Santamaría et al. World Allergy Organization Journal (2020) 13:100461
http://doi.org/10.1016/j.waojou.2020.100461

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Nasal specific IgE to Der p is not an acceptable screening test to predict the outcome of the nasal challenge test in patients with non-allergic rhinitis

Luis Santamaría, Ana Calle, Manuela Tejada-Giraldo Biol, Victor Calvo, Jorge Sánchez* and Ricardo Cardona

ABSTRACT

Objectives: Nasal specific IgE (NsIgE) is the most common marker to identify type-2 inflammation in local allergic rhinitis (LAR). However, the comparison of NsIgE in different types of rhinitis, its frequency in tropical countries, and its diagnostic performance for predicting the outcome of a nasal challenge test (NCT) has had limited study. The main objective of this study was to explore the diagnostic performance of NsIgE to *Dermatophagoides pteronyssinus* (Der p) among different types of rhinitis and control subjects in a tropical population.

Methods: We evaluated the frequency of NsIgE, systemic atopy (serum sIgE and Skin Prick Test), and nasal eosinophils, and we performed nasal challenge tests (NCTs) with Der p in 3 groups of patients; rhinitis without atopy (RWoA) (n = 25), rhinitis with atopy (RWA) (n = 25), and control subjects (n = 18).

Results: NsIgE had a low sensitivity and specificity to predict a positive NCT in the RWoA group: 48% had NsIgE, but only 28% had a positive NCT. Among the RWA group 84% had NsIgE and 80% had a positive NCT; the association of NsIgE and positive NCT was high (>80%). In the control group 27.8% had NsIgE, but none had a positive NCT.

Conclusions: NsIgE performs poorly in predicting NCT results in patients with non-allergic rhinitis. More methodical investigations are needed in this complex area of rhinitis. In patients with allergic rhinitis, NsIgE was useful in predicting a positive nasal challenge, but not superior to the systemic atopic test.

Keywords: Atopy, Mites, Nasal challenge test, Immunoglobulin E, Rhinitis

INTRODUCTION

The term chronic rhinitis refers to a set of nasal symptoms that may have different pathogenesis.[1,2] In allergic rhinitis (AR), atopy against a clinically relevant allergen is demonstrated by specific immunoglobulin E

Group of Clinical and Experimental Allergy (GACE), Clinic "IPS Universitaria", University of Antioquia, Cra 27 n 37 B sur 69 apto 510, Medellín, Colombia
*Corresponding author. E-mails: jorgem.sanchez@udea.edu.co; jotamsc@yahoo.com
Full list of author information is available at the end of the article
http://doi.org/10.1016/j.waojou.2020.100461

Received 26 June 2020; Received in revised from 19 August 2020; Accepted 20 August 2020
Online publication date xxx

(sIgE) in serum, or by the skin prick test (SPT).[3,4] Non-allergic rhinitis is less common, but includes several entities with different mechanisms.[5,6] In recent years, a new entity called local allergic rhinitis (LAR) has been proposed, characterized by the absence of systemic sensitization, but with the presence of type 2 inflammation (eg, sIgE) of the nasal mucosa and a positive nasal challenge test (NCT) to an allergen.[7]

In AR and LAR, sIgE is the principal biomarker that defines the presence of type 2 inflammation.[8,9] In AR, sIgE can be detected circulating in the serum or in the mast cells of the skin (systemic atopy), but it can also be found localized in different tissues.[8,9] On the other hand, in LAR, sIgE can only be measured in the nasal mucosa (NsIgE). Other markers (eg, eosinophils, Th2 cells, and some cytokines) have been proposed,[10] but so far none of them is superior to sIgE in detecting the allergenic trigger that induces the inflammatory response.

Few studies have evaluated the frequency of LAR in tropical cities, which is of great importance since this is where 40% of the world population lives.[4] The tropical zone has its own environmental characteristics, so the frequency of LAR may be different from that in other regions.[4] House dust mites (HDM) are the most frequent cause of IgE sensitization and respiratory symptoms.[4,11] Dermatophagoides spp. explain 80–90% of RA in tropical countries and seem to be the main source of allergens in LAR.[12]

Despite the fact that sIgE is useful to determine suspected allergic triggers, 10–30% of the general population have atopy but not an allergic disease; 40–70% of AR patients may have sIgE from different triggers, but usually not all are clinically relevant.[13] Although several studies have emerged evaluating the frequency of LAR, especially in seasonal countries, little has been done about the performance of sIgE in nasal mucosa as a predictor of the outcome of an NCT (eg, false positives, false negatives).

The NCT is the gold standard test to confirm the clinical relevance of sIgE in patients, but it is a time-consuming test for doctor and patient, and also it has the risk of inducing systemic symptoms.[13] If markers such as NsIgE or nasal eosinophils have a good association with NCT, they could reduce the need for NCTs and the subsequent risks, by serving as predictive markers for the test.

Based on these observations, the main objective of this study was to evaluate the diagnostic performance of NsIgE as a predictor of NCT results, and explore the frequency of NsIgE response to *Dermatophagoides pteronyssinus* (Der p) in a population located in the tropics.

METHODS

Study population

This is a cross-sectional, analytical, observational study. Patients were selected in a non-randomized manner according to their order of attendance at an allergy service during the recruitment period. The patients were selected from individuals aged between 18 and 40 years for the epidemiological peak of LAR reported in other studies,[9,14] with chronic persistent moderate/severe rhinitis, defined according to the criteria of the ARIA guidelines.[1]

We excluded patients with nasal or systemic comorbidities that could affect the interpretation of the NCT (nasal polyposis, septal perforation, pregnancy, use of medications such as oral steroids, cyclosporine, omalizumab, and immunotherapy). In addition, the control group of healthy volunteers who shared sociodemographic characteristics with patients with rhinitis was included.

Definition of groups

Patients with rhinitis were divided into 2 groups; a group of people with rhinitis with atopy (RWA), and a group with rhinitis without atopy (RWoA). The atopy was evaluated by SPT and serum sIgE to Der p.

We avoid the use of the terms "allergic rhinitis group", "non-allergic rhinitis group", or "LAR group", since the presence of systemic or local IgE does not confirm these diagnoses until the nasal challenge test is done.

Bioethical considerations

The study protocol was approved by the institutional ethics committee (code IN20-2017) and is in line with the Helsinki declaration. Each of the

participants signed to indicate their informed consent.

Atopy evaluation

The patients underwent a skin prick test (SPT) (Inmunotek Laboratory, Madrid, Spain) using standardized extracts with Der p. The interpretation of the test was based on the presence of a wheal with a diameter greater than 3 mm compared to the negative control, according to international guidelines, and histamine was used as positive control.[15,16] The Der p sIgE from serum was measured by the ImmunoCAP system. The cut-off value for the serum sIgE was 0.35 kU_A/L, based on the recommendations of the instrument and previous studies.[17]

Other common allergens in the region were also evaluated to determine the fraction of atopy to Der p among all sensitizations.[11,18]

Nasal challenge test (NCT)

Challenge tests were performed with Der p after a rhinoscopy. The Der p extract (Laboratory Inmunotek®, Spain) at a concentration of 10,000 UB/mL was applied with a nasal spray in a measured dose of 100 µL/puff in each nostril. Previously, the presence of non-specific nasal hyperreactivity was ruled out by performing the same procedure with saline solution. The result of the test was evaluated objectively by performing acoustic rhinometry (acoustic rheometer ECCOVISION) with a reduction greater than 20% considered positive, and also subjectively with the Lebel score and the visual analog scale (VAS).[19] To define a positive NCT, the criteria proposed by the "European Academy of Allergy and Clinical Immunology" (EAACI) was used;[13] we considered a positive NCT result to be achieved when the test was "clearly positive" or "moderately positive" according to the EAACI definition.

Collection of nasal mucus for measurement of NsIgE

Thirty minutes after the NCT, a nasal lavage was performed using the technique described by Naclerio et al,[20–22] with some modifications. Briefly, 6 mL of distilled water was applied to the nostril, and 10 s later the samples were collected in 50 mL conical tubes and were centrifuged for 15 min at 1500 g and 4 °C; the supernatant was stored at −20 °C until the time of detection of IgE.

The Der p sIgE from the nasal mucus was measured by the ImmunoCAP system. For the detection of NsIgE, a calibration curve was made using the ImmunoCAP system; the value of 0.12 kU_A/L was considered as the cut-off point according to the mean and two standard deviations observed in the control group.

Eosinophil count in the nasal mucus and peripheral blood

The eosinophil count in the nasal mucus was performed 30 min after the NCT. The sample was taken by brushing the nasal mucosa in each nostril and subsequent staining according to the Hansel method, and was analyzed by light microscopy. Eosinophilia in the nasal mucus were considered present when the eosinophil count was greater than or equal to 10% of total leucocytes or more than 10 eosinophils for high power field.[23] The measurement of eosinophils in peripheral blood was performed following the routine methods of clinical laboratories.[24]

Statistical analysis

For the descriptive analysis, absolute frequencies, relative frequencies, and summary measures, such as the median or the interquartile range, were used. The criteria of normality of age and laboratory tests were established through the Shapiro-Wilk test. To establish the relationship between the results of the NCT and NsIgE with respect to the study groups, the Pearson's Chi square test of independence and the likelihood ratio test were applied. The Kruskal-Wallis test was applied to establish the relationship between age, laboratory test, and symptom score in the study groups; a p value < 0.05 was considered statistically significant. For the correlation between the levels of NsIgE and serum sIgE, the Spearman correlation coefficient and the coefficient of determination were used. Indicators of diagnostic accuracy of NsIgE were evaluated based on the result of the NCT (gold test) for groups of patients who were sensitized and not sensitized to mites. The statistical program STATA version 14 was used.

RESULTS

Sociodemographic characteristics

A total of 50 patients with chronic rhinitis were recruited: 25 in the RWoA group and 25 in the RWA group. In addition, 18 control subjects agreed to participate in the study (Table 1). In the RWoA group, a higher age at the time of diagnosis and higher frequency of females were observed in comparison with the RWA group.

The presence of asthma, atopic dermatitis, and conjunctivitis was significantly more frequent in the RWA group. The RWA group had a median serum sIgEs for Der p of 22.1 kU_A/L (RI: 41.49), and in the RWoA group the median was 0.02kU_A/L (RI: 0.01). The correlation between serum sIgEs and NsIgE was moderate in the RWA group (r 0.5918, $p < 0.05$).

Sensitization to other allergenic triggers different to Der p or other mites was present in 34% and 0% of patients in the RWA and RWoA group, respectively.

Diagnostic performance of NsIgE

The RWA group had a higher frequency of positive NsIgE and NCTs than the RWoA group (NsIgE 84% vs 48% and NCT 80% vs 28%, $p < 0.05$) (Fig. 1). The highest levels of NsIgE were observed in the RWA group (Fig. 2).

The diagnostic performance of NsIgE for Der p was evaluated using the NCT as a reference test. The usefulness of the NsIgE to predict a positive NCT (sensitivity) was better in the RWA group (Fig. 3). The specificity of the test was low in both groups.

Seven patients in the RWoA group had a positive NCT, but only 3 (42.8%) of them had NsIgE. In patients with RWA, 17 (85%) of 20 patients with a positive NCT had NsIgE. Five (27.8%) healthy subjects had a positive NsIgE, but none had a positive NCT.

The point of 0.14 kU_A/L was used as a comparator of the cutoff 0.12 kU_A/L, considering some previous publications[25] (Supplemental Materials Table 1). Although the specificity of the test

Characteristics	Categories	Study groups			p
		RWoA n = 25	RWA n = 25	CS n = 18	
Sex	Female	20 (80%)	16 (64%)	7 (38.9%)	0.021
	Male	5 (20%)	9 (36%)	11 (61.1%)	
Age group*		Me: 34 (RI: 6)	Me: 29 (RI: 7)	Me: 27 (RI: 9)	<0.001
Age of diagnosis*		Me: 19 (RI: 16)	Me: 8 (RI: 10)	NA	<0.001
Comorbidities	Asthma	2 (8%)	13 (52%)	NA	<0.001
	Atopic Dermatitis	2 (8%)	10 (40%)	NA	<0.001
	Conjunctivitis	11 (44%)	16 (64%)	NA	<0.001
Cigarette smoke	Smoker	1 (4%)	3 (12%)	2 (11,1%)	0,526
	Passive smoker	5 (20%)	3 (12%)	3 (16,7%)	0,739
Eosinophils count	Peripheric blood count*	Me: 140 (RI: 160)	Me: 200 (RI: 220)	Me: 95 (RI: 80)	0,014
	Frequency in nasal mocus	0	3 (13%)	0	0,041
Symptom	symptom score**	Me: 2 (RI: 2)	Me: 2 (RI: 5)	Me: 0 (RI: 0)	0,0001

Table 1. Sociodemographic and clinical characteristics of patients. **The data are presented as the median (Me) and interquartile range. RWoA: rhinitis without atopy. RWA: rhinitis with atopy. CS: control subjects. NA: not applicable. **Lebel score.*

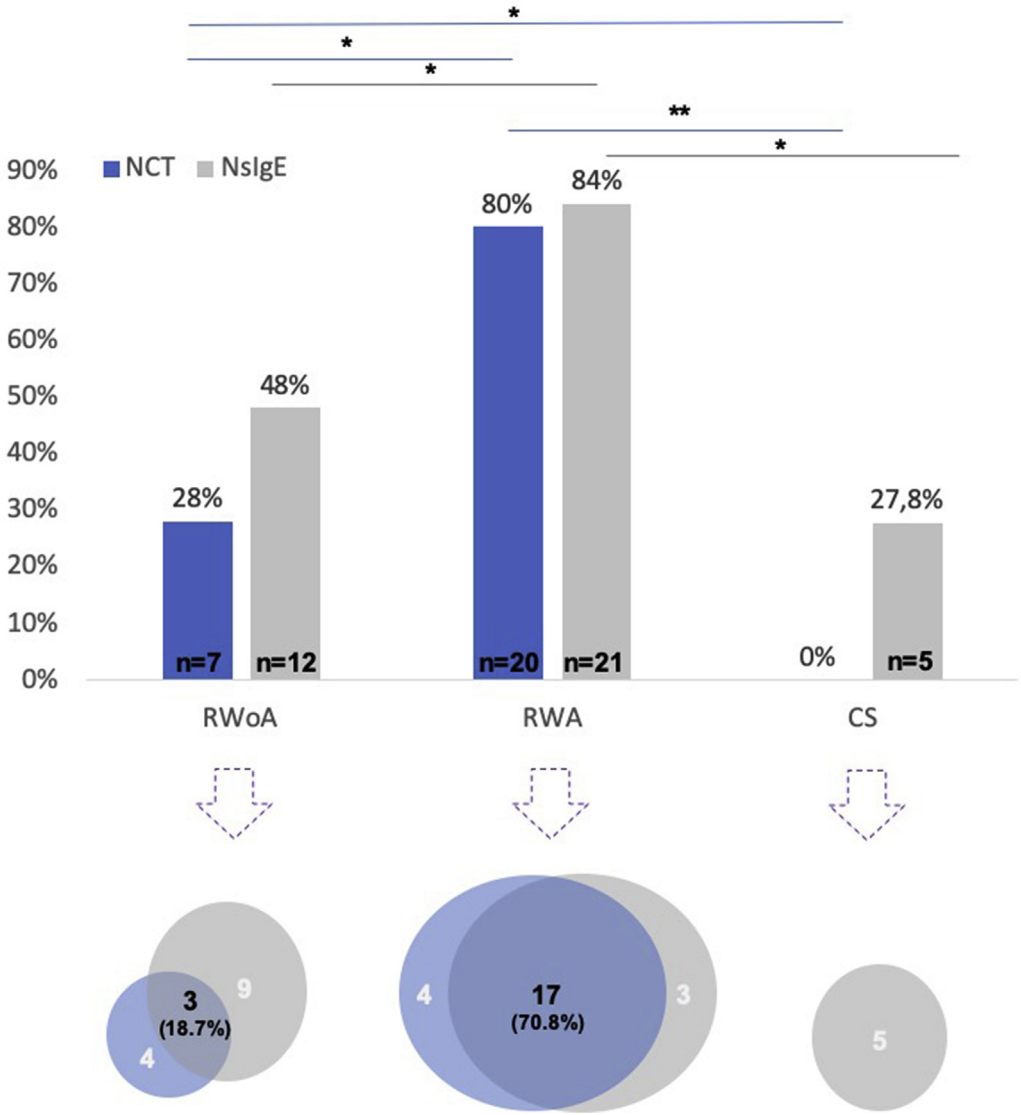

Fig. 1 Proportion of positive NCTs and NsIgE. The bars represent the frequency of NsIgE and positive NCTs in each group. The circles represent the number of patients with both positive tests (black numbers) or one of the two (white numbers). RWoA: rhinitis without atopy. RWA: rhinitis with atopy. HS: healthy subjects. *p <0.05, ** p <0.01

increased, no significant differences were observed in the diagnostic performance of the test in the RWoA or RWA groups.

Frequency of LAR and non-allergic rhinitis

In the RWoA group, the frequency of LAR to Der p (NsIgE to Der p plus positive NCT) was found in 3 (12%) of the 25 patients. These 3 patients represented 25% of the patients with NsIgE and 42.8% of the patients with a positive NCT in the RWoA group. Non-allergic rhinitis (no sIgE, no SPT and negative NCT) was found in 18 (72%) of the RWoA group patients. Four (16%) patients without nasal or systemic sIgE had a positive NCT with Der p.

Eosinophil count

Eosinophil counts in peripheral blood and in the nasal mucus were higher in the RWA group (Table 1), but there was not a correlation with serum sIgE or NsIgE (data not shown). There were no eosinophils in the nasal mucus of patients from the RWoA group and the control subjects.

DISCUSSION

The prevalence of LAR varies among populations; in Spain it is 25.7%, while in cities in China and Korea it is 8% and 11%, respectively.[26-28] The

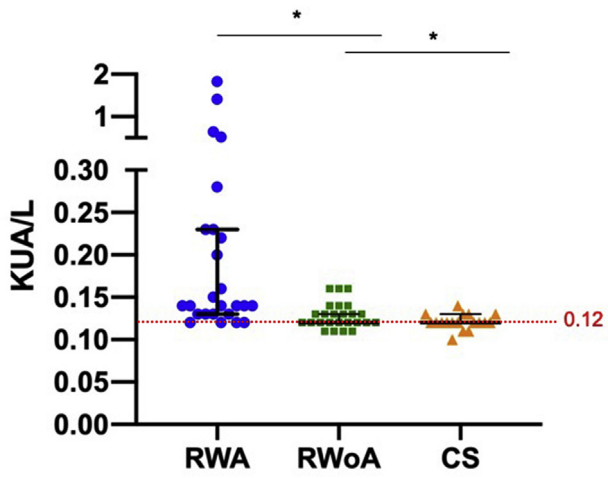

Fig. 2 Levels of nasal sIgE for Der p. The NsIgE levels of each subject in each group and group median and confidence interval 95% are represented with circles (RWoA group), squares (RWA group), and triangles (control group). RWoA: rhinitis without atopy. RWA: rhinitis with atopy. HS: healthy subjects. *p <0.05

variability of these results can be explained by multiple environmental factors, such as allergenic levels and the technique used to measure NsIgE. When measurements are made after nasal lavage detection of NsIgE in non-allergic rhinitis patients, a rate of 22–40% is found,[12,29] while 42.8% test positive when the solid phase of ImmunoCAP is applied directly in the nostril.[25] Our study shows that LAR is present in 28% of patients with rhinitis without serum sIgE, a percentage similar to that reported in other populations.[12,30]

Although the pathogenesis of LAR and non-allergic rhinitis is not completely understood,[31-33] these types of rhinitis usually start in the fourth decade of life; in non-allergic rhinitis, there are several mechanisms associated with an effect only on the nasal mucosa. Some results *in vivo* suggest that serum and nasal concentrations of IL-10 and nasal TGF-β concentrations are higher in LAR, suggesting a greater immunomodulatory property than in patients with allergic rhinitis.[32] Because the RWoA group was made up of patients with LAR and patients with non-allergic rhinitis, this could explain the older age of patients in the RWoA group and the lower frequency of some comorbidities, such as asthma or dermatitis.[34-36]

Traditionally, sIgE has been of great value in the clinical routine of the diagnostic approach to rhinitis. It allows us to identify possible environmental triggers for the patient and define the best immunotherapy and, if necessary, it guides us to which allergen to test with the NCT.

Because in LAR the conventional diagnostic approach through SPT or serum sIgE is insufficient,[37] NsIgE has become a key tool in identifying the allergenic trigger associated with the symptoms.

Despite the high exposure to Der p in the study population and the fact that *Dermatophagoides* spp. has been identified as the main cause of atopic and allergy in the tropics,[4,11] we observed that the frequency of positive NsIgE in the RWoA group (n = 12, 48%) was similar to in the control group (n = 5, 27.8%), and most of these patients had a negative challenge. These results support the previous data of Gelardi et al,[38] who observed NsIgE in 50% of a healthy group, and suggested that the production of NsIgE may represent a form of spontaneous immune response and is not a specific finding of nasal symptoms.

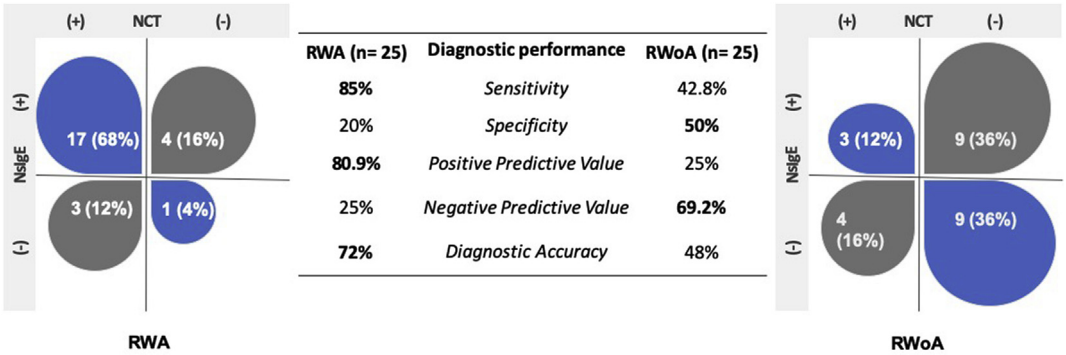

Fig. 3 Diagnostic performance of NsIgE in the RWA and RWoA groups. RWoA: rhinitis without atopy. RWA: rhinitis with atopy

Dermatophagoides spp. are the main cause of IgE sensitization in the tropics and are the main allergenic trigger involved in LAR.[26,39] Since we investigated only one (Der p), we cannot rule out LAR due to other triggers. Additionally, the relatively small number of participants in our study could affect the reported frequency. Nevertheless, these observations do not affect our main objective, which was to explore the diagnostic performance of NsIgE to predict the outcome of an NCT. Considering that only 3 of the 12 patients with NsIgE had a positive NCT, it is clear that the presence of NsIgE in the nasal mucus is not enough to define clinical relevance. Therefore, we consider performing an NCT to confirm the suspicion of LAR as indispensable.

Four patients in the RWoA group had a positive challenge but had no NsIgE or serum sIgE. We are not clear why this happened. Before performing the allergen NCT we performed a saline challenge to rule out an irritative effect. This is supported by the fact that none of the people in the control group had a positive challenge, even though 5 (27.8%) subjects had NsIgE. All analyses were performed in duplicate, so a technical error is also unlikely. A possible explanation is that the nasal mucosa of patients with rhinitis can make them more sensitive than healthy subjects to different triggers by non-IgE mediated mechanisms, for example unspecific degranulation of mast cells. An inflammation mediated by eosinophils (eosinophilic rhinitis) was ruled out since only in the RWA group was there an increase in these cells in the nasal mucus.

In AR, there is a strong association between sIgE and allergy, but 10–20% of the general population have serum sIgE without allergic symptoms.[40] A similar result was found for NsIgE in the RWA group, which had a better diagnostic performance than in the RWoA group or in the control subjects. In this study, 80% of the patients in the RWA group had a positive NCT, and an association between NsIgE and a positive NCT was observed in 17 of 25 (68%) of the cases. These results suggest that in the case of allergic rhinitis it is not necessary to routinely measure NsIgE, and a suggestive clinical history, added to the evidence of systemic sIgE in patients with chronic rhinitis, allows adequate diagnostic accuracy, reducing the need for confirmatory tests like the NCT.

Some studies suggest that allergen specific immunotherapy is a therapeutic alternative for patients with LAR.[41,42] However, given the lack of clinical relevance of NsIgE in a number of patients, a better understanding of the pathogenesis of this disease is necessary before suggesting immunotherapy as a routine treatment.

In conclusion, the diagnostic performance of NsIgE is not adequate as a predictor of the response to a nasal challenge in non-allergic patients. To confirm LAR, it is always necessary to perform the nasal challenge test with the suspected allergen.

Abbreviations

AR: Allergic Rhinitis; LAR: Local Allergy Rhinitis; NCT: Nasal Challenge Test; NsIgE: Nasal Specific IgE; RWoA: Rhinitis Without Systemic Atopy; RWA: Rhinitis With Systemic Atopy; SPT: Skin Prick Test; sIgE: Specific Immunoglobulin E

Authorship contribution

All the authors contributed equally to the conception, analysis, and writing of the manuscript. LS, AC and JS contributed the central idea of the article.

Consent for publication

All authors agree that this version be published.

Availability of data

The data used for this project are available to the public with the prior authorization of the authors and the ethics committee.

Ethics approval

The study protocol was approved by the institutional ethics committee (code IN20-2017).

Declaration of competing interest

The authors declare they have no conflict of interest.

Acknowledgements and Funding

We thank the University of Antioquia and the Clinic "IPS Universitaria" from Medellín, Colombia (ID grant number code IN20-2017) for their support.

Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2020.100461.

Author details
Group of Clinical and Experimental Allergy (GACE), Clinic "IPS Universitaria", University of Antioquia, Cra 27 n 37 B sur 69 apto 510, Medellín, Colombia.

REFERENCES

1. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(Suppl 86):8–160.
2. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126(3):466–476.
3. Wise SK, Lin SY, Toskala E. International consensus statement on allergy and rhinology: allergic rhinitis-executive summary. *Int Forum Allergy Rhinol*. 2018;8(2):85–107.
4. Caraballo L, Zakzuk J, Lee BW, et al. Particularities of allergy in the tropics. *World Allergy Organ J*. 2016;9:20.
5. Papadopoulos NG, Bernstein JA, Demoly P, et al. Phenotypes and endotypes of rhinitis and their impact on management: a PRACTALL report. *Allergy*. 2015;70(5):474–494.
6. Hellings PW, Klimek L, Cingi C, et al. Non-allergic rhinitis: position paper of the European Academy of allergy and clinical Immunology. *Allergy*. 2017;72(11):1657–1665.
7. Shin YS, Jung CG, Park HS. Prevalence and clinical characteristics of local allergic rhinitis to house dust mites. *Curr Opin Allergy Clin Immunol*. 2018;18(1):10–15.
8.. Castelli S, Arasi S, Tripodi S, et al. IgE antibody repertoire in nasal secretions of children and adults with seasonal allergic rhinitis: a molecular analysis. *Pediatr Allergy Immunol*. 2020;31(3):273–280.
9. Meng Y, Wang Y, Lou H, et al. Specific immunoglobulin E in nasal secretions for the diagnosis of local allergic rhinitis. *Rhinology*. 2019;57(4):313–320.
10. Al Ahmad M, Arifhodzic N, Nurkic J, Jusufovic E, Hanoun AL, Rodriguez T. Role of nasal challenge and local eosinophilia in indirect exposure to cat in allergic rhinitis patients. *Eur Ann Allergy Clin Immunol*. 2018;50(3):125–131.
11. Fernández-Caldas E, Puerta L, Caraballo L. Mites and allergy. *Chem Immunol Allergy*. 2014;100:234–242.
12. Hamizan AW, Rimmer J, Husain S, et al. Local specific Immunoglobulin E among patients with nonallergic rhinitis: a systematic review. *Rhinology*. 2019;57(1):10–20.
13. Augé J, Vent J, Agache I, et al. EAACI Position paper on the standardization of nasal allergen challenges. *Allergy*. 2018;73(8):1597–1608.
14. Rondón C, Eguíluz-Gracia I, Shamji MH, et al. IgE test in secretions of patients with respiratory allergy. *Curr Allergy Asthma Rep*. 2018;18(12):67.
15. Heinzerling LM, Burbach GJ, Edenharter G, et al. GA(2)LEN skin test study I: GA(2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. *Allergy*. 2009;64(10):1498–1506.
16. Sekerel BE, Sahiner UM, Bousquet J, et al. Practical guide to skin prick tests in allergy to aeroallergens: some concerns. *Allergy*. 2012;67(3):442. author reply 3.
17. Leimgruber A, Mosimann B, Claeys M, et al. Clinical evaluation of a new in-vitro assay for specific IgE, the immuno CAP system. *Clin Exp Allergy*. 1991;21(1):127–131.
18. Sanchez J, Diez S, Cardona R. Sensibilización a aeroalergenos en pacientes alérgicos de Medellín. *Colombia Revista Alergia México*. 2012;59(3):139–147.
19. Dordal MT, Lluch-Bernal M, Sánchez MC, et al. Allergen-specific nasal provocation testing: review by the rhinoconjunctivitis committee of the Spanish Society of Allergy and Clinical Immunology. *J Investig Allergol Clin Immunol*. 2011;21(1):1–12. quiz follow.
20. Naclerio RM, Creticos PS, Norman PS, Lichtenstein LM. Mediator release after nasal airway challenge with allergen. *Am Rev Respir Dis*. 1986;134(5):1102.
21. Norman PS, Naclerio RM, Creticos PS, Togias A, Lichtenstein LM. Mediator release after allergic and physical nasal challenges. *Int Arch Allergy Appl Immunol*. 1985;77(1-2): 57–63.
22. Naclerio RM, Meier HL, Kagey-Sobotka A, et al. Mediator release after nasal airway challenge with allergen. *Am Rev Respir Dis*. 1983;128(4):597–602.
23. Miller RE, Paradise JL, Friday GA, Fireman P, Voith D. The nasal smear for eosinophils. Its value in children with seasonal allergic rhinitis. *Am J Dis Child*. 1982;136(11):1009–1011.
24. Briggs C, Carter J, Lee SH, et al. ICSH Guideline for worldwide point-of-care testing in haematology with special reference to the complete blood count. *Int J Lab Hematol*. 2008;30(2):105-116.
25. Campo P, Del Carmen Plaza-Seron M, Eguiluz-Gracia I, et al. Direct intranasal application of the solid phase of ImmunoCAP® increases nasal specific immunoglobulin E detection in local allergic rhinitis patients. *Int Forum Allergy Rhinol*. 2018;8(1):15–19.
26. Rondón C, Campo P, Galindo L, et al. Prevalence and clinical relevance of local allergic rhinitis. *Allergy*. 2012;67(10):1282–1288.
27. Cheng KJ, Xu YY, Liu HY, Wang SQ. Serum eosinophil cationic protein level in Chinese subjects with nonallergic and local allergic rhinitis and its relation to the severity of disease. *Am J Rhinol Allergy*. 2013;27(1):8–12.
28. Jang TY, Kim YH. Nasal provocation test is useful for discriminating allergic, nonallergic, and local allergic rhinitis. *Am J Rhinol Allergy*. 2015;29(4):e100–e104.
29. Meng Y, Lou H, Wang Y, Wang C, Zhang L. The use of specific immunoglobulin E in nasal secretions for the diagnosis of allergic rhinitis. *Laryngoscope*. 2018;128(9):E311–E315.
30. Bozek A, Ignasiak B, Kasperska-Zajac A, Scierski W, Grzanka A, Jarzab J. Local allergic rhinitis in elderly patients. *Ann Allergy Asthma Immunol*. 2015;114(3):199–202.
31. Lee KS, Yu J, Shim D, et al. Local immune responses in children and adults with allergic and nonallergic rhinitis. *PloS One*. 2016;11(6), e0156979.

32. Yang Q, Li C, Wang W, et al. Infiltration pattern of gammadelta T cells and its association with local inflammatory response in the nasal mucosa of patients with allergic rhinitis. *Int Forum Allergy Rhinol*. 2019;9(11):1318–1326.
33. Kim YH, Park CS, Jang TY. Immunologic properties and clinical features of local allergic rhinitis. *J Otolaryngol Head Neck Surg*. 2012;41(1):51–57.
34. Rondon C, Campo P, Eguiluz-Gracia I, et al. Local allergic rhinitis is an independent rhinitis phenotype: the results of a 10-year follow-up study. *Allergy*. 2018;73(2):470–478.
35. Buntarickpornpan P, Veskitkul J, Pacharn P, et al. The proportion of local allergic rhinitis to Dermatophagoides pteronyssinus in children. *Pediatr Allergy Immunol*. 2016;27(6): 574–579.
36. Tsilochristou O, Kyriakakou M, Manolaraki I, et al. Detection of local allergic rhinitis in children with chronic, difficult-to-treat, non-allergic rhinitis using multiple nasal provocation tests. *Pediatr Allergy Immunol*. 2019;30(3):296–304.
37. Rondón C, Eguiluz-Gracia I, Campo P. Is the evidence of local allergic rhinitis growing? *Curr Opin Allergy Clin Immunol*. 2018;18(4):342–349.
38. Gelardi M, Quaranta N, Passalacqua G. When sneezing indicates the cell type. *Int Forum Allergy Rhinol*. 2013;3(5):393–398.
39. Ha EK, Na MS, Lee S, et al. Prevalence and clinical characteristics of local allergic rhinitis in children sensitized to house dust mites. *Int Arch Allergy Immunol*. 2017;174(3-4): 183–189.
40. Dennis RJ, Caraballo L, García E, et al. Prevalence of asthma and other allergic conditions in Colombia 2009-2010: a cross-sectional study. *BMC Pulm Med*. 2012;12:17.
41. Rondón C, Blanca-López N, Campo P, et al. Specific immunotherapy in local allergic rhinitis: a randomized, double-blind placebo-controlled trial with Phleum pratense subcutaneous allergen immunotherapy. *Allergy*. 2018;73(4): 905–915.
42. Bożek A, Kołodziejczyk K, Jarząb J. Efficacy and safety of birch pollen immunotherapy for local allergic rhinitis. *Ann Allergy Asthma Immunol*. 2018;120(1):53–58.