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LOCAL ALLERGIC RHINITIS: NASAL ALLERGEN PROVOCATION TESTING AS A GOOD TOOL IN THE DIFFERENTIAL DIAGNOSIS

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Abstract
Local allergic rhinitis (LAR) is a specific phenotype of allergic rhinitis. One characteristic feature of LAR is a medical history indicative of an allergic disease, negative skin-prick test results, undetectable levels of specific IgE, and a positive allergen-specific nasal provocation test. This paper presents a case of a patient with LAR and underlying house dust mite allergy, who was ultimately diagnosed >10 years after the onset of his first symptoms. Currently, there are only pharmacological treatments available for LAR. However, some studies show encouraging results with the use of allergen-specific immunotherapy in LAR, which offer hope for a future use of this causative treatment in LAR patients. Int J Occup Med Environ Health. 2020;33(2):241–6

Key words:
dermatophagoides farinae, nasal mucosa, nasal provocation test, dermatophagoides pteronyssinus, entopy, local allergic rhinitis

INTRODUCTION

Rhinitis is an inflammatory condition of the nasal mucosa, characterized by such symptoms as: watery nasal discharge, sneezing, and nasal congestion persisting for >1 h each day for a number of days each year [1]. Rhinitis can be etiologically classified into allergic and non-allergic types. Allergic rhinitis (AR) involves an IgE-mediated inflammation of the nasal mucosa triggered by exposure to a sensitizing allergen, and is the most common type of non-infectious rhinitis. According to the current state of knowledge, AR may take 1 of the following 2 forms:

– AR, which is a sign of a systemic allergic condition with systemic atopy and positive skin-prick test results or detectable/diagnostic levels of specific IgE (sIgE);
– local AR, which is a local allergic reaction (or entopy) limited to the nasal mucosa, with no systemic atopy [1].

The term "local allergic rhinitis" (LAR) was introduced by Carmen Rondón, a renowned researcher in this field, in 2010 [2]. However, the earliest studies on local nasal reactions date back to the 1970s. In 1975, Huggings and Brostoff found sIgE in the nasal secretions of patients who demonstrated symptoms suggestive of AR but tested negative in allergy tests [3]. In 2003, Powe et al. [4] introduced the term "entopy" to describe local IgE production, as opposed to atopy, i.e., systemic IgE production. Local allergic rhinitis is a peculiar rhinitis phenotype with clinical manifestations similar to those of AR. In contrast to AR, however, LAR involves

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a local (localized) Th2-cell-mediated inflammatory response and sIgE production in the nasal mucosa, with no detectable sIgE either on skin mast cells or in blood serum. This means that patients with LAR have negative skin-prick test results and undetectable sIgE serum levels, while having positive nasal allergen provocation test results. Nasal allergen provocation testing (NAPT) plays a strategic role in the diagnostic protocol for differentiating various types of rhinitis, since it helps monitor the body's response to allergen exposure and, as one of the few diagnostic methods, may guide the treatment of LAR [5–7].

Although not as common as AR, LAR may affect up to approx. 25% of rhinitis patients. A study by Rondón et al., conducted in a group of 428 adults suffering from rhinitis, demonstrated LAR, AR, and non-allergic AR (NAR) in 25.7%, 63.1%, and 11.2% of the study subjects, respectively [5].

MATERIAL AND METHODS

A 28-year-old man presented to the Allergy Outpatient Clinic with an over 10-year history of rhinitis symptoms, such as sneezing, nasal congestion, rhinorrhea, nasal itching and postnasal drip, with no cough, dyspnea, or wheezing. His rhinitis symptoms tended to persist throughout the year, exacerbating in the fall and winter seasons, particularly in the period of central heating. He reported that contact with dust aggravated his sneezing and rhinorrhea. The patient denied any childhood allergies. However, his family history revealed nickel allergy in his mother, and grass and cereal allergy in his younger brother. The patient denied any chronic conditions or taking any regular medication. Social history revealed him to be an office worker leading an active lifestyle and keeping no pets at home.

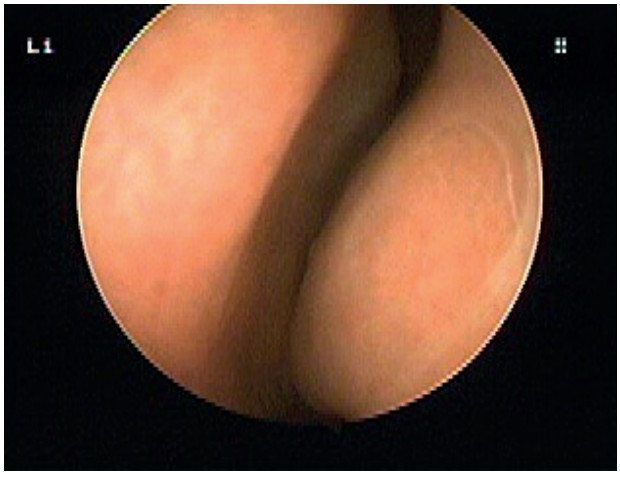
Over the previous 10 years, the patient had been undergoing allergist- and otolaryngologist-ordered diagnostic assessments, including skin-prick tests (conducted 3 times) and measurements of the levels of serum IgE specific to inhaled and food allergens, which yielded negative results. In 2017, a computed tomography scan of the paranasal sinuses showed a slight inferior turbinate hypertrophy and the bony nasal septum minimally deviated to the right; with normally pneumatized frontal, maxillary, and sphenoid sinuses as well as anterior and posterior ethmoidal air cells, with bilaterally patent ostiomeatal complexes. There were no indications for surgical treatment. Attempts at conservative treatment with intranasal glucocorticoids and oral antihistamines resulted in noticeable improvement; however, once the medications were discontinued, the symptoms always recurred.

The patient underwent a complete physical examination at the Clinic. Anterior rhinoscopy and an endoscopic examination showed a pink, moist mucosa; the nasal septum positioned in the midsagittal plane, mildly hypertrophied inferior turbinates, mucous secretions; no polyps or other tumors were found (Figure 1).

Skin-prick tests were conducted with Allergopharma allergens. Both the inhaled and food allergen panel tests yielded negative results, with the positive control (histamine) score of 3/20 and the negative control score of 0/0. Moreover, the levels of serum IgE specific to inhaled and food allergens were undetectable. In light of these negative test results and the patient's medical history suggestive of house dust mite allergy, house dust mite-specific NAPT was conducted, demonstrating a very dynamic course in terms of the observed nasal and extranasal symptoms. The NAPT procedures were conducted separately for the allergens *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (Table 1) at a dose of 5000 standardized biological units (SBU)/ml each, administered at 0.2 ml via a calibrated atomizer into both nostrils at room temperature.

The NAPT sessions were spaced 2 weeks apart to minimize the risk of nasal mucosa sensitization. The relevant measurements were taken 3 times:

a)



b)

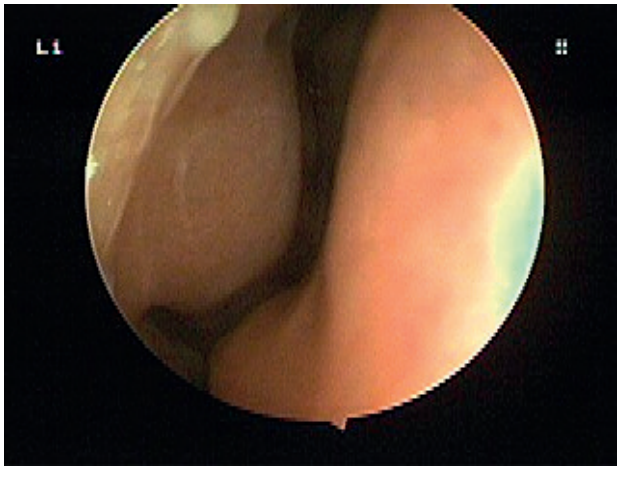


Figure 1. Nasal endoscopy – a slight hypertrophy of the inferior turbinate: a) the left side of the nasal cavity, b) the right side of the nasal cavity

- at baseline (following a 20-min adaptation to the conditions in the testing room with the ambient temperature of 21°C, and relative humidity of 40–50%);
- following the administration of a control solution (0.9% NaCl + 0.4% phenol – excipient of the test allergen solution);
- following intranasal allergen application.

Nasal and extranasal symptoms were scored with relevant scales, and a rhinomanometric examination (Rhinotest, MES) was performed (the flow range ±18 l/s, flow measurement accuracy <2%, usable flow resolution ±10 ml/s, measured pressure range ±1.25 kPa, pressure measurement accuracy ±1%, pressure measurement resolution ±1 Pa; measuring headpiece MES TYPE DV40, DV40 dead space 40 ml, DV40 resistance <0.2 cm H_2O/l/s, at a flow rate of 1 l/s). The rhinomanometric examination served to analyze nasal airway resistance for the flow rates (V, SD) measured in the right and left nasal passage separately, during normal breathing.

The early phase of the allergic reaction (occurring 20 min after local allergen application) was assessed. Subjective, patient-reported nasal congestion was present from the second stage of the examination (following control solution administration), and exacerbated considerably following allergen administration. Other associated NAPT-induced symptoms were nasal itching and rhinorrhea. The patient developed extranasal symptoms in the form of dyspnea and cough, following NAPT with both *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. The total symptom scores in the early phase of the allergic reaction were 8 pts for *Dermatophagoides pteronyssinus* and 11 pts for *Dermatophagoides farinae* (in comparison to the baseline of 1 pt for the nasal congestion recorded in both NAPT sessions during the second stage of the examination). The rhinomanometric curve showed high nasal air flow resistance (68% for *Dermatophagoides pteronyssinus* and 74% for *Dermatophagoides farinae)* (Figure 1).

In light of the symptoms reported before and after NAPT, the authors decided to perform a spirometry test (which is an optional assessment according to the standard NAPT recommendations [3]). Despite no significant functional abnormalities in the lower respiratory tract, the spirometry performed during the first stage of NAPT showed evidence of bronchial tree obstruction (forced expiratory volume in 1 s % of vital capacity (FEV_1%VC) 83%, SD 1.87, third percentile; FEV_1 86%, peak expiratory flow (PEF) 71%, forced expiratory time (FET) 6.78).

Table 1. Rhinomanometry in a nasal allergen provocation test (*Dermatophagoides farinae*)

Parameter	Flow rate value [kPa/l/s]		
	V	SD	current
Preliminary examination – stage I			
1. Rn RSIn	3.664	0.029	0.796
2. Rn RBIn	3.853	0.029	0.751
3. Rn RSEx	4.693	0.038	0.818
4. Rn RBEx	4.623	0.036	0.778
5. Rn LSIn	5.479	0.061	1.088
6. Rn LBIn	6.365	0.070	1.094
7. Rn LSEx	4.081	0.020	0.485
8. Rn LBEx	17.074	0.089	0.515
Test after control solution – stage II			
9. Rn RSIn	3.044	0.023	0.744
10. Rn RBIn	7.972	0.049	0.621
11. Rn RSEx	2.930	0.023	0.763
12. Rn RBEx	4.397	0.033	0.754
13. Rn LSIn	10.283	0.256	2.692
14. Rn LBIn	8.415	0.225	2.656
15. Rn LSEx	8.093	0.144	1.853
16. Rn LBEx	4.903	0.092	1.831
Test after the nasal allergen provocation test – stage III			
17. Rn RSIn	6.711	0.077	1.130
18. Rn RBIn	8.687	0.102	1.124
19. Rn RSEx	7.543	0.071	0.956
20. Rn RBEx	11.138	0.100	0.922
21. Rn LSIn	17.963	0.559	3.377
22. Rn LBIn	14.201	0.563	3.866
23. Rn LSEx	9.165	0.154	1.445
24. Rn LBEx	9.649	0.150	1.425

Rn RSIn – standard right-side nasal resistance during inspiration; Rn RBIn – Brom's right-side nasal resistance during inspiration; Rn RSEx – standard right-side nasal resistance during expiration; Rn RBEx – Brom's right-side nasal resistance during expiration; Rn LSIn – standard left-side nasal resistance during inspiration; Rn LBIn – Brom's left-side nasal resistance during inspiration; Rn LSEx – standard left-side nasal resistance during expiration; Rn LBEx – Brom's left-side nasal resistance during expiration.

Based on clinical examination findings (a medical history suggestive of AR, negative skin-prick test results, undetectable sIgE serum levels, and markedly positive NAPT results with the allergens *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), the patient was diagnosed with LAR. The following medical treatment was

initiated: mometasone furoate nasal aerosol at 100 μg twice a day and a 20-mg bilastine tablet once a day. Due to abnormal spirometry findings (evidence of mild bronchial obstruction) prior to NAPT, the patient was also prescribed salbutamol aerosol to be administered for dyspnea, at 100 μg, if needed. A follow-up spirometry examination was scheduled to take place 3 months later. The patient was informed on the nature of his condition, and advised on how to avoid the triggering allergens and on house dust mite prevention measures. The patient continues to be under the care of the Clinic and regularly reports for his follow-up examinations.

DISCUSSION

This paper presents the case of a male patient with LAR, whose condition had been posing a diagnostic challenge for over a decade. This patient, with a medical history suggestive of AR, had repeatedly undergone skin-prick tests and blood tests for sIgE serum levels, the results of which, however, were always negative. Moreover, the patient had undergone comprehensive diagnostic otolaryngological assessments and computed tomography scans of his paranasal sinuses, which yielded unremarkable findings. It was only following NAPT with house dust mite allergens that the patient was correctly diagnosed.

The authors conducted their diagnostic investigations according to the protocol suggested by Rondón et al. [6], who recommend that patients with rhinitis and a history suggestive of AR undergo skin-prick tests and blood tests for sIgE serum levels. If the results of these tests are negative, Rondón et al. suggest NAPT or testing nasal lavage fluid for sIgE.

Generally, LAR treatment is medical and involves administering oral second-generation antihistamines and intranasal glucocorticoids. Allergen-specific immunotherapy has been increasingly considered in the treatment of LAR. Based on randomized double-blind placebo-controlled studies, Rondón et al. presented promising results on allergen-specific immunotherapy as the treatment of LAR in patients allergic to grass pollens and house dust mites [7,8].

The NAPT procedure, which is a highly specific and sensitive method compared to other methods used in differential diagnostics, seems to be the key assessment in qualifying patients for allergen-specific immunotherapy [7,8]. Assessing the early and late phase responses (the latter recorded 4–48 h following allergen administration) both via objective and subjective techniques helps accurately determine the extent of response and, consequently, provides a stepping-stone towards subsequent therapeutic decisions, particularly when there are discrepancies between the clinical presentation and the suspected diagnosis [8]. The authors would like to emphasize that, according to current guidelines, LAR is not an indication for allergen-specific immunotherapy, and the use of this treatment method requires further studies.

CONCLUSIONS

The authors suspect that this patient would benefit from a causative allergy treatment (in the form of allergen-specific immunotherapy). However, immunotherapy is not part of current LAR treatment guidelines. Thus, this treatment has not been initiated.

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