

Patients with NAR have negative skin prick test and a lack of serum sIgE. However, over the past decade, several studies showed that a greater number of patients with negative skin prick test, negative intradermal skin test and the absence of serum sIgE had nasal symptoms following nasal provocation tests with airborne allergens, including house dust mites, pollens and others [8, 9]. Further studies have shown that the local production of specific IgE occurs in these patients [8, 9, 12, 13]. As a result of the above mentioned, the term LAR is preferred, leading to a new etiological classification of rhinitis [14, 15]. After describing LAR in patients previously labeled with the diagnosis of NAR, further studies were aimed at defining the clinical and immunological differences between idiopathic rhinitis (IR), NARES and LAR.

Prevalence

According to the studies performed by European centers, the prevalence of LAR among patients with negative skin prick test and negative serum specific IgE is about 47% to 62.5% of patients with perennial and seasonal symptoms of the disease [6, 8, 9, 11]. LAR was previously diagnosed in many patients with IR or NARES, thus indicating that this is a common entity. Large-scale studies including adults and children, which use the procedure of the nasal provocation test, nasal secretion collection and laboratory analysis are aimed at identifying the epidemiological characteristics of LAR. Their objective is to define whether LAR has one or more unique clinical phenotypes, including co-morbidities, which will distinguish them from other forms of rhinitis.

Is this entity more common in some areas due to different levels of allergens? Do external factors such as air pollution, smog and air temperature affect the development of LAR in relation to the development of AR? The answer is still in the research phase and it is the subject of numerous studies conducted in different geographical areas with different airborne allergens, different levels of air pollution and climatic factors.

Previously published studies indicate that LAR is usually caused by dust mites, house dust, grass pollen and olives [1, 6, 8, 9, 11, 13]. However, it is unknown whether some less common allergens are involved. Other possible triggers include mold, animal hair and professional aeroallergens. In the study performed by Carney et al., which included 13 patients with LAR, only one patient responded to nasal provocation with cat/dog hair [6]. It is also necessary to determine the appropriate, optimal dose of the allergen for nasal allergen provocation (NAP) and to develop a more practical method.

Pathophysiology

Certain genetic predisposition and pathophysiological reaction mechanisms to airborne allergens (endotype) and the expression of specific problems-clinical manifestations (phenotype) are required for the development of LAR.

An allergen in the nasal mucosa causes the production of a local sIgE response, which launches a Th2 inflammatory mechanism, increasing the levels of inflammatory mediators and the consequent reduction in nasal volume, but with negative skin prick test and the absence of IgE antibodies in the peripheral blood.
Local Production of Inflammatory Mediators and sIgE in Patients with AR and NAR

Several authors have studied the concept of local production of IgE in the nasal mucosa of patients with AR. Platt-Mills showed the increased levels of sIgE to grass pollen in the nasal secretions of patients with AR. Durham et al. found the expression of the $\varepsilon$ embryonic gene and the $m$ ribonucleic acid (RNA) transcript of the $e$ heavy chain of IgE in the nasal B cells. Further research has shown the existence of class switch recombination to IgE in the nasal mucosa of patients with AR [2–4]. Upon detection of nasal sIgE in patients with NAR [1], Rondon et al. [8, 9] demonstrated the presence of nasal sIgE in patients with seasonal and perennial LAR symptoms during the natural exposure to aeroallergens in earlier (22%) and later (35%) responses.

A possible reason for the inability to detect local sIgE to a large extent in patients with LAR and positive nasal allergen provocation test (NAPT) response may be the low sensitivity of diagnostic tests, dilution effect of nasal lavage, lack of inclusion of occult allergen, existence of other immune mechanisms as well as the possibility of non-specific protease activity of stimulation of house dust mites (HDM) on the innate immune cells of the respiratory system and others. The development of non-invasive in-vitro diagnostic techniques with high sensitivity detection of nasal sIgE would be a breakthrough in diagnosing and screening of LAR.

Recently published research data corroborate the concept of the synthesis of local sIgE in nasal mucosa [26]. Powe et al. have demonstrated the localization of free light chains (FLCs) in the tissue and nasal secretions of patients with AR and patients with NAR, assuming that they can mediate a hypersensitive immune response including the mast cells [26]. Further studies are needed to shed light on whether FLCs has a helpful or independent role in patients with IgE-mediated allergy and shed light on the presence of FLCs in patients with LAR.

TH2 Nasal Inflammatory Response (Mechanism)

Although the cause of IR is unknown, a number of pathophysiological mechanisms have been proposed including the inflammatory and neurogenic mechanism as well as a change in mucosal permeability [14]. The importance of the inflammatory mechanisms in patients with NAR was much disputed in the past. Though several histological and in situ hybrid studies found a Th2 inflammatory mechanism with an increase in the number of mast cells, eosinophils, IgE + B cells and T cells [5, 10], other studies found no significant difference between subjects with NAR and the controls [5, 10, 27, 28]. These apparently contradictory results can be explained by heterogeneity of NAR and recently diagnosed LAR in non-atopic patients. These early studies included patients with different pathogenesis that was predominantly inflammatory in patients with NARE and possibly patients with LAR [5, 10] and neurogenic mechanisms for patients with IR or vasomotor rhinitis [5, 8–10, 27, 28].

The existence of a TH2-mediated inflammatory IgE response has recently been confirmed in patients with LAR [8, 9]. Flow cytometric studies of a nasal lavage sample have shown that the patients with LAR and those with AR have a similar leukocytic-lymphocytic phenotype with an increase in the level of eosinophils, basophils and mast cells, CD3 + T cells, and CD4 + T cells during the exposure to aeroallergens [8, 9].

In addition, more than 70% of patients with NAR and LAR have characteristics of NARES (nasal eosinophilia> 20%). Previously, Powe et al. found an increase in CD8 + prior to CD4 + T-cells in patients with NAR and patients with AR compared to the numbers in the control studies and the reduction in number of antigen-presenting cells in patients with IR compared to those seen in patients with AR [10]. In this study, sIgE antibodies were not determined, neither was NAPT used. Therefore, the number of patients with LAR and their pathophysiological characteristics were not evaluated.

Positive Response to Nasal Allergen Provocation Test

Several studies have confirmed that more than 47% of patients with a previous diagnosis of IR have LAR with a positive NAPT response followed by a subjective (symptomatic) score and objective parameters (acoustic rhinometry, anterior rhinomanometry, nasal secretions with presence of sIgE and inflammatory mediators) [6, 8, 9, 11–13]. The first kinetic study of local production of IgE and inflammatory mediators after NAPT was administered to patients with LAR sensitized to grass pollen [12]. The results showed the activity of mast cells, eosinophils and IgE production caused by nasal stimulation with airborne allergens. Patients had a direct or dual response to NAPT, followed by release of tryptase, ECP and sIgE in nasal secretions. A kinetic study involving tryptase showed a strong correlation with nasal itching and secretions (runny nose) with the release of tryptase, which varied with the type of response. An immediate response was presented with a significant increase in the level of tryptase 15 minutes to 1 h after the exposure compared with the baseline values where patients with delayed dual responses reacted to increased tryptase from 15 minutes to 6 hours [12]. López et al. confirmed these results in patients with perennial LAR with positive response to the NAPT for Dermatophagoides pteronyssinus [13]. A significant finding in the two studies was a progressive increase in the level of the nasal sIgE from 1 to 24 hours after the NAPT [12, 13].

This sudden secretion of sIgE upon provocation with the basic detection of sIgE in some patients su-
sported the presence of the local production of sIgE in the nasal mucosa, which was increased upon allergic stimulation. All these findings prompt the scientists to consider the need to evaluate whether there is a local production of sIgE in patients with other non-allergic respiratory diseases, such as chronic rhinosinusitis with or without nasal polyps, asthma or conjunctivitis [29–33].

**Local Production of IgE Associated with Nasal Polyps**

Nasal polyposis is a chronic inflammatory process of the nasal and sinus mucosa of unknown etiology. In recent years, scientists have shown that *Staphylococcus aureus* can modify respiratory disease by inducing the synthesis of polyclonal IgE antibodies against *S. aureus* super antigen and environmental allergens in tissues of nasal polyps [29, 30]. This mucosal polyclonal IgE production against several antigens (aeroallergens or not) represents a model of the local synthesis of IgE different from LAR. In this model, the specific antibodies to aeroallergens correlate with the clinical response and allergen-specific activation of B cells, mast cells and eosinophils, often associated with low total IgE levels. However, the clinical significance of this phenomenon needs to be explained.

**Local Production of IgE Associated with Asthma**

Evidence suggests some overlapping between atopic and non-atopic asthma. There is an increased number of B cells with an increase in IL4 and IL5 mRNA expression in lung tissue of asthmatic patients, who may be either atopic or non-atopic ones [31, 32]. These findings lead to important questions: Is there the sameness of LAR among patients with asthma, conjunctivitis or both? Do patients with asthma also produce local IgE antibodies and bronchial allergic response in the absence of systemic atopy? A recent study by Campo et al. described the presence of positive response to bronchial stimulation of *D. pteronyssinus* with the number of eosinophils and basophils in the sputum of non-atopic asthma patients, justifying further studies [33].

**Clinical Manifestations**

**Nasal Symptoms and Comorbidities**

Patients with LAR have typical symptoms of AR (rhinorrhea, nasal blockage, runny and itching nose), which is usually associated with ocular symptoms and a good response to oral antihistamines and nasal corticosteroids [8, 9, 12]. Patients with LAR, as well as those with AR, have anterior rhinorrhea, nasal itching and secretion as the most common symptoms [8, 9]. Patients with LAR are classified according to the classical division of seasonal, perennial and occupational AR instead of the new division of intermittent and persistent AR [14] (Table 1). The earlier division was made according to the time of allergen exposure, while the new division is based on the presence of symptoms [14]. Most patients with LAR have persistent rhinitis with moderate to severe symptoms often associated with conjunctivitis (25% to 57%) and asthma (33% to 47%) [8, 9, 34]. So far, no data on the topic of LAR in the pediatric population have been published. Large epidemiologic studies including both the adult and pediatric population are required to define the prevalence, severity of symptoms, comorbidities, impact of airborne allergens and clinical effects of LAR.

**Pre-Investigation of Allergic March**

Since LAR occurs relatively late in life with a high percentage of patients who do not report any symptoms referring to systemic allergy, the question remains whether these patients are truly atopic. Furthermore, a large group of patients with NAR having had negative skin prick test (SPT) and serum sIgE levels throughout life become positive in 24% of cases. This suggests that the vast majority remains negative [35]. In this context, the concept of atopy must certainly be expanded. If patients with LAR develop AR over time, this event would then support the atopic march. For this purpose, more details as well as more prospective studies including patient groups should be evaluated in the case of LAR associated with asthma and/or conjunctivitis. One study that helps clarify atopic march is the study of the evolution of LAR during immunotherapy. Developing studies indicate that patients with LAR undergoing immunotherapy for grass pollen with an initially negative skin prick test become positive and have serum sIgE antibodies, regardless of clinical improvement, which occurs during classical AR [34].

**Diagnostic Protocol**

Awareness of the existence of local allergic response of the nasal mucosa suggests that allergy processing is necessary. Rondon et al. proposed a new protocol with nasal allergen evaluation in all patients with clinical history indicative of AR but having negative SPT and sIgE antibodies or in those whose clinical history is not coherent [36] (Graph 1).

Diagnosis of LAR can be done by detecting nasal sIgE or according to the positive NAPT response or both, provided that systemic atopy is absent. Laboratory testing of nasal lavage (mucus) is a non-invasive method for examining cells, inflammatory mediators and other immunological markers. Determination of the level of sIgE with nasal lavage has been proven to be useful for detecting local hypersensitivity during natural exposure and after NAPT. This in vitro assay has a high specificity but a low sensitivity of 22% to 40% [8, 9]. Whether the effect of dilution of lava-
ge samples, non-specific response to the HDM, other factors or both may contribute to this low sensitivity is still under consideration. The nasal provocation test with one aeroallergen (NAPT-S) is a highly useful diagnostic tool in patients with LAR, having high sensitivity of discovery of nasal sIgE, trypase or ECP levels [6, 8, 9, 11, 12]. However, it is a very time-consuming technique and its application in clinical practice can be problematic. Due to this fact, a new NAPT protocol was designed with multiple aeroallergens in a single session. It has since been proved to be useful, specific, sensitive, reproducible and less time-limited for screening patients with LAR. The sequential application of a number of airborne allergens in a single session did not cause any irritating response and showed 100% compatibility with the gold standard, that is NAPT-S. This application resulted in a 75% decrease in the total number of visits required for a definitive diagnosis in a patient group with NAR and a 55% decrease in patients with LAR compared with NAPT-S results [37].

Therapeutic Options

Distinguishing between LAR and NAR is the main basis for further successful treatment. AR therapy includes avoidance of allergens, pharmacological treatment, immunotherapy and education [14]. Patients with LAR respond well to topical nasal corticosteroids and oral antihistamines [8, 9]. This may be one of the phenotypic characteristics of the patients with LAR compared to those with the non-atopic rhinitis. A double-blind, placebo-controlled clinical study is of great importance when comparing the efficacy of pharmacological therapy in patients with LAR and AR. An important question is whether patients with LAR can benefit from immunotherapy. A pilot study by Rondón et al. included patients with LAR who were allergic to grass pollen [35]. Fifty percent of the patients were treated with subcutaneous immunotherapy (SCIT) for grass pollen for 6 months and, when necessary, they were medically treated in spring (the SCIT group), while the other half of patients received medication only (the control group). In this study, SCIT with grass pollen increased tolerance to aeroallergens and reduced symptoms as well as the amount of medication in patients with LAR, compared to those in the control group. These interesting results have increased the necessity for phase II double-blind placebo-controlled clinical trials for evaluating whether LAR can be regarded as a new indicator for the specific immunotherapy [34].

Future Research

The increasing amount of data on the localized allergic response in non-atopic individuals asks for many answers on the subject of LAR. These answers can be given by studies on the prevalence and incidence in children and adults, impact of positive family atopy in the development of the disease, impact of diseases of the lower respiratory tract and conjunctiva, effectiveness of drug treatment and the issue of administration of specific immunotherapy. It is very important to know if patients remain stable over the years or their symptoms turn into a form of allergic rhinitis. The fact that many patients have history of LAR for numerous years without the progression of systemic AR supports the idea that this is an independent entity. However, there is a possibility that local sensitization would be the primary event in each AR and could later develop into classic systemic AR over time. This claim requires further prospective studies [38].

In addition, further research should discover more characteristics of the inflammatory response in patients with LAR. This can be achieved by carrying out comparative studies among the patients with LAR and those with AR, by assessing the presence of a local allergic response in patients with professionally induced rhinitis with or without asthma, by considering feasibility of genetic studies in large groups of patients diagnosed with LAR and by comparing them with patient groups having systemic AR and NAR.


