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Diagnostic markers of local allergic rhinitis

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ABSTRACT

Local allergic rhinitis is a new atopic disease recognized in modern allergy and rhinology. Its clinical symptoms are currently well described and compared with conventional allergic rhinitis, however, diagnostic and therapeutic protocols, including antigen-specific immunotherapy (ASIT), should be specified.

Therefore, local allergic rhinitis often remains underdiagnosed and by mistake is referred to non-allergic rhinitis. Yet, the pathogenesis and mechanisms of allergen tolerance breakdown in this endotype of allergic rhinitis remain understudied. Researchers continue to study the network of tolerogenic cells and biomolecules, such as regulatory T cells, tolerogenic dendritic cells, interleukin (IL)-10, IL-35, transforming growth factor-β (TGF-β), vegetative innervation of the nose, and neurotransmitters.

The review focuses on diagnostic markers of local allergic rhinitis.

Key words: local allergic rhinitis, nasal endoscopy, nasal allergen provocation test, nasal specific IgE, basophil activation test.

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Диагностические маркеры локального аллергического ринита

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РЕЗЮМЕ

Локальный аллергический ринит является новой атопической болезнью в современной аллергологии и ринологии. Его клинические симптомы в настоящее время хорошо описаны с проведением сравнения с классическим аллергическим ринитом, но диагностические и терапевтические протоколы, включая аллерген-специфическую иммунотерапию, еще уточняются.

Таким образом, локальный аллергический ринит остается недостаточно диагностированной патологией

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и по ошибке часто относится к группе неаллергических ринитов. Однако патогенез и особенно механизмы срыва аллергенной толерантности при этом эндотипе аллергического ринита остаются неизученными. Продолжаются исследования сети протолерогенных клеток и молекул, включая Т-регуляторные клетки, протолерогенные дендритные клетки, интерлейкин (IL)-10, IL-35, трансформирующий фактор роста β, вегетативную иннервацию носа и нейротрансмиттеры.

Цель настоящего обзора сфокусирована на диагностических маркерах локального аллергического ринита.

Ключевые слова: локальный аллергический ринит, видеориноскопия, назальный провокационный тест, специфические назальные иммуноглобулины, тест активации базофилов.

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INTRODUCTION

Since D.G. Powe et al. [1] described “entopy” as a “local allergy paradigm”, local atopic disorders in the unified airway have become an interesting and hot topic in allergy. To date, local allergic asthma [2–5], local allergic rhinitis [6–10], dual allergic rhinitis [11, 12], and local allergic conjunctivitis [13] have been described. Conventional atopic disorders of the unified airway have been largely studied for many years and included in global consensus position statements on diagnosis and therapy [14–16]. However, diagnostic and proper therapeutic approaches to local allergic respiratory disorders are still being developed.

A comparative study of conventional allergic rhinitis (AR) and local allergic rhinitis (LAR) has been carried out both from theoretical and clinical viewpoints over the last decade [12, 17]. Patients with LAR have the same clinical symptoms as those with AR, such as nasal obstruction, sneezing, itching, and rhinorrhea. The difference is in comorbid conditions. Both endotypes of rhinitis develop in children and adults, share similar clinical characteristics, and are associated with sensitization to house dust mites (HDMs) *D. pteronissinus* and *D. farinae*, sometimes displaying severe persistent clinical presentation, often with ocular and asthma symptoms [8, 18, 19].

From a theoretical viewpoint, the pathogenesis of AR and LAR shares almost all features of allergic inflammation in the nose but differs in the mechanisms and level of allergen tolerance breakdown. It is worth noting that the number of people with a family history of atopic diseases with simultaneous clinical allergic manifestations does not coincide with the number of persons with a family history of atopic diseases but without clinical symptoms (i.e. practically healthy people) due to the *phenomenon of allergen tolerance* [20–23]. Practically healthy, though sensitized, persons always prevail over patients with AR and LAR.

At the systemic level, maintenance of allergen tolerance seems to be associated with a network of tolerogenic cells and biomolecules, such as regulatory T cells, tolerogenic dendritic cells, interleukin (IL)-10, IL-35, transforming growth factorβ (TGFβ), etc. [20, 24]. At the local (nasal) level, allergen tolerance appears to depend on peculiarities of innervation of the nose and an appropriate set of neurotransmitters [25–27]. Local concentrations of pathogen-associated molecular patterns (PAMPs), generated from the microbiota, and allergen-associated molecular patterns (AAMPs) [28] can also matter.

In contrast to the skin and gastrointestinal tract, innervation of the unified airway is characterized by a distinctive feature. The unified airway is innervated by the somatic nervous system and the autonomic nervous system (ANS), the latter mediating symptoms of allergic inflammation.

The ANS consists of both parasympathetic neurons, whose cell bodies reside in the brainstem and act via the vagus nerve and sympathetic neurons,

whose cell bodies reside in the paravertebral ganglia. Conversely, the gastrointestinal tract has its own autonomic nervous system called the enteric nervous system that consists of intrinsic primary afferent neurons, interneurons, and myenteric and submucosal plexuses [25]. This system appears to support allergen tolerance in the gastrointestinal tract.

If systemic allergen tolerance is maintained at the systemic level but a neurotransmitter imbalance takes place in the nose, the ANS may be responsible for the autonomous allergen tolerance breakdown that results in LAR [27].

DIAGNOSTIC MARKERS OF LOCAL ALLERGIC RHINITIS

Initially, any suspected allergic rhinitis patient should be examined according to the consensus statement on rhinology / allergy [14]. This algorithm includes history taking, clinical examination, nasal endoscopy (video rhinoscopy), rhinomanometry and acoustic rhinometry, spiral computed tomography (CT) of the paranasal sinuses, nasal cytology or histology, allergic skin tests, and serum total IgE level.

An initial routine ENT examination of patients with unverified allergic rhinitis mainly includes video rhinoscopy and CT. Endoscopy does not allow to detect the difference between AR and LAR. Commonly, swelling and cyanosis of the nasal musoca and nasal obstruction (Figure) are revealed, and in some patients, septal deviation, rhinosinusitis, and polyps are detected. CT specifies the anatomical features and inflammatory comorbidities, such as nasal crest, rhinosinusitis, polyps, turbinate hypertrophy, central compartment atopic disease, etc. [29, 30].

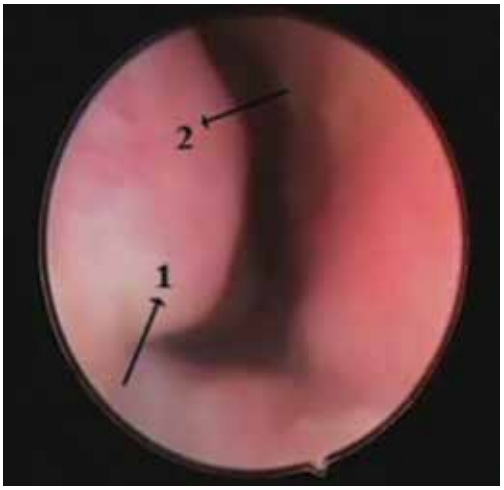

Figure. Endoscopic imaging in local allergic rhinitis. Edema (1) and cyanosis (2) of the mucosa in the inferior nasal turbinate

Allergic skin tests have been used in clinical allergy for about 150 years. There are skin prick tests [31] and intradermal tests. According to several prospective studies and systematic reviews, skin prick tests demonstrated to be a safe method of allergy testing. Besides, skin prick tests can be performed in any age group [14]. Given the limited penetration depth, skin prick tests are safe with very infrequent reports of anaphylaxis and no reported fatalities [32].

Intradermal testing is rarely used as a primary testing modality, and it is often a secondary method *in vivo* following skin prick tests. Interestingly, intradermal tests appear to be more sensitive and specific, when indoor allergens, such as HDMs, are being tested. However, it is unclear what such higher sensitivity depends on [14].

Performance and reliability of serum total IgE measurement depend on several factors, including the choice of reagents and the quality of equipment. Some authors demonstrated insufficient accuracy of this marker for allergen diagnosis, regardless of the concentration [32–34].

According to the ongoing scientific discussion [35], new techniques of IgE detection, such as new component-resolved diagnosis methods for specific IgE detection, cannot replace skin prick tests [36]. IgE is the only cytophilic antibody among other immunoglobulin isotypes. High-affinity FcεRI is expressed on basophils and mast cells and binds to the IgE – allergen complex triggering atopic inflammation [37].

DIAGNOSTIC MARKERS CONFIRMING LOCAL ALLERGIC RHINITIS

Confirmation of LAR identification is based on the following algorithm [17, 38]:

1) absence of systemic atopic disorders, such as food, insect allergy or atopic dermatitis;

2) negative skin prick tests;

3) absence of the elevated level of serum total IgE;

4) evidence of IgE sensitization at the local level.

A lack of systemic atopic diseases, elevated serum total IgE, and negative skin prick tests confirm maintenance of allergen tolerance at the systemic level in these patients. However, local atopic disorders in the unified airway, including LAR, may be manifested in some of the patients. Hence, the

evidence of IgE presence in the nose is essential for proper diagnosing and eliminating diagnostic errors.

There are three methods of nasal specific IgE detection:

(a) nasal allergen provocation test (NAPT), or allergen challenge test [14, 19, 39–41], using the Visual Analogue Scale (VAS) (a, i) or rhinomanometry;

(b) nasal specific IgE determination [14; 42–44] in the nasal secretion (b, i) or nasal tissue obtained by nasal mucosal brush biopsy (MBB) (b, ii);

(c) basophil activation test (BAT) [12, 14, 45, 46].

These methods are characterized by different specificity and sensitivity (Table).

Table

Specificity and sensitivity of HDM-specific IgE detection in local allergic rhinitis

Tests	Specificity, %	Sensitivity, %
(a, i) nasal provocation test (NAPT) according to VAS;	90.6 [19]	73.4 [19]
(a, ii) nasal provocation test (NAPT) according to rhinomanometry	100 [41]	83.7 [41]
(b,i) nasal specific IgE detection in the nasal secretion;	> 90 [17]	22–40 [17]
(b, ii) nasal specific IgE detection using MBB	100 [47]	–
(c) basophil activation test (BAT)	93 [46]	50 [46]

The allergen for NAPT may be administered by some devices, including syringes, nasal sprays, nose droppers, micropipettes, etc. The result of NAPT can be evaluated 20 min after allergen application by several methods, such as VAS, rhinomanometry, acoustic rhinometry, inflammatory markers in the nasal secretion, and nasal NO concentration. NAPT is conducted separately for HDM allergens *D. pteronyssinus* and *D. farinae* at a dose of 5,000 standardized biological units (SBU) / ml for each allergen, with 0.2 ml administered via a calibration device in both nostrils at room temperature [40].

VAS allows to assess changes in the nasal symptoms, such as rhinorrhea, itching, sneezing, and nasal obstruction, and carry out differential diagnosis of LAR and non-allergic rhinitis [19]. Currently, special VAS-incorporating applications have been developed for smartphones to assess the disease control with high efficiency [39, 48].

Rhinomanometric interpretation of NAPT results is based on analyzing nasal airway resistance measured in the right and left nasal passage separately during normal breathing [40]. Due to high specificity and sensitivity (Table), NAPT is recognized as the gold standard for the diagnosis of LAR [9, 12].

Evidence of the presence of nasal specific IgE in the nasal secretion is essential for LAR diagnosis but is difficult to obtain [14]. Using the immunoCAP technique [42], the concentration of IgE > 0.35 kU / l is considered positive [42]. Nasal secretions are collected via absorptive filter paper applied to the inferior nasal turbinates for 5 minutes [49], and HDM-specific IgE is then assayed using the immunoCAP technique. Different methods have been described for the most effective identification of nasal specific IgE, including nasal lavage, mucosal biopsy, and MBB [14, 43, 47]. However, in clinical practice, non-invasive methods are preferable [12]. Therefore, nasal allergen-specific IgE has high specificity and medium sensitivity for the diagnosis of LAR.

BAT is a flow cytometry-based assay performed on the peripheral blood, where the expression of activation markers like CD63 is measured following stimulation with HDM or other allergens [12]. BAT may be a useful additional diagnostic method when LAR is doubtful, when the allergen responsible for clinical symptoms is unknown, and it is necessary to assess the response to ASIT [14, 45]. As seen in Table, BAT has high specificity and medium sensitivity.

From a clinical viewpoint, eosinophil cationic protein, tryptase, cytokines, and chemokines are additional, specifying markers for both LAR and AR [7, 50]. According to the peculiarities of allergen tolerance breakdown, psychosomatic markers are more typical of LAR than of AR. For this reason, the questionnaire proposed by R.L. Spitzer et al. [51] can be a useful tool for the differential diagnosis of these endotypes of allergic rhinitis.

CONCLUSION

LAR and AR share similar clinical and endoscopic symptoms. However, the diagnosis of LAR is based on NAPT, the detection of nasal specific IgE, or a positive BAT in the absence of systemic IgE sensitization [14]. NAPT is the gold standard for LAR identification, as it displays optimal specificity and sensitivity [9]. Unfortunately, LAR often remains underdiagnosed and by mistake is referred to non-allergic rhinitis.

Currently, only protocol-based pharmacological treatment is available for LAR [40]. However, some investigations show encouraging results with

the use of ASIT in LAR [52]. On the whole, LAR remains an understudied disorder in modern allergy and rhinology requiring further research [7, 12, 14, 17, 19].

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