Local Allergic Rhinitis: Concept, Clinical Manifestations, and Diagnostic Approach

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Abstract

Local allergic rhinitis is a newly described type of rhinitis involving nasal production of specific immunoglobulin (sIg) E antibodies in the absence of atopy. It can affect patients previously diagnosed with non-allergic rhinitis. Evidence for this entity is supported by clinical symptoms, local production of sIgE, a type 2 helper T cell inflammatory pattern in nasal secretions during natural exposure to aeroallergens, and a positive response to nasal allergen provocation with local nasal production of sIgE to aeroallergens, tryptase, and eosinophil cationic protein (ECP).

Based on 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 determination. Detection of local sIgE in nasal secretions during natural exposure to aeorallergens and a positive nasal allergen provocation test with local production of tryptase, ECP, and sIgE are useful for detecting patients with local allergic rhinitis.

Key words: Local allergic rhinitis. Local IgE. Nasal challenge. NARES. Nonallergic rhinitis.

Resumen

La rinitis alérgica local es un nuevo tipo de rinitis con producción nasal de anticuerpos IgE específicos en ausencia de atopia sistémica que puede afectar a sujetos previamente diagnosticados de rinitis no alérgica. Esta nueva entidad se apoya en la existencia de síntomas clínicos de rinitis, producción local de IgE específica y presencia de un patrón inflamatorio Th2 en las secreciones nasales durante la exposición natural a los aeroalérgenos, así como respuesta positiva al test de provocación nasal con alérgenos con producción local de IgE específica nasal a alérgenos inhalantes, triptasa y proteína catiónica de eosinófilos (ECP).

Basado en estos nuevos hallazgos, se propone realizar un diagnóstico alergológico avanzado en pacientes con síntomas sugestivos de rinitis alérgicas en los que el prick test y la determinación de IgE específica sérica sean negativos. La detección local de IgE específica en las secreciones nasales durante la exposición natural a aeroalérgenos y la respuesta positiva al test de provocación nasal con aeroalérgenos con producción local de triptasa, ECP e IgE específica han demostrado ser técnicas útiles para detectar pacientes con rinitis alérgica local.

Palabras clave: Rinitis alérgica local. IgE local. Provocación nasal. NARES. Rinitis no alérgica.

Introduction

Rhinitis is a global health problem that affects 20%-40% of the population in developed countries and whose incidence is rising. It can be induced by different mechanisms and involves several etiological agents [1,2]. Rhinitis has traditionally been classified as allergic rhinitis (AR) and nonallergic rhinitis (NAR) [3]. The diagnosis of AR is based on clinical manifestations and supported by a positive result for skin prick test (SPT) or serum specific immunoglobulin E (sIgE) antibodies to aeroallergens [4,6]. In contrast, rhinitis is diagnosed 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].

Nonallergic rhinitis is a very heterogeneous group of conditions that can be subdivided into several phenotypes, the largest of which are idiopathic rhinitis and nonallergic rhinitis with eosinophilia syndrome (NARES) [9].

It is important to differentiate between AR and NAR, as management differs for each. Treatment of AR includes avoidance of airborne allergens to which the patient is sensitized, pharmacologic therapy with oral antihistamines and

intranasal corticosteroids, and specific immunotherapy. Treatment of NAR depends on phenotype: patients with an inflammatory phenotype present a good response to intranasal corticosteroids [10,11], while those with noninflammatory phenotypes may react favorably to treatment with capsaicin [12,13].

In recent years, several studies have shown that many patients previously diagnosed with NAR or idiopathic rhinitis (IR) develop local allergic rhinitis (LAR) [14,15], or entopy [7]. This review analyzes the most recent data on LAR in order to understand its pathophysiology and clinical characteristics.

Classification of Nonallergic Rhinitis

Nonallergic rhinitis can be divided into disorders with a known etiology and disorders with an unknown etiology, or IR.

Up to 60% of patients with NAR have IR, which is usually diagnosed by exclusion [3], ie, the cause of the symptoms is unknown and diagnosis is made after ruling out other possible causes [3,15]. Over the years it has been known by different terms, such as noninfectious, nonallergic rhinitis (NINAR), nonallergic noninfectious perennial rhinitis (NANIPER), perennial nonallergic rhinitis, intrinsic rhinitis, and vasomotor rhinitis (a term that should be reserved for patients where a neurogenic pathophysiology is involved) [4,15,16]. Although the etiology of NAR is unknown, several pathophysiologic mechanisms have been proposed, including an inflammatory process with local production of sIgE in the nasal mucosa, neurogenic mechanisms, and changes in mucosal permeability [1,3,6].

Nonallergic rhinitis with eosinophilia syndrome (NARES) was first described in 1981 by Jacobs et al [17] as perennial nasal symptoms of sneezing paroxysms, profuse watery rhinorrhea, and nasopharyngeal itching with profound eosinophilia in nasal secretions and no signs of allergy.

Classification of NARES is controversial. Some authors consider this syndrome a different phenotype from IR [4], because patients seem to respond well to nasal corticosteroids [18]. Other authors, however, include it within the same category as IR, [9,15]. In this review, we also include NARES in the IR category. NARES is usually associated with eosinophilic nasal polyps, bronchial hyperreactivity, nonallergic asthma, and sleep apnea syndrome [19]. Nasal polyposis in asthmatic patients who are intolerant to NSAIDs is called the ASA triad [20,21].

Pathophysiological Mechanisms of Idiopathic Rhinitis

Understanding pathophysiology is very important for the diagnosis and therapeutic management of IR. Numerous studies have examined the pathophysiology of AR, although the specific mechanisms responsible for IR remain unclear. Neurogenic and inflammatory pathways have been proposed.

Neurogenic Mechanisms

The neurogenic mechanisms proposed include parasympathetic/sympathetic neural imbalance [22], hyperactive nonadrenergic noncholinergic (NANC) or peptidergic neural system leading to neurogenic inflammation [23,24], hyperesthesia or dysesthesia of the central nervous system [25], and strong localization of nitric oxide synthase in the vascular smooth muscle cells of the cavernous sinuses [26].

Inflammatory Mechanisms

Inflammation involves the influx of inflammatory cells to the affected tissue. Nasal biopsy studies performed in AR patients have shown an inflammatory phenotype with an increase in counts of eosinophils, mast cells, and mononuclear cells [27,28] that correlates positively with nasal symptoms [28,29]. However, less is known about the inflammatory process in NAR [30-33].

The presence or absence of inflammation in the nasal mucosa of patients with IR is controversial. Although some patients with IR present predominantly eosinophilic infiltration (NARES) and responsiveness to nasal corticosteroids [18], there are no significant differences for nasal mucosal lymphocytes, antigen-presenting cells (APC), eosinophils, macrophages, monocytes, mast cells, or other IgE-positive cells between patients with IR and controls [33,34]. Accordingly, IR has been considered essentially a noninflammatory disease with a lack of responsiveness to corticosteroids. These seemingly contradictory results can be explained by the heterogeneity of IR. The presence or absence of an inflammatory process in the nasal mucosa of patients with IR could be because studies may have included patients with a different pathophysiological phenotype (predominantly inflammatory or neurogenic mechanisms). Recent studies have demonstrated a nasal inflammatory infiltrate in a subgroup of patients with IR that was very similar to AR, suggesting the existence of LAR, or entopy, in the absence of systemic atopy [7,8,14,30,35].

Local Allergic Rhinitis

Is Nonallergic Rhinitis Really Nonallergic?

Since the discovery of IgE [36], an association has been observed between the expression of IgE and predisposition to allergic disease. AR is clinically defined as an IgE-mediated inflammatory response to allergens in the nasal mucosa involving a type 2 helper T cell (T_H2) pathway [37]. Symptoms include rhinorrhea, nasal obstruction, nasal itching, and sneezing [4]. It is often associated with ocular symptoms. Diagnosis is based on clinical history, as well as a positive response to SPT, serum sIgE antibodies to aeroallergens, or both [4-6].

In NAR, no specific physiological responses can be used to define this condition and, despite reports of a diagnostic test for neurogenic (vasomotor) rhinitis [38], diagnosis is usually made by exclusion.

Differentiation between AR and NAR is not always clear. A review of the literature shows that many patients with NAR

have clinical criteria indicative of AR [4], with perennial [8] or seasonal symptoms [30,39], moderate to severe symptoms [3,8,14], a high rate of comorbidity [8,14,18], and impaired quality of life [14,40].

The similarities between AR and NAR raise some interesting questions. Does the absence of atopy, as detected by SPT and serum sIgE, provide an accurate diagnosis of NAR? Is it necessary to explore the allergic response in the target organ? Either undetected systemic atopy or its true absence may explain this clinical observation. Causes include false-negative results in conventional atopic testing due to inadequate quality of the aeroallergens used in SPT, low IgE sensitivity detection, or existence of AR to an unidentified allergen. An alternative explanation may be the existence of a local allergic response in the nasal mucosa in the absence of systemic atopy.

Local Allergic Response in Patients With Allergic Rhinitis

An IgE-mediated response involving T_H2 cells, basophils, Langerhans cells, eosinophils, and mast cells can be observed in the nasal mucosa of patients with AR [41,42]. Mucosal surfaces are widely distributed in the organism and constitute one of the first lines of contact between the immune system and allergens. The inhaled aeroallergens are deposited mainly in the nasal mucosa, where APCs are processed and presented to T cells. This leads to induction of IgE production via isotype switching in B cells. Dendritic cells are professional APCs that are abundant in the upper and lower respiratory mucosa in AR [43] and NAR [32].

In the 1970s, several authors detected sIgE antibodies in the nasal secretions of patients with AR [44-46]. Platts-Mills [46] showed increased levels of rye-grass sIgE, IgG, and IgA in nasal secretions and absence in saliva. These early results suggested that patients with AR may have a local allergic response in the nasal mucosa.

T lymphocytes play a crucial role in IgE-mediated immune responses. They are the only cells able to recognize antigens after processing by APCs, and their release of the mediators interleukin (IL) 4, IL 13, and CD40L induces selective somatic recombination of the Ig heavy chain regions in B cells before maturation into plasma cells [47].

Mast cells are important effector cells in the immediate-phase of allergic reactions and in maintenance of IgE production. The mast cells of the nasal mucosa in patients with AR secrete higher levels of IL-4 and IL-13 and induce higher levels of IgE synthesis than T cells [48]. IgE antibodies are synthesized by plasma cells in the nasal mucosa of AR

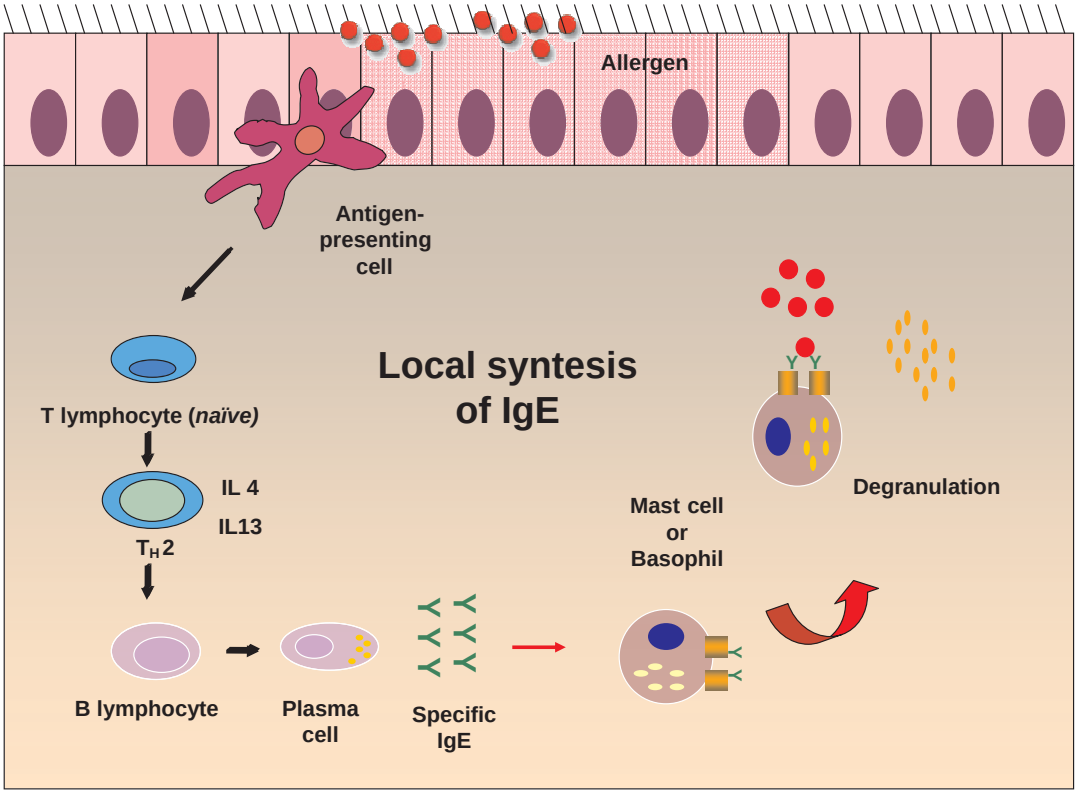

Figure 1. The IgE-mediated hypersensitivity response proposed in allergic rhinitis classically restricted to lymphoid tissue has been shown to occur in nasal mucosa. Ig indicates immunoglobulin; IL, interleukin; T_H, helper T cell.

patients, thus providing a local source for sensitization of mast cells to common aeroallergens [49]. Several authors have reported expression of ε germline transcripts and mRNA for the ε heavy chain of IgE in nasal and bronchial mucosa [50-53]. IgE production has been detected in the nasal mucosa of patients with AR in vivo [8,30,54] and in vitro [55,56] (Figure 1).

Pathophysiological Characteristics of Local Allergic Rhinitis

Studies have increasingly detected the presence of a nasal inflammatory T_H2 response, with production of specific IgE to aeroallergens, increased levels of inflammatory mediators, and a positive response to the nasal allergen provocation test (NAPT) in patients with LAR previously diagnosed as NAR.

Specific IgE and Inflammatory Mediators in Nasal Secretion

In 1975, Huggins and Brostof [57] detected specific IgE in nasal secretions and a positive response to NAPT with *Dermatophagoides pteronyssinus* monitored by nasal symptoms in a group of patients with a clinical history suggestive of house dust mite allergy, but a negative result for SPT and serum sIgE to *D pteronyssinus*.

Our group recently conducted 2 comparative studies including patients with IR, patients with AR, and healthy controls. We found the presence of specific IgE against *D pteronyssinus* [8] and grass/olive pollens [30]. We also observed increased levels of eosinophil cationic protein (ECP) in secretions during natural exposure in patients with LAR and a positive NAPT result but negative SPT and intradermal test results, and nondetectable serum sIgE to aeroallergens.

T_H2 Nasal Inflammatory Pattern

Immunohistochemistry and in situ hybridization studies of nasal mucosa biopsies have shown that patients with AR and a large proportion of those with IR share localized cellular immunopathogenesis mediated by T_H2 and IgE. These patients also have significantly higher counts of mast cells [35,58], eosinophils, IgE+ cells [27], T lymphocytes, lymphocyte subpopulations, and $CD3^+CD45RA^+$ cells [32] than healthy controls.

Noninvasive studies with flow cytometry have proven very useful to study leukocyte and lymphocyte subpopulations in nasal secretions from allergic and nonallergic patients. Flow cytometry performed during natural exposure to aeroallergens has revealed that LAR patients with positive results in NAPT with *D pteronyssinus* [8] and grass/olive pollen [30] had a very similar leukocyte–lymphocyte phenotype to that of patients with AR and increased levels of eosinophils, basophils, mast cells, $CD3^+$ T cells, and $CD3^+CD4^+$ T cells. In these studies, over 70% of patients with IR and LAR presented criteria for NARES with nasal eosinophils >20%.

Positive Response to Nasal Allergen Provocation Test

Several studies have demonstrated that patients with LAR present positive immediate, late, and dual responses to NAPT with different aeroallergens in more than 45% of patients previously diagnosed with NAR [8,30,39,58].

In 2002, Carney et al [59] performed NAPT with different aeroallergens (*D pteronyssinus*, *Dermatophagoides farinae*, cat and dog epithelia, and grass pollen mix) in a group of 21 patients with IR and observed that 62% had a positive response to NAPT evaluated by anterior active rhinomanometry, mainly to house dust mite. In 2005, Wedbäck et al [39] detected a 47% positive response rate to NAPT with birch pollen in a group of patients with seasonal IR.

In 2007, our group conducted a comparative study during natural exposure to house dust mite and after bilateral NAPT with *D pteronyssinus* in a large group comprising 50 patients with perennial IR, 30 patients with perennial AR, and 30 healthy controls [8]. NAPT was positive in 54% of the patients with perennial IR. Of these, 63% had an immediate response and 37% a dual response. No isolated late response was detected. We replicated these results in 2008 in a subsequent study [30], in which we compared 2 groups of patients (32 with seasonal NAR and 35 with AR to grass pollen, olive pollen, or both) and a control group (50 healthy controls). Of the patients with NAR, 63% had a positive immediate or dual response to NAPT with pollens (grass, *Olea europea*, or both). All the patients reported nasal symptoms exclusively during April-June; their symptoms improved with intranasal corticosteroids and oral antihistamines, even though they had negative SPT and intradermal skin test results, with negative serum sIgE. In both these studies, nasal response to NAPT was evaluated using acoustic rhinometry and a visual analog scale of nasal symptoms.

NAPT is useful when studying the pathophysiology of AR and describing the time course of release for inflammatory mediators in nasal secretions [60-63]. Our group recently published the first study on the kinetics of local production of specific IgE, ECP, and tryptase in response to NAPT with grass pollen in LAR patients [64]. We found that activation of mast cells and eosinophils and IgE synthesis was induced locally by inhalation of aeroallergens. Patients with LAR showed an immediate positive and dual response to NAPT with grass pollen, and this was accompanied by increased release of tryptase, ECP, and sIgE antibodies in nasal secretions. The release kinetics of tryptase showed a strong correlation with nasal symptoms (itching and sneezing) and a release pattern that varied with the type of response. Isolated immediate responders presented significantly higher levels at 15 minutes and 1 hour after challenge compared to baseline, while dual responders showed significantly elevated levels at 15 minutes, 1 hour, and 6 hours.

There were no differences in the release kinetics of ECP and specific IgE between immediate and dual responders. Significantly elevated levels of ECP were detected 15 minutes after challenge, and these gradually increased over the observation period (1 h, 6 h, and 24 h). An important finding was the detection of a gradual increase in levels of nasal specific IgE against grass pollen from 1 hour to 24 hours, with

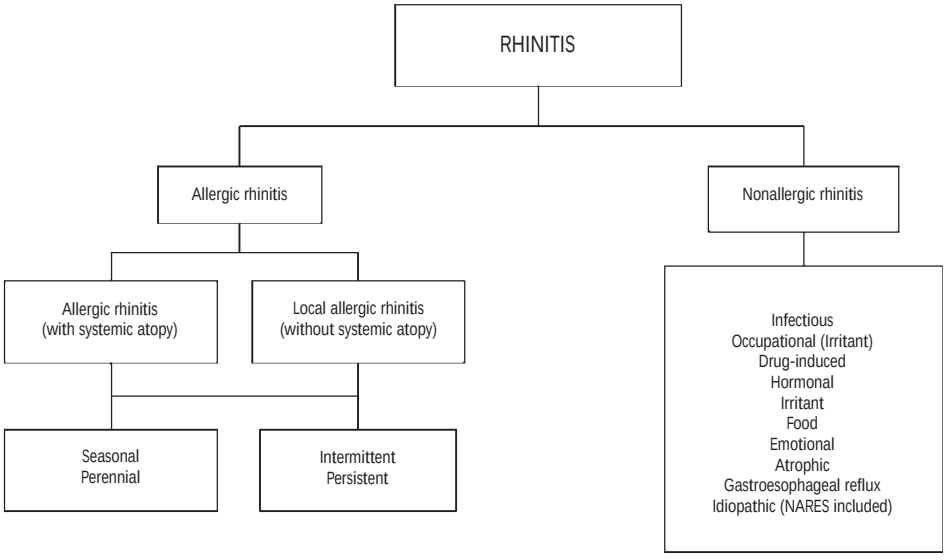

Figure 2. Etiological classification of rhinitis. NARES indicates non-allergic rhinitis with eosinophilia syndrome.

a peak 24 hours after provocation. This rapid nasal release of specific IgE after nasal challenge, with detection in some patients of baseline levels of sIgE outside spring, supports the existence of persistent local synthesis of sIgE in nasal mucosa from patients with LAR that rapidly increases after local allergen stimulation [64].

Recent studies on the mechanisms involved in the pathophysiology of nasal allergic responses in atopic and nonatopic patients have advanced our understanding of the different phenotypes of rhinitis, which in turn will lead to better diagnosis and treatment of these patients. A new etiological classification of rhinitis may include LAR as a new phenotype of AR without atopy (Figure 2).

Clinical Characteristics of Local Allergic Rhinitis

Nasal Symptoms and Comorbid Conditions

Several studies have demonstrated that LAR shares clinical nasal symptoms with AR, such as itching, sneezing, rhinorrhea, and obstruction. These are often associated with ocular symptoms, and show a good response to nasal corticosteroids and oral antihistamines [8,30,64]. Patients with LAR may present both persistent and intermittent symptoms perennially or seasonally [8,30,39], with severity that can be classified as mild, moderate, or severe, as with AR patients. Also noteworthy is the close association with conjunctivitis and bronchial asthma detected in LAR [8,30,64].

Diagnostic Approach

Knowledge of the existence of a localized allergic response in the nasal mucosa demonstrates the need for a thorough allergological workup in the target organ.

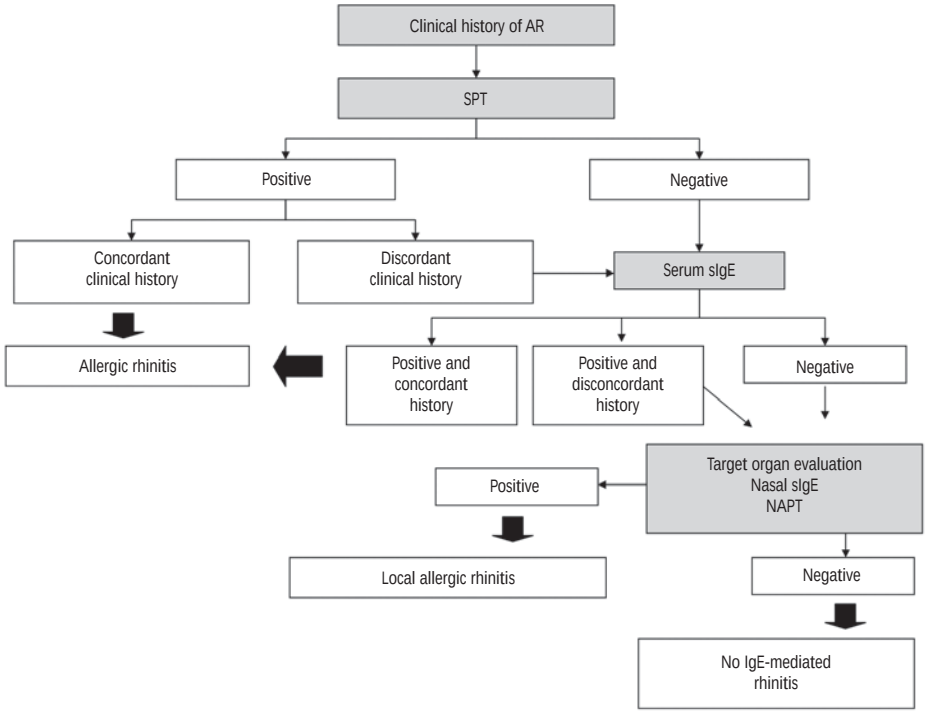

Figure 3. Diagnostic approach to allergic rhinitis. AR indicates allergic rhinitis; NAPT, nasal allergen provocation test; sIgE, specific IgE antibodies; SPT, skin prick test.

A possible diagnostic approach in LAR patients is shown in Figure 3. This involves taking a detailed clinical history followed by SPT to a panel of allergens including those that are relevant in the patient's environment. If negative, serum total and specific IgE antibody titers may be determined. If specific IgE antibody results are negative, the next step is to evaluate the target organ by quantifying nasal specific IgE antibodies and to carry out a nasal provocation test with the suspect allergen or allergens.

Natural Disease Course

Few data are available on the natural history of NAR, including whether it progresses to AR [65,66]. A recent study in a group of 180 NAR subjects diagnosed during 2000-2004 and re-evaluated in 2007 demonstrated de novo sensitization to aeroallergens in 24% of patients, as assessed by SPT, serum sIgE, or both [14]. These results suggest that LAR may be part of AR with a positive SPT result at the beginning of the natural course of the disease. Our group is currently undertaking a larger follow-up study in a group of patients with LAR to evaluate the natural course of the disease.

Specific Treatment

Further research is necessary to determine whether patients with LAR respond favorably to specific immunotherapy with aeroallergens.

Because an important number of patients present persistent LAR with moderate-severe symptoms that require continuous administration of nasal corticosteroids and oral antihistamines, it is important to verify whether they will benefit from specific immunotherapy for the responsible allergen. A preliminary study indicates that these patients benefit from specific treatment, although more precise data are required [67].

Conclusions

LAR is a newly identified entity that can affect a large number of patients. The mechanisms involved include local production of specific IgE that recognizes common aeroallergens such as house dust mite and pollens. Clinical evaluation indicates that both seasonal and perennial rhinitis symptoms exist. The nasal allergen provocation test shows local production of tryptase and ECP with equivalent kinetics to that of patients with classic AR and a positive result for SPT and/or serum specific IgE. Furthermore, the natural course of these conditions indicates that some patients may develop AR. Whether these patients will benefit from specific immunotherapy is currently under evaluation by our group.

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CONTINUING MEDICAL EDUCATION EXAMINATION

Local Allergic Rhinitis: Concept, Clinical Manifestations, and Diagnostic Approach

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CME Items

1) Which of the following statements about rhinitis is true?
   a) Rhinitis is an important health problem worldwide, with an incidence of 20-40% in developed countries.
   b) From an etiological point of view, rhinitis can be divided into 2 large groups: allergic rhinitis and nonallergic rhinitis.
   c) Rhinitis is often associated with other respiratory disorders, such as bronchial asthma.
   d) All of the above are true.

2) Which of the following subtypes of nonallergic rhinitis is most frequent?
   a) Occupational rhinitis
   b) Drug-induced rhinitis
   c) Idiopathic rhinitis
   d) Emotional rhinitis

3. Which of the following types of nonallergic rhinitis is most likely to be associated with eosinophilia?
   a) Vasomotor rhinitis
   b) Nonallergic, noninfectious rhinitis
   c) Hormonal rhinitis
   d) Nonallergic rhinitis with eosinophilia syndrome

4. Which of the following pathophysiological mechanisms could be involved in idiopathic rhinitis?
   a) Neurogenic mechanisms
   b) Inflammatory mechanisms
   c) Changes in mucosal permeability
   d) All of them

5. Which of the following neurogenic mechanisms has not been proposed in the pathophysiology of idiopathic rhinitis?
   a) Hyperactive nonadrenergic noncholinergic or peptidergic neural system (NANC)
   b) Parasympathetic/sympathetic neural imbalance
   c) Hypoesthesia of the central nervous system
   d) None of the above

6. Which of the following findings has been detected in the pathogenesis of allergic rhinitis?
   a) Allergic rhinitis is an IgE-mediated inflammatory disease with an infiltrate of T_H2 cells, basophils, Langerhans cells, eosinophils, and mast cells in nasal mucosa.
   b) The expression of IgE is not associated with a predisposition to develop allergic disease.
   c) Antigen-presenting cells are abundant within the upper and lower respiratory mucosa in allergic rhinitis, but not in nonallergic rhinitis.
   d) All of the above.

7. For a patient with a 3-year history of persistent rhinitis and symptoms related to house dust mite and a recent allergological study with negative SPT and serum specific IgE to aeroallergens, what is the best approach?
   a) Diagnose with nonallergic rhinitis
   b) Diagnose with idiopathic rhinitis
   c) Perform a NAPT with house dust mite
   d) Repeat SPT within 12 months

8. Which of the following conditions are present in the pathophysiology of local allergic rhinitis?
   a) Local production of specific IgE antibodies directed against aeroallergens
   b) Increased secretion of ECP in nasal fluids during natural exposure to aeroallergens
   c) Similar leukocyte-lymphocyte phenotype to allergic rhinitis patients with increased levels of eosinophils, basophil-mast cells, $CD3^+$ T cells, and low levels of $CD3^+CD4^+$ T cells
   d) A and B are true.

9. Which of the following are false in the response to NAPT in local allergic rhinitis?
   a) Patients with LAR may present immediate, late and dual responses to NAPT.
   b) The release kinetics of tryptase shows a strong correlation with the nasal symptoms of itching and sneezing.
   c) After NAPT, a gradual increase in the levels of nasal specific IgE against aeroallergens has been detected from 1 to 24 hours, peaking 24 hours after provocation.
   d) The release kinetics of tryptase and ECP shows a different release pattern depending on whether the patient is an immediate or dual responder.

10. Which of the following is false in the local allergic response in allergic patients?
    a) The release of IL-4, IL-13, and CD40L mediators by T lymphocytes induces selective somatic recombination of the Ig heavy chain regions in B cells preceding their maturation into plasma cells.
    b) The mast cells of the nasal mucosa secrete greater levels of IL-4 and IL-13 and induce increased levels of IgE synthesis than T cells.
    c) The inhaled aeroallergens are deposited mainly in the nasal mucosa, where antigen-presenting cells are processed and presented to T cells.
    d) Expression of ε germline transcripts and mRNA for the ε heavy chain of IgE has not been detected in nasal and bronchial mucosa