

Local allergic rhinitis: a new entity, characterization and further studies

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Current Opinion in Allergy and Clinical Immunology 2010, 10:000–000

Purpose of review

The purpose of this review is to describe new insights into the pathophysiology and clinical characterization of 'local allergic rhinitis', a new phenotype of rhinitis that may affect individuals previously diagnosed with nonallergic rhinitis.

Recent findings

Several studies have shown the existence of local allergic rhinitis with nasal production of specific IgE (sIgE) antibodies in the absence of atopy in over 40% of nonallergic rhinitis patients. Evidence for this entity is supported by the clinical symptoms, the local production of sIgE and a leukocyte–lymphocyte inflammatory pattern, with an increase in the nasal fluids of eosinophils, mast cells and T lymphocytes during natural exposure to aeroallergens, as well as a positive immediate and dual response to a nasal allergen provocation test with local production of tryptase and eosinophil cationic protein and an increase of nasal sIgE to inhalant allergens.

Summary

On the basis of these new findings, an advanced diagnostic approach is proposed in patients with symptoms suggestive of allergic rhinitis but negative results in skin prick test and serum sIgE. Detection of local sIgE in nasal secretions during natural exposure to aeroallergens and a positive nasal allergen provocation test with local production of tryptase, eosinophil cationic protein and sIgE are useful to detect patients with local allergic rhinitis.

Keywords

local allergic rhinitis, local IgE, nasal challenge, nonallergic rhinitis, nonallergic rhinitis with eosinophilic syndrome

Curr Opin Allergy Clin Immunol 10:000–000
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1528-4050

Introduction

Rhinitis is a common respiratory disease that affects 20–40% of the western population, and its incidence is rising [1,2]. Etiologically, rhinitis can be divided into two types: allergic rhinitis and nonallergic rhinitis (NAR) [3]. Allergic rhinitis is clinically defined as an IgE-mediated inflammatory response after allergen exposure of the nasal mucosa. Symptoms of rhinitis include rhinorrhea, nasal obstruction, nasal itching and sneezing [4]. The diagnosis is based on clinical manifestations and a positive skin prick test (SPT) or serum-specific IgE (sIgE) antibodies to aeroallergens [5–7]. In contrast, rhinitis is defined as nonallergic when an allergic cause has been ruled out by the presence of an inconsistent clinical history, a negative SPT and the absence of serum sIgE antibodies [5,8,9].

Over recent years, increasing evidence has shown that an important number of patients previously diagnosed with

NAR or idiopathic rhinitis develop a local allergy with nasal production of sIgE [8,9] and a positive response to a nasal allergen provocation test (NAPT) [8,9,10]. This entity has been suggested to be entopy [8] or local allergic rhinitis (LAR) [11].

The purpose of this review is to describe the new insights that help to understand the pathophysiology of the immune response and the clinical characterization of LAR.

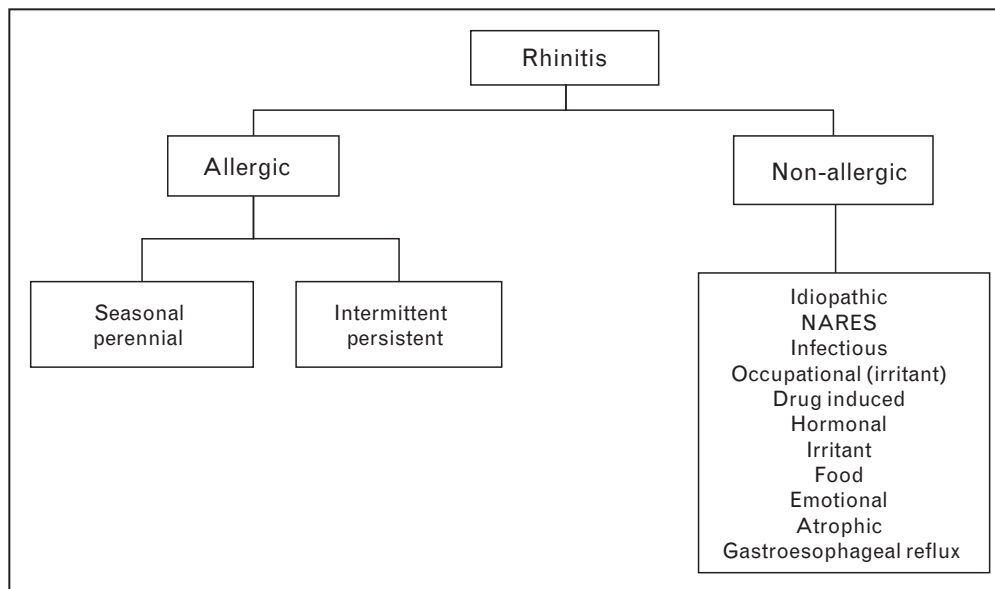
Classification of nonallergic rhinitis

NAR can be divided into several subgroups (Fig. 1), with idiopathic rhinitis and NAR with eosinophilic syndrome (NARES) being the most frequent [12].

Idiopathic rhinitis

Up to 60% of NAR patients have idiopathic rhinitis with an unknown etiology, usually diagnosed by

Figure 1 Classification of rhinitis



NARES, nonallergic rhinitis with eosinophilic syndrome.

exclusion [3]. Idiopathic rhinitis is, therefore, an entity that has not been well defined clinically, and the term NAR encompasses entities that may have several causes and different mechanisms. Over the years, idiopathic rhinitis has been known by several terms, including noninfectious NAR (NINAR), nonallergic, noninfective, perennial rhinitis (NANIPER), perennial NAR, intrinsic rhinitis and vasomotor rhinitis (a term that should be reserved for patients for which a neurogenic pathophysiology is implicated) [4^{••},5,13[•]]. Although the etiopathology of idiopathic rhinitis is poorly understood, immunological, neurogenic or other pathophysiological mechanisms may participate [2,3,5].

Nonallergic rhinitis with eosinophilia syndrome

NARES was originally described in 1981 by Jacobs *et al.* [14] as perennial nasal symptoms of sneezing paroxysms, profuse watery rhinorrhea and nasopharyngeal itching, with a profound eosinophilia in nasal secretions and no signs of allergy.

Nowadays, NARES is considered to be a subgroup of NAR that is different from idiopathic rhinitis [4^{••}]. However, the exclusion of NARES from this category is controversial [1] because, although NARES patients seem to respond well to nasal corticosteroids [15], in contrast to other patients with idiopathic rhinitis, the cause of their characteristic mucosal eosinophil infiltration remains unknown. Nevertheless, this review will include NARES and NANIPER in the idiopathic rhinitis group, as they have an unknown cause.

Possible pathophysiological mechanisms of idiopathic rhinitis

The pathophysiology of idiopathic rhinitis remains largely unknown. Neurogenic and inflammatory pathways have been proposed as possible pathophysiological mechanisms.

Neurogenic mechanisms

The neurogenic mechanisms proposed include parasympathetic/sympathetic neural dysbalance [16], hyperactive nonadrenergic, noncholinergic (NANC) or peptidergic neural system, leading to neurogenic inflammation [17,18], hyperesthesia or dysesthesia of the central nervous system (CNS) [19] and strong localization of nitric oxide synthase in the vascular smooth muscle cells of the cavernous sinuses [20].

Inflammatory mechanism

An important characteristic in the pathophysiological inflammatory concept is the influx of inflammatory cells to the affected tissue. Nasal biopsy studies performed in allergic rhinitis patients have shown an inflammatory phenotype with an increase of eosinophils, mast cells and mononuclear cells [21,22] that correlates positively with nasal symptoms [22,23]. However, less is known about the inflammatory process in NAR [9^{••},24–26]. Although some idiopathic rhinitis patients present a predominantly eosinophilic infiltration (NARES) and responsiveness to nasal corticosteroids [15], other studies [24,26] found no significant difference for nasal mucosal

lymphocytes, antigen-presenting cells (APCs), eosinophils, macrophages, monocytes, mast cells or other IgE-positive cells between idiopathic rhinitis patients and controls. Accordingly, idiopathic rhinitis has been suggested to be essentially a noninflammatory disease with a lack of responsiveness to corticosteroids. Nevertheless, these results contrast with other histological findings demonstrating the presence of active mucosal inflammation in idiopathic rhinitis [27], with a significant infiltration of eosinophils, mast cells and T cells [25,28].

The presence or absence of an inflammatory process in nasal mucosa from idiopathic rhinitis patients may be explained by the fact that the studies may have included patients with a different pathogenesis (predominantly inflammatory [24,25,27,29] or neurogenic mechanisms [26,30]). Recent studies [7,8,9^{••},25,29] have demonstrated a nasal inflammatory infiltrate in a subgroup of idiopathic rhinitis patients with great similarities to allergic rhinitis, suggesting the existence of a LAR or entopy in the absence of systemic atopy.

The allergic response is located in the mucosa of allergic rhinitis patients

Patients with allergic rhinitis have an IgE-mediated response with infiltration of the nasal mucosa by Th2 cells, basophils, Langerhans cells, eosinophils and mast cells [30–32]. When aeroallergens are inhaled, they are deposited mainly in the nasal mucosa, in which they are presented to T cells by APCs in the presence of an appropriate cytokine milieu. This results in the induction of IgE production via the isotype switching of B cells.

Mucosal surfaces are widely distributed in the organism and constitute the first line of contact between the immunological system and allergens. Dendritic cells are professional APC that are abundant within the upper and lower respiratory mucosa in allergic patients [33], and also in the mucosa of NAR patients [25].

In the 1970s, several researchers detected sIgE antibodies in nasal secretions from allergic rhinitis patients [34,35]. These early results suggested that the allergic response might be a local response in the nasal mucosa. Since then, several studies have demonstrated local IgE synthesis in nasal mucosa. In 1979, Platts-Mills [36] detected increased levels of rye-grass sIgE, IgG and IgA in nasal secretions with an absence in saliva in allergic rhinitis patients. The site of production was inferred from the ratio of the 'specific activity' of each class in nasal secretion to the 'specific activity' of that class in serum.

T lymphocytes are one of the most important cells involved in IgE-mediated immune responses, as they are the only cells able to recognize antigens after proces-

sing by APC, and their release of IL-4, IL-13 and CD40L mediators induces selective somatic recombination of the immunoglobulin heavy chain regions in B cells, preceding their maturation into plasma cells [37]. Mast cells, important effector cells in the immediate-phase allergic reaction, are also involved in maintaining IgE production. Pawankar *et al.* [38] demonstrated that nasal mast cells can secrete greater levels of IL-4 and IL-13 and induce increased levels of IgE synthesis than T cells. IgE antibodies are synthesized by plasma cells in nasal mucosa of allergic rhinitis patients, providing a local source for the sensitization of mast cells to common aeroallergens [39]. It is estimated that in allergic rhinitis, one of 25 B cells and one of five plasma cells in the nasal mucosa, compared with one of 10 000 in peripheral blood B cells, express IgE [40,41]. Several studies [42–45] have found expression of epsilon germline transcripts and mRNA for the epsilon heavy chain of IgE in nasal and bronchial mucosa. IgE production has been detected in nasal mucosa of allergic rhinitis patients *in vivo* [8,9^{••},46] and *in vitro* [47,48].

Causes of undetected atopy in rhinitis patients

Patients with idiopathic rhinitis are considered nonallergic because they have a negative SPT and a lack of serum sIgE to aeroallergens [5,7,8,9^{••}]. However, many of these patients have clinical criteria indicative of allergic rhinitis [4^{••}] with perennial [8] or seasonal symptoms [9^{••},49].

An undetected 'systemic atopy' or else its true absence may be the explanation for this clinical observation. Causes for this include false-negative results in the conventional atopic test, because of inadequate quality of aeroallergens used in SPT or low IgE sensitivity detection, or the existence of allergic rhinitis to a non-identified allergen. An alternative explanation may be the existence of a local allergic response located in nasal mucosa in the absence of systemic atopy.

Evidence of local allergic rhinitis in idiopathic rhinitis patients

In order to identify these patients, a detailed clinical history that excludes patients with vasomotor or infectious rhinitis is appropriate before initiating pathophysiological studies in LAR or entopy [7,8,9^{••}]. Since 1975 [50], several studies have supported the existence of LAR in patients previously diagnosed with idiopathic rhinitis. These studies involve the processes that are discussed below.

Detection of specific IgE and inflammatory mediators in nasal secretion

One of the earliest studies was published by Huggins and Brostoff [50] in 1975. The authors detected a positive

response to NAPT with *Dermatophagoides pteronyssinus*, with development of nasal symptoms and sIgE in nasal secretions in a group of patients with a clinical history suggestive of house dust mite allergy but a negative SPT and serum sIgE to *D. pteronyssinus*.

Recently, two comparative studies including idiopathic rhinitis and allergic rhinitis patients and healthy controls detected sIgE antibodies against *D. pteronyssinus* [8] and grass/olive pollen [9**] with increased levels of eosinophil cationic protein (ECP) during natural exposure in LAR patients, with positive NAPT but negative SPT and intradermal test, and nondetectable serum sIgE to aeroallergens.

Similar pattern of inflammatory cells in nasal mucosa and secretions from allergic rhinitis and local allergic rhinitis patients

Studies performed in nasal biopsies and nasal secretions from patients with idiopathic rhinitis suggest that allergic rhinitis patients and an important proportion of idiopathic rhinitis patients share a localized Th2, IgE-mediated cellular immunopathogenesis. Immunohistochemistry and in-situ hybridization studies in nasal biopsies found an increased number of mast cells [29,51], eosinophils [29], IgE⁺ cells [29] and T cells [25] in nasal mucosa from both allergic rhinitis and idiopathic rhinitis patients compared with healthy controls.

Immunohistochemical study of the mucosal T-cell phenotypes [25] showed that idiopathic rhinitis and allergic rhinitis patients present an increased number of CD3⁺ and CD45RA⁺ T cells and the presence of activated lymphocytes (CD25⁺) compared with healthy individuals. Idiopathic rhinitis patients differ from allergic patients in that they show significantly reduced numbers of epithelial human leukocyte antigen (HLA)-DR α + cells and increased numbers of CD8⁺ lymphocytes. In both rhinitis groups, basophils were present in very low numbers [25].

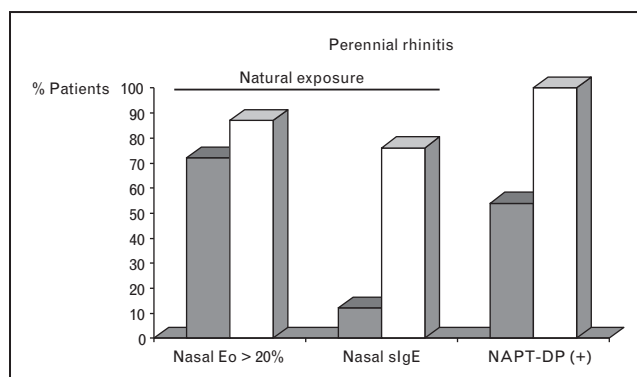
Flow cytometry is a very useful technique to study leukocyte and lymphocyte subpopulations in nasal secretions from allergic rhinitis and NAR patients. Flow cytometry studies of the nasal lavage from LAR patients with positive NAPT-*D. pteronyssinus* [8] and NAPT-grass/olive pollen [9**] during natural exposure to aeroallergens showed a very similar leukocyte-lymphocyte phenotype to the allergic rhinitis patients, with increased levels of eosinophils, basophils, mast cells, CD3⁺ T cells and CD3⁺ CD4⁺ T cells compared with healthy controls. In these studies, over 70% of idiopathic rhinitis and LAR patients presented criteria of NARES with nasal eosinophilia more than 20%. These data suggest that an important proportion of patients with LAR are misdiagnosed with NARES.

Nasal allergen provocation test studies

NAPT is a useful tool to study the pathophysiology of allergic rhinitis and describe the time course of the release of several inflammatory mediators in nasal secretions [52,53–55].

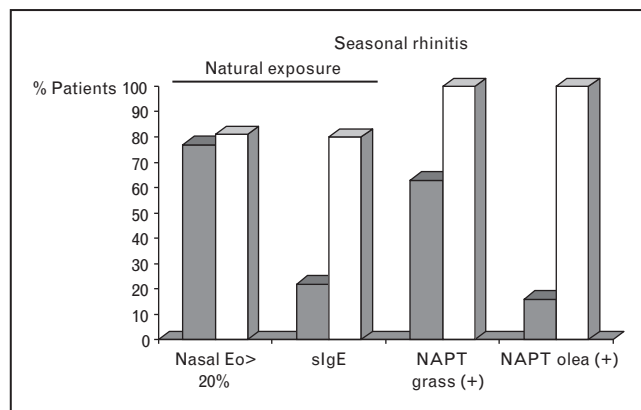
Carney *et al.* [10] in 2002 performed weekly bilateral nasal challenges with different aeroallergens (*D. pteronyssinus*/*D. farinae*, cat/dog epithelia and grass pollen mix) in a group of 21 patients with idiopathic rhinitis and observed a 62% positive response rate to NAPT, mainly to house dust mite, expressed as an increase in unilateral nasal resistance of more than 50% of baseline values assessed by anterior active rhinomanometry. In 2005, Wedback *et al.* [49] detected a 47% positive response rate to NAPT with birch pollen in a group of patients with seasonal idiopathic rhinitis. In 2007, our team [8] evaluated an important group of patients with perennial idiopathic rhinitis during natural exposure to house dust mite and after bilateral NAPT with *D. pteronyssinus* (Fig. 2). All the patients with idiopathic rhinitis had a history of perennial rhinitis, with a negative SPT and serum sIgE to aeroallergens and a negative intradermal skin test to *D. pteronyssinus*; 54% of the idiopathic rhinitis patients had a positive NAPT-*D. pteronyssinus*, and of these, 63% had an immediate response and 37% a dual response. No isolated late response was detected. In another study by the same group in 2008 [9**] in patients with seasonal idiopathic rhinitis (Fig. 3), a positive immediate or dual response to NAPT with pollens (grass and/or *Olea europea*) was detected in 62.5% of the patients. All the patients reported nasal symptoms exclusively during April–June, and their symptoms improved with intranasal

Figure 2 Patients with perennial idiopathic ($n = 50$) and allergic rhinitis to *Dermatophagoides pteronyssinus* ($n = 30$) during natural exposure and after nasal allergen provocation test with *D. pteronyssinus*



Eo, eosinophil; NAPT-DP, nasal allergen provocation test with *Dermatophagoides pteronyssinus*; sIgE, specific IgE. ■, idiopathic rhinitis; □, allergic rhinitis.

Figure 3 Patients with seasonal idiopathic ($n = 32$) and allergic rhinitis ($n = 35$) during natural exposure (in spring) and after nasal allergen provocation test with grass and *Olea* pollen



Eo, eosinophil; NAPT, nasal allergen provocation test; sIgE, specific IgE.
■, idiopathic rhinitis; □, allergic rhinitis.

corticosteroids and oral antihistamines, but had a negative SPT and intradermal skin test, with a negative serum sIgE. In both these studies, nasal patency was assessed by acoustic rhinometry, and a positive NAPT was considered to be an increase of more than 30% in the total visual analog scale (VAS) symptoms and a decrease of more than 30% in nasal patency (vol. 2–6 cm) compared with the baseline test.

A very interesting study [56^{••}] recently explored the kinetics of the local production of sIgE and the eosinophil and mast cell activation in response to NAPT with grass pollen (NAPT grass) in patients with LAR. A total of 30 patients with LAR to grass pollen and 30 healthy controls were challenged out of spring; 40% of patients had an immediate response and 70% a dual response. A significant number of patients presented nasal release of tryptase, ECP and grass sIgE antibodies after NAPT. The patients with an isolated immediate response had a stronger nasal response with a significantly higher decrease of vol. 2–6 cm in acoustic rhinometry and a higher peak of maximum nasal concentration of tryptase 15 min after challenge than the dual responders. The nasal levels of tryptase decreased over time and returned to baseline levels at 6 h. Dual responders showed sustained high nasal levels of tryptase during the first 6 h after challenge. Nasal release of ECP was detected 15 min after challenge, increasing progressively and reaching the maximum concentration at 24 h. An important finding was the detection of a progressive increase in the levels of grass sIgE at 1, 6 and 24 h after NAPT. This rapid nasal release of sIgE after nasal challenge, with the detection in some patients of baseline levels of sIgE out of spring, supports

the existence of a persistent local synthesis of sIgE in nasal mucosa from LAR patients that rapidly increases after local allergen stimulation.

Long-term evolution and further research in local allergic rhinitis

Few data are available on the natural history of NAR, including whether it progresses to allergic rhinitis [57,58]. In a recent study [11^{••}] by our group performed in a sample of 180 NAR patients diagnosed during 2000–2004 and re-evaluated in 2007, de-novo sensitization to aero-allergens was detected in 24% of the patients, as demonstrated by SPT and/or serum sIgE. These results support the idea that LAR may progress to allergic rhinitis. Our team is currently undertaking a larger follow-up study in a group of patients with LAR to evaluate the natural evolution of these patients.

Another important question concerns whether LAR may respond favorably to specific immunotherapy with aero-allergens. Further research is also needed to evaluate this question.

Conclusion

Recent evidence supports the existence of a localized mucosal allergic response or LAR in an important proportion of patients previously diagnosed with NAR. This new entity shares clinical symptoms, a positive response to NAPT, nasal production of sIgE antibodies and a Th2 nasal inflammatory pattern with classical allergic rhinitis. Preliminary data suggest that LAR patients could progress over time to allergic rhinitis, but further studies are needed to support these findings.

Acknowledgements

We thank Ian Johnstone for help with the final English language version of this manuscript.

This work was supported by grants from the Spanish Health Ministry (FIS PI08/1572), Health Division of Andalusia Government (PI-0181/2008) and Network RIARAA (RD07/0064).

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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