

Local Allergic Rhinitis in Adult Patients with Chronic Nasal Symptoms

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Abstract

Background: Local allergic rhinitis (LAR) remains an underdiagnosed condition characterized by the local production of IgE antibodies during the natural exposure to aeroallergens. The prevalence of LAR in adult patients with a previous diagnosis of non-AR was assessed. **Material and Methods:** Eighty-four patients with perennial nasal allergy symptoms but a negative skin prick test and specific IgE antibodies against common inhalant allergens were included in the study. Nasal provocation tests were performed with the inhalant allergens *Dermatophagoides pteronyssinus*, *Alternaria*, and cat allergen, followed by the detection of nasal-specific IgE antibodies in the lavage during the challenge. **Results:** LAR was confirmed in 21 (25%) study patients. In the remaining 63 (75%) patients, non-AR was diagnosed. In addition, LAR was found following exposure to *D. pteronyssinus* in 19 (22.6%) patients, *Alternaria* in 3 (3.6%) patients, and the cat allergen in 1 (1.2%) patient. In 2 patients, concomitant allergies to *D. pteronyssinus* and *Alternaria* were observed. **Conclusion:** LAR can be a form of chronic perennial rhinitis that has previously been considered to be non-AR.

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Introduction

Chronic rhinitis continues to be a significant problem that decreases the quality of life of many people [1]. The mechanism of chronic rhinitis can be complex and include allergic and nonallergic reactions. It is sometimes difficult to diagnose allergic rhinitis (AR); for example, some patients with typical allergic symptoms have negative allergy tests. The presence of local AR (LAR) as a new type of disease has been widely discussed in the literature in recent years [2, 3]. LAR is characterized by the local production of allergen-specific IgE (sIgE) antibodies during natural exposure to aeroallergens. These patients have negative skin prick tests (SPT) and negative serum sIgE antibodies but have positive nasal provocation tests (NPT) for aeroallergens [2, 3]. Up to 50% of patients have a previous diagnosis of chronic non-AR, which means that LAR may be underdiagnosed [2, 4]. Misdiagnosis can lead to treatment errors and inefficient treatment approaches. Unfortunately, research on LAR and mechanisms associated with AR is lacking [5, 6].

The aim of this study was to determine the prevalence of LAR in adult patients with a previous diagnosis of non-AR or suspicion of allergy, previous negative results on diagnostic allergy tests, and typical chronic nasal symptoms.

Table 1. Patient characteristics

	Study group (n = 84)	Patients with AR (n = 102)	Controls (n = 69)	p
Mean age ± SD, years	29.4±9.1	31.1±11.4	27.5±8.2	0.351
Women	43 (51.1)	57 (55.9)	35 (50.7)	0.162
Mean total IgE ± SD, kU/L	51.8±24.1	231.8±63.5	32.1±10.5	0.023
Family atopy	33 (39.2)	67 (65.9)	11 (15.9)*	0.006
Moderate rhinitis	40 (47.6)	54 (52.9)	–	0.089
Severe rhinitis	44 (52.4)	48 (47.1)	–	0.081

Values are presented as n (%) unless otherwise stated. AR, allergic rhinitis. * Significant difference in the ANOVA.

Materials and Methods

This prospective study of randomly selected patients was performed in 2015–2016.

Patients

Eighty-four patients with perennial nasal symptoms, including blockage, runny nose, sneezing, and itching of the nose were selected from 185 patients prescreened at the outpatient allergy clinic based on the inclusion criteria.

The study patients fulfilled the following inclusion criteria:

1. moderate or severe persistent rhinitis according to the ARIA (Allergic Rhinitis and Its Impact on Asthma) guidelines [1];
2. a negative SPT and/or negative test for serum sIgE antibodies to common, previously reported, inhalant allergens (described below); and
3. lack of bronchial asthma.

Exclusion criteria were chronic rhinosinusitis and/or nasal polypsis, and respiratory infections within 4 weeks prior to study initiation; other serious diseases or chronic unstable disease; nose deformity; use of antihistamines or other anti-allergic drugs within the washout period of the drug; use of decongestants 2 days prior to the NPT; use of nasal steroids 6 weeks prior to the NPT; contraindications to adrenaline; and exacerbation of allergic and/or other diseases based on the contraindications to performing a nasal allergen challenge [7].

The patients' characteristics are presented in Table 1. Adult patients with perennial AR due to *Dermatophagoides pteronyssinus*, *Alternaria*, and/or cat allergies were compared to the study group. There were 102 patients, 65 of whom were allergic to *D. pteronyssinus*, 41 were allergic to *Alternaria*, and 38 were allergic to cats.

The control group included 69 healthy, nonallergic volunteers without symptoms of rhinitis.

The Study Protocol

The patients who met the inclusion criteria were selected to undergo the following further procedures: medical examinations, SPT, and determination of serum total IgE, and sIgE and nasal-specific IgE (nsIgE) antibody levels during NPT. The patients avoided systemic steroids (6 months), antihistamines (2 weeks), intranasal corticosteroids (6 weeks), and vasoconstrictors (1 week) before undergoing any study procedure.

Medical Examination

A full rhinolaryngological examination was performed using anterior and posterior rhinoscopy. Rhinitis was classified according to the following ARIA guidelines: rhinitis is considered persistent when symptoms are present for >4 days/week or persist for >4 consecutive weeks. Rhinitis severity was based on estimations of activity impairment (sleep, daily activities, work/school performance, and troublesome behavior) and was classified as severe or moderate [1].

Skin Prick Test

SPT was performed with a panel of the following aeroallergens: *D. pteronyssinus*, *D. farinae*, *Phleum pratense*, *Artemisia*, birch, alder, hazel, *Alternaria*, *Cladosporium*, *Aspergillus*, and dog and cat epithelia (Allergopharma, Reinbek, Poland). A positive control (10 mg/mL histamine) and a negative control (saline) were included. An allergic reaction was defined as a positive SPT for at least 1 allergen, with a maximum wheal diameter at least 3 mm greater than that of the negative control. Patients who did not exhibit a reaction to histamine were excluded from further analyses [8].

Serum IgE and sIgE

Serum total IgE and sIgE antibody levels to the aeroallergens used in the SPT panel were determined using a fluoroenzyme immunoassay (UniCAP, Uppsala, Sweden). The positive cut-off value for sIgE levels was >0.35 kU/L.

nsIgE Detection

The aeroallergens examined for nsIgE were identical to those for serum sIgE and were determined using an immunoassay (ImmunoCAP 100; ThermoFisher Scientific, Uppsala, Sweden). These measurements were performed at baseline, immediately (30 s) after allergen provocation, and 15 min, 1 h, and 6 h after NPT.

A bilateral nasal lavage was performed according to Naciere et al. [9]. First, 6 mL of physiological saline (at room temperature) was added dropwise into each nostril. The mucus and saline samples were expelled after 10 s, and samples were stored on ice. The fluid was centrifuged at 4°C for 15 min at 1,500 g, and the solid phase was separated. The samples were stored at –80°C before further analysis. For analysis, 25-μL samples were maintained for 90 min at room temperature and subsequently incubated with a biotin-labeled goat anti-human IgE antibody (1:1,000; Vector Lab,

Table 2. Comparison of the frequency of positive results for the skin prick test (SPT+), specific IgE (sIgE+), nasal-specific IgE (nsIgE+), and clinical nasal provocation test (NPT+) in patients with local allergic rhinitis (LAR), allergic rhinitis (AR), and the controls

	Study patients (n = 84)	Patients with AR (n = 102)	Controls (n = 69)	p
<i>D. pteronyssinus</i>				
SPT+	0 (0)	64 (62.7)	0 (0)	–
sIgE+	0 (0)	65 (63.7)	0 (0)	–
nsIgE+	19 (22.6), 2.05±0.76	65 (63.7), 1.99±0.67	0 (0)	0.005*
NPT+	19 (22.6), 72.19±10.17	65 (63.7), 70.95±21.77	1 (1)	0.001*
<i>Alternaria</i>				
SPT+	0 (0)	41 (40.2)	0 (0)	–
sIgE+	0 (0)	43 (42.2)	0 (0)	–
nsIgE+	3 ^a (3.6), 1.63±0.59	43 (42.2), 2.54±0.89	0 (0)	–
NPT+	3 ^a (3.6), 54.54±22.16	40 (39.2), 74.87±17.54	0 (0)	–
Cat				
SPT+	0 (0)	38 (37.3)	0 (0)	–
sIgE+	0 (0)	37 (36.3)	0 (0)	–
nsIgE+	1 ^a (1.2), 1.35	38 (37.3), 1.04±0.43	0 (0)	–
NPT+	1 ^a (1.2), 44.03	40 (39.2), 42.52±28.11	0 (0)	–

Numbers (%) of patients with positive results, kU/L (±SD; nsIgE+), and visual analogue scale scores (mean ± SD; NPT+) are shown. * Significant difference in the ANOVA. ^a Nonsignificant.

CA, USA) to detect specific IgE antibodies. After washing, the plates were incubated with streptavidin-peroxidase conjugate (1:1,000) and anti-goat-antiperoxidase (1:10,000) for 1 h at room temperature. After a further washing step, *o*-phenylenediamine was added as a substrate solute, and optical densities were measured using an ELISA reader (Metertech S-960; Metertech Inc., Taipei, Taiwan, ROC). Additionally, 3 mL of normal saline were added to each sample, and the concentrations of local antibodies were recalculated using the total protein concentration for each measurement to correct for the dilution effect of the samples (Bradford protein analysis). Calculated protein ratios are presented.

Nasal Provocation Test

Nasal patency was assessed by acoustic rhinomanometry using an SRE 2000 rhinometer (Rhinometrics, Lynge, Denmark) and was performed according to the guidelines of the Standardization Committee on Acoustic Rhinometry [10]. NPT were performed from March to May because the concentrations of the examined allergens are lower during this time in Poland. First, using a metered pump spray, the patients were intranasally challenged with saline to exclude nasal hyperreactivity. If the NPT was negative, it was performed again 2 weeks later with extracts of the previously discussed aeroallergens (the concentration of each allergen was 5,000 Standard Biological Units/mL; Allergopharma, Reinbek, Germany). The solution (100 µL) was applied to each nostril. The total volume of both nasal cavities was determined from 2 to 6 cm using acoustic rhinometry, and the results were compared with the baseline test. The immediate reaction was analyzed at 15 min, 1 h, and

6 h. Each subject was first subjected to an NPT with saline (to exclude nonspecific hyperreactivity). Two weeks later, an NPT with 1 of the 3 study allergen extracts (*D. pteronyssinus*, *Alternaria*, or cat epithelia) was performed, and 2 additional NPTs were performed with one of the other extracts at 1-week intervals.

NPT Monitoring

Nasal symptoms (nasal obstruction, rhinorrhea, itching, and sneezing) were monitored using the 100-mm horizontal visual analogue scale. Symptom severity was classified as severe (71–100), moderate (31–70), or mild (0–30). The response to an allergen was evaluated at baseline, immediately after allergen challenge, 15 min after saline application, and 15 min after aeroallergen application. The response was determined using a visual analogue scale and the total volume of the nasal cavity from 2 to 6 cm. An increase of ≥30% in the total visual analogue scale score and a decrease of ≥30% in the 2- to 6-cm volume were considered positive responses. As previously described, both nostrils underwent lavage.

Statistical Analysis

The Statistica computer program (version 8.1; SoftPOL, Kraków, Poland) was used for statistical analyses. Continuous data are presented as means and standard deviations, and categorical data are presented as percentages. Clinical and demographic data were compared between groups using χ^2 analyses and one-way ANOVA. The Spearman rank correlation test was used to compare nonparametric values. Values of $p < 0.05$ were considered statistically significant.

Fig. 1. Changes in nasal specific IgE (nsIgE)/protein ratios after a nasal provocation test with *Dermatophagoides pteronyssinus*. There were no differences in the mean nsIgE values between patients with local allergic rhinitis (LAR) or allergic rhinitis (AR), but there was a statistically significant difference in comparison to the control group for all time points analyzed ($p < 0.001$).

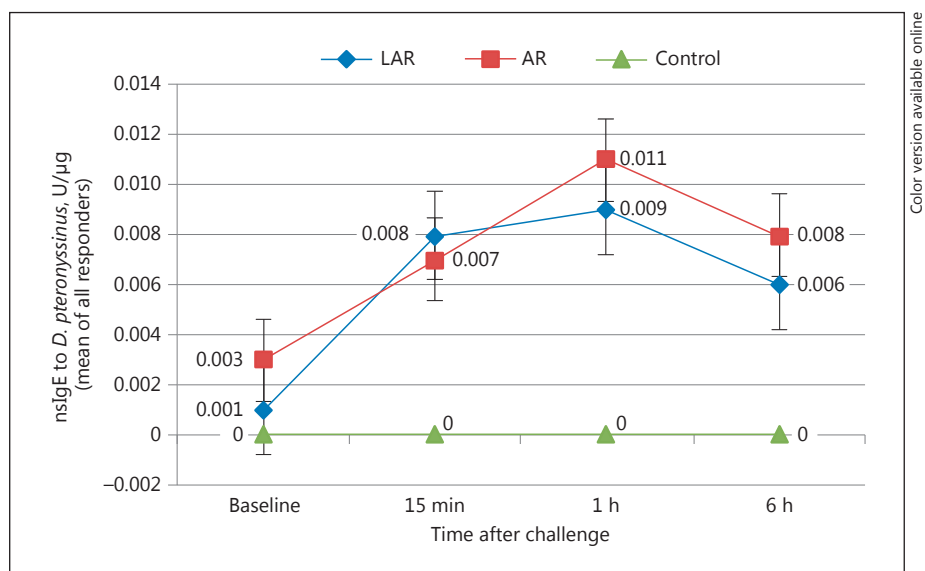
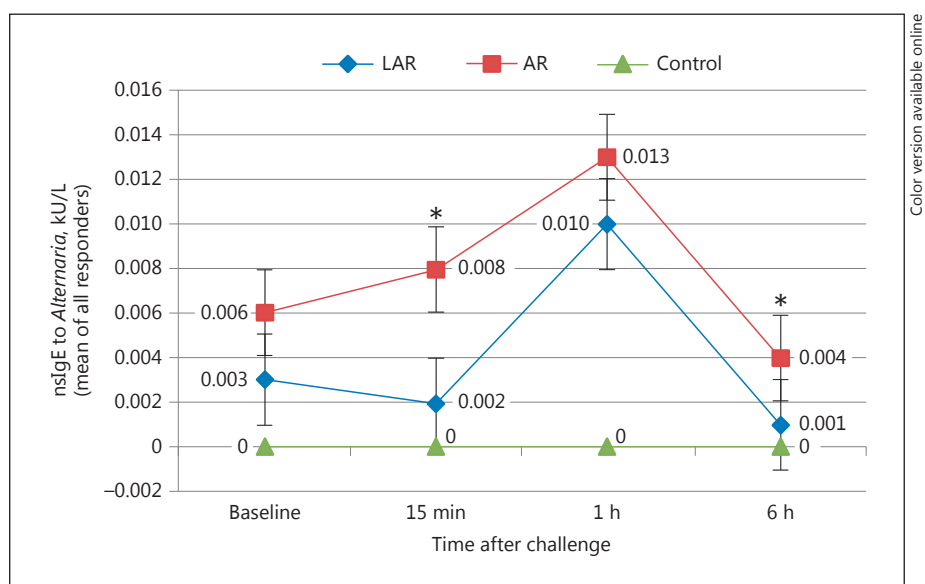


Fig. 2. Changes in nasal specific IgE (nsIgE)/protein ratios after a nasal provocation test with *Alternaria*. Changes in the mean nsIgE values between patients with local allergic rhinitis (LAR)/allergic rhinitis (AR) and controls for all time points analyzed (* $p < 0.001$ –0.013).



Results

LAR was confirmed in 21 (25%) study patients. These patients were positive for nsIgE antibodies against at least 1 of the 3 allergens analyzed. Among the first subgroup of patients, LAR was observed to the following allergens: 19 patients (22.6% of all patients in the study group) were allergic to *D. pteronyssinus*, 3 (3.6%) were allergic to *Alternaria*, and 1 (1.2%) was allergic to cat allergen. Among them, 2 patients were allergic to both *D. pteronyssinus* and *Alternaria*. In the remaining 63 (75%) patients, non-AR was diagnosed. Detailed results are shown in Table 2.

NPT and nsIgE

Results of intranasal challenges and concentration fractions of nsIgE antibodies were comparable between groups, except for a lower reactivity to *Alternaria* mold in the study group. In patients with LAR, mean nsIgE significantly increased from baseline to 1 h after NPT (from 0.5 ± 0.43 to 1.8 ± 0.39 kU/L; $p = 0.002$) for *D. pteronyssinus* and also increased for *Alternaria* (from 0.5 ± 0.13 to 1 ± 0.19 kU/L; this sample was too small for statistical analysis). Similar trends were observed in the control group. The graph shows the changes in the nsIgE/protein ratios after NPT with the allergens *D. pteronyssinus* (Fig. 1) and *Alternaria* (Fig. 2).

The nsIgE concentration after a positive NPT correlated positively with the sIgE antibody levels in patients with AR for *D. pteronyssinus* ($r = 0.81$, $p = 0.004$). A similar relationship between SPT and nsIgE was observed for *D. pteronyssinus* ($r = 0.63$, $p = 0.037$) in the same patient group (detailed data not shown). Eleven patients with AR were allergic to other allergens (*Aspergillus*, *Cladosporium*, dog, and guinea pig).

Only 1 positive result of the NPT to *D. pteronyssinus* was observed in the control group. However, this patient had no symptoms of rhinitis and had negative results for nsIgE, SPT, and sIgE to *D. pteronyssinus*.

Discussion

The study results showed that the prevalence of LAR is underestimated among adult patients previously diagnosed with non-AR. Based on the obtained results, *D. pteronyssinus* was the predominant allergen that caused AR or LAR in the analyzed groups, a result in agreement with previous data, which showed that *D. pteronyssinus* may have great importance in the induction of LAR among various age groups [11, 12]. The course of nasal symptoms, regardless of severity, in this type of allergy can mimic chronic non-AR; therefore, in a significant group of patients, the true diagnosis of LAR was significantly delayed. This problem has also been reported by other authors [13, 14]. In accord with other studies, NPT with a suspected allergen helped resolve the proper mechanism of chronic rhinitis in some study patients [15, 16].

The *Alternaria* allergen was the second most commonly observed cause of LAR. This mold is frequently regarded as a seasonal allergen; however, significant concentrations of its spores are present in the dust in Polish homes all year round. Therefore, we decided to include *Alternaria* in our study; however, there were only a few patients with positive results. Unfortunately, we were unable to make an accurate assessment of the statistical results. The same problem was encountered with the only positive result of LAR to the cat allergen.

The 1 positive NPT result in the control group might be false positive or the first sign of a nasal response to the allergen. The remaining test results clearly differentiated the control group from patients with rhinitis and were predictive of AR and LAR diagnoses.

The main limitation of this study is the small number of patients. Unfortunately, this limitation is due to the fairly uncomfortable research protocol. In everyday prac-

tice, the nasal challenge procedure can be simplified with a shortened time assessment, i.e., with an evaluation after only 1 h of provocation, in accordance with the observed trends.

We also excluded asthmatic patients because asthma was not commonly found among the group of pre-screened patients. We were also concerned about the influence of an NPT on the bronchial reactivity in such patients. The nasal lavage that was performed 30 s after the challenge might influence nasal patency and clinical symptoms; therefore, a study that compares the results obtained at different post-NPT lavage times should be conducted.

However, the present study is one of very few studies that analyze LAR among adult patients concomitant with an additional assessment of nsIgE antibodies.

Conclusion

LAR was found to be the accurate diagnosis in some patients who were previously considered nonallergic. In addition, *D. pteronyssinus* may be an important inducer of local allergic responses. In these patients, in addition to the elimination of the allergen, immunotherapy may be effective [17].

Statement of Ethics

The local ethics committee approved the study (Medical University of Silesia, Katowice, Poland, in 2014), and all participants gave informed consent.

Disclosure Statement

The authors have no conflicts of interest to declare.

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