New Findings in Nonallergic Rhinitis and Local Allergic Rhinitis

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Abstract Research in rhinitis has primarily focused on allergic rhinitis and important aspects of the disease such as the IgE-mediated inflammatory cascade, the impact on quality of life, the impact on the lower airways, and control and severity of the disease, especially in those patients in which control is not easily obtained. However, a significant number of patients with persistent rhinitis do not show systemic sensitization to aeroallergens or signs of infection. These patients are defined under the umbrella term “non-allergic rhinitis” or “noninfectious rhinitis.” Nonallergic rhinitis comprises a large number of phenotypes and endotypes, such as rhinitis medicamentosa, drug-induced rhinitis, rhinitis of the elderly, idiopathic rhinitis, and local allergic rhinitis. This review describes the new pathophysiology and clinical insights into these different forms of nonallergic rhinitis with special emphasis on local allergy. New recommendations in diagnosis and treatment are given.

Keywords Nonallergic rhinitis · Local allergic rhinitis · Allergic rhinitis · Mixed rhinitis · Entopy

Introduction

Rhinitis is one of the commonest chronic inflammatory diseases, affecting 30–50 % of the population. Rhinitis can be subdivided into viral rhinitis (common cold), a disease that almost everyone encounters at least once a year, and more chronic forms of rhinitis, such as allergic rhinitis (AR), nonallergic rhinitis (NAR), and infectious rhinitis. In this review we will discuss AR, NAR, and additional phenotypes of rhinitis. Research has primarily focused on AR and important aspects of the disease, focusing on the impact of increasing prevalence [1], quality of life [2, 3], the effect on the lower airways [2, 3, 4•], measurement of control of disease [5•], and treatment of patients with severe disease in which control is not easily obtained [5•, 6, 7].

In the last two decades increasing interest has developed in other forms of persistent rhinitis [8•, 9]. Interestingly, only half of patients with persistent rhinitis tend to have pure AR without other etiologic factors beyond allergy being responsible for the nasal symptomatic inflammation [10, 11]. It is now accepted that NAR comprises a heterogeneous group of rhinitis phenotypes in which no systemic sensitization and clinical signs of infection are present, and includes hormonal rhinitis, rhinitis medicamentosa, smoke-induced rhinitis, and some forms of occupational rhinitis [12, 13]. “Idiopathic rhinitis” refers to those patients in which no underlying cause can be found by the classic or recommended diagnostic tools [12, 14•, 15, 16].

In clinical reality, the distinction between different forms of rhinitis is not always easily made or even possible. Patients with only seasonal sensitizations to allergens may have symptoms the entire year in addition to their seasonal exacerbations. Apparently these patients experience AR with the additional involvement of a nonallergic component

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in the manifestation of the disease [9, 17, 18•]. In addition to mixed forms of rhinitis, some patients show a clear picture of AR with all the symptoms fitting the diagnosis of AR (including a positive and specific reaction on nasal allergen provocation) without any signs of systemic sensitization [19, 20]. The term, “local allergy” was suggested to describe these patients [21•, 22, 23]. In asthma, more and more emphasis is placed on categorizing disease subtypes into endotypes instead of phenotypes. A disease “phenotype” describes “clinically observable characteristics” of a disease sometimes with unique responses to treatment but without a direct relationship to an underlying pathophysiologic mechanism. “Endotypes,” however, describe subtypes of a disease defined by an intrinsically “distinct pathogenetic mechanism,” based on cellular and molecular mechanisms, including the reactivity of structural cells [24]. Endotyping based on disease mechanisms could eventually lead to individualized disease management.

The purpose of this review is to describe the history and increasing knowledge of NAR, the different endotypes, including local allergy, and to put local allergy in the perspective of other endotypes of rhinitis.

Atopy

“Atopy” refers to a genetic predisposition to produce immunoglobulin E (IgE) in response to minute amounts of environmental protein allergens. Nonatopic individuals can produce IgE, but normally do so only transiently [25]. In atopic individuals, the production of IgE continues and leads to various atopic disorders, such as AR, asthma, atopic dermatitis, and food allergy.

Allergic Rhinitis

By definition, AR is a symptomatic disorder of the nose induced by allergen exposure caused by an IgE-mediated inflammation of the membranes lining the nose [4•]. AR is characterized by symptoms of sneezing, watery rhinorrhea, and nasal blockage. Very often the nasal symptoms are accompanied by conjunctival symptoms, justifying the more descriptive term “allergic rhinoconjunctivitis” [1]. As one third of patients with AR have bronchial hyperresponsiveness or asthma, there is a clinical need to explore the presence of asthma in all patients with AR [4•].

The diagnosis of AR is usually made by the history of the characteristic symptoms complemented by demonstration of systemic sensitization to aeroallergens by the skin prick test (SPT) or measurement of specific IgE in the serum [26]. When aeroallergen sensitization is in concordance with the symptoms and the time of exposure, the

diagnosis of AR is established. Around 98 % of sensitizations to allergens are discovered with standard SPT sets such as the European standard SPT [26]. However, in clinical reality, the concordance between symptoms and SPT results is not always clear. Sometimes patients present with a clear history of AR but the sensitizations do not match or no sensitizations can be found at all [27–29, 30•]. The first step in this case is to go back to the history and try to find out whether there is a chance that the patient encounters allergens that are not normally tested for routinely [14•, 31]. Therefore, a good history should contain questions on the occupational environment, living conditions, and hobbies [31]. Nasal allergen provocation tests (NAPT) are recommended in cases of doubt about the reliability of the SPT results or blood analyses for allergen-specific IgE, mainly prior to the onset of immunotherapy, occupational avoidance, or when significant socioeconomic implications are involved [14•, 31]. Also in clinical research settings, NAPT are performed in order to unravel the immunologic mechanisms underlying the allergic inflammatory cascade [14•, 31]. A proper allergy diagnosis is essential to guarantee an adequate treatment based on allergen avoidance and possibly induction of tolerance to the allergen. The mainstay of the treatment of allergies is still the avoidance of the allergen [32]. Especially in situations where exposure to the allergen is high, e.g., in occupational allergy, avoidance is essential to achieve control of disease but also to prevent disease progressing from AR to asthma [31, 33].

General treatment including antihistamines or local corticosteroids will be effective also when the exact allergen is unknown, but as soon as a more specific treatment such as immunotherapy is considered, exact knowledge of the most important allergens is crucial [34–38].

Nonallergic Rhinitis

NAR is diagnosed when no systemic sensitizations to aeroallergens can be found and infectious causes have been excluded [12]. NAR encompasses rhinitis of several causes, some with a known cause such as medication-induced, occupational, senile, smoking, and hormonal rhinitis, and some with an unknown cause (idiopathic/vasomotor). The reported prevalence of NAR differs, similarly to the reported prevalence of AR. In a representative sample of the Belgian population ($n = 4,959$) with an overall prevalence of self-declared recent rhinitis symptoms of 39.3 %, AR was reported in 29.8 % of subjects and NAR in 9.6 % of subjects [39]. In a recent Danish study involving 3,442 subjects from the general population based on questions and measurements of specific IgE, 17.6 % were classified as having AR, 5.3 % as being sensitized to aeroallergens,

and 23.5 % as having NAR [40]. In a random selection from an allergy practice of 428 patients, Rondon et al. [30•] found AR in 63.1 % of the patients, NAR in 11.2 % of the patients, and local AR (LAR) (see later) in 25.7 % of the patients.

The history is the most important part of the diagnosis of NAR. Answers to questions asking for trigger factors that provoke the symptoms, including physical and chemical stimuli, strong emotions, ingestion of alcoholic beverages, changes in hormone levels (menstrual period), medications, and occupation, can provide hints for the clinical diagnosis.

An important subgroup of NAR is idiopathic rhinitis, formerly called vasomotor rhinitis. Research underlying the pathophysiologic mechanism of NAR has moved from autonomic neural imbalance to inflammatory disorders (local allergy), the nonadrenergic, noncholinergic peptidergic neural system, and/or central neural hyperesthesia still without convincing solid ground or proof [18•, 41–46]. Cold dry air, which can be used to measure hyperreactivity in NAR and AR patients [47, 48], has been shown to be a solid way to discriminate idiopathic rhinitis patients from controls [47] with high sensitivity and specificity.

A variety of treatment options exist for NAR. Most of the known causes have a tailored treatment [anticholinergics, vidian neurectomy, intranasal corticosteroids (INCS), or antihistamines] or avoidance of triggers. Specifically, INCS have been tried in many types of NAR because of their anti-inflammatory and possible vasoconstrictive properties, although a vasoconstrictive effect of INCS has never been proven to exist. INCS are considered the first choice of treatment; however, several studies both support [49, 50] and question [51•, 52] the effectiveness of INCS in NAR. Although the evidence is lacking, it is generally thought that INCS are effective in those patients with NAR and a classic eosinophilic inflammation, whereas they are less effective or not effective in those NAR patients who do not show this pattern of inflammation within the nasal mucosa, but proof for this concept is lacking.

Mixed Rhinitis

Patients with AR often present with symptoms in periods of the year when they do not encounter the allergens to which they are sensitized. This form of rhinitis in which allergic and nonallergic symptoms are combined is called mixed rhinitis. “Mixed rhinitis” does not describe allergic patients who react to nonallergic triggers as most AR patients are hyperreactive to nonspecific stimuli [43, 48].

The USA National Rhinitis Classification Task Force reported on an analysis of 975 patients in allergy practices with the goal of determining the prevalence of “pure” AR,

“pure” NAR, and mixed rhinitis in allergy practices [53]. Forty-three percent of patients were classified as having pure AR, 23 % pure NAR, and 34 % mixed rhinitis. Of all patients presenting with chronic rhinitis, 57 % were classified as having NAR, either pure or mixed. Unfortunately, no definition of mixed rhinitis was given in this article. The definition of AR, NAR, and mixed rhinitis is becoming even more complicated because it has recently been reported that some in patients NAR was found to develop into AR in 3–6 years [54].

Systemic Sensitization Without Clinical Symptoms

The synthesis of IgE against allergens is required for the development of allergic diseases, but many individuals with allergen-specific IgE do not develop symptoms.

Serum allergen-specific IgE to common aeroallergens or positive results of SPTs for common aeroallergens are observed in asymptomatic subjects [55–58]. In longitudinal studies, positive SPT results in nonsymptomatic subjects predict the onset of allergic symptoms [59, 60].

Local IgE Production

Class switching to IgE was originally considered a process restricted to the germinal centers of lymphoid tissue, such as the regional lymph nodes and spleen. For a long time it was believed that the IgE found in the nasal and bronchial mucosa migrated from the regional lymphoid tissue or serum into the tissue. As long ago as the 1970s there were strong indications that local IgE production occurred [61, 62]. The nasal mucosa contains all cell types (dendritic cells, type 2 helper T cells, and B cells in clusters) required for an IgE immune response. The availability of IL-4 and IL-13 produced in the nasal mucosa creates the possibility for isotype switching of B cells to IgE-positive B cells and proliferation and maturation of B cells to IgE-producing plasma cells. The IgE positivity of B cells and plasma cells implied that IgE production occurs in the nasal mucosa [63, 64]. Epsilon germline transcripts were shown to be formed after local allergen provocation in the nasal mucosa of AR patients [65]. However, it was Durham and Gould who finally showed that local IgE production occurs [66, 67]. They showed in a nasal tissue culture system with an enzyme-linked immunosorbent assay a direct and quantitative measurement of de novo IgE synthesis in the nasal mucosa of hay fever patients [68]. They reported that this allergen-specific local IgE found in the nasal mucosa of their patients was synthesized locally, persisted between seasons, and was not the result of peripheral blood B cells contaminating the tissue studied.

Local IgE Production in Tissues Other Than Nasal Mucosa

Local IgE production has been described in a number of other tissues and diseases.

Just as in the nasal mucosa, the bronchial mucosa of atopic and nonatopic asthmatic patients has all the necessary components for local IgE production [69, 70]. However, until recently we could not find proof of *de novo* IgE synthesis in the bronchial mucosa. Interestingly, in the lower airways of intrinsic asthma patients, local IgE production has been found that partly recognizes Der p antigens [71]. However, this IgE reactivity did not translate into clinical responses to Der p exposure, despite specificity to major allergens and functionality to activate effector cells *in vitro*. Mouthuy et al. [71] postulated that a second signal that promotes IgE-mediated asthmatic responses through FcεRI is lacking in intrinsic asthma.

Recently, the occurrence of both local immunoglobulin class switching to IgE and IgE production in the esophageal mucosa has been shown in patients with eosinophilic esophagitis [72]. Also, when the concentration of pollen-specific IgE in tears was compared with the concentration of pollen-specific IgE in serum samples, it was found that pollen-specific IgE levels in tears increased earlier than those in sera and decreased out of season, although the serum levels remained relatively high, pointing to local IgE production [73].

In the upper airway mucosa, local IgE production is not limited to allergy to (aero)allergens since in chronic rhinosinusitis with nasal polyps, where IgE is “polyclonal,” local IgE production not necessarily related to allergy, class switch recombination, and receptor revision are found [74].

Very recently Eckl-Dorna et al. [75] even claimed that most allergen-specific IgE in the peripheral blood is not derived from IgE-secreting cells in the blood and that the local IgE production in tissues is the major source of allergen-specific IgE and a possible target for therapeutic intervention.

Local Allergy

In the 1990s, Carney et al. [76, 77] for the first time suggested that a subset of patients with NAR did have local IgE-mediated inflammation without systemic sensitization. They showed that IgE-positive plasma cells could be found in rhinitis patients without systemic sensitization [19, 78]. They called this phenomenon *entopy* [19].

The explanation of local IgE inflammation as a potential pathophysiologic mechanism to explain NAR was not repeated by others until Rondon et al. [23] in 2007

described a similar group of patients with persistent rhinitis and an inflammatory cell pattern in their nasal lavage similar to that of AR patients during natural exposure to aeroallergens and a positive response to nasal house dust mite provocation in about half of their patients. Nasal IgE specific to house dust mite was found in 22 % of the patients in this group. In a series of publications, Rondon’s group further elaborated on this theme. In the first kinetic studies of local production of specific IgE and inflammatory mediators after nasal allergen-specific provocation in LAR [79•, 80], they demonstrated activation of nasal mast cells and eosinophils, with local production of specific IgE, and nasal secretion of tryptase and eosinophil cationic protein induction after specific nasal stimulation with grass [79•] and house dust mite [80].

Recently they showed that LAR is a common respiratory disease, with a prevalence of 25.7 % of the rhinitis population in their practice. LAR and AR patients had a similar clinical profile: nonsmoking woman with severe, persistent perennial rhinitis frequently associated with conjunctivitis and asthma [30•]. More than 36 % of LAR patients reported onset of rhinitis in childhood and a subset of these patients with local allergy developed AR [30•, 54]. Furthermore, they found that the patients with LAR showed an inflammatory response after nasal allergen provocation [79•, 80].

Diagnosis of LAR

Knowledge of the existence of a localized allergic response in the nasal mucosa demonstrates the need for a more thorough allergologic workup. Rondon et al. [22] proposed a new diagnostic approach with a nasal allergologic evaluation in all patients with a clinical history suggestive of AR but with negative SPT results and lack of systemic specific IgE antibodies, or in those whose clinical history is not concordant.

Diagnosis of LAR can be confirmed by the detection of a positive specific nasal response to nasal allergen provocation, detection of nasal specific IgE, or both, in the absence of systemic atopy. Determination of specific IgE in nasal lavage has proved useful for detecting local sensitization both during natural exposure and following nasal allergen provocation, with high specificity but with low sensitivity (22–40 %) [81]. However, nasal allergen provocation with single allergens is a very time consuming technique. For this purpose, Rondon et al. [82•] have designed a new NAPT protocol with multiple aeroallergens in one session that reaches 100 % concordance with the gold standard NAPT with a single aeroallergen and 55 % and 75 % reduction in the number of visits required for the diagnosis of LAR and NAR, respectively. So far, it is

unclear if this phenomenon also applies to other types of allergens and geographical regions.

Treatment of LAR

The management of LAR includes allergen avoidance, pharmacologic treatment, immunotherapy, and education [32, 38, 83]. An important number of LAR patients have reported improvement with topical nasal corticosteroids and oral antihistamines [21•]. A pilot observational open study has shown that 6 months of specific subcutaneous immunotherapy with grass pollen increased tolerance to the aeroallergen, and reduced symptoms and rescue medication in LAR patients compared with the control group [84]. Double-blind, placebo-controlled clinical trials are necessary to compare the effectiveness of (pharmacologic) treatment in LAR patients.

Conclusion

NAR comprises a large number of phenotypes and endotypes, such as rhinitis medicamentosa, drug-induced rhinitis, rhinitis of the elderly, idiopathic rhinitis, and LAR. LAR is a localized nasal allergic response in the absence of systemic atopy characterized by local production of specific IgE. For the diagnosis of LAR, an NAPT is needed. Further studies are needed to examine the prevalence of this phenomenon in different areas, to improve the diagnostic methods, and to develop therapeutic approaches.

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