



Nasal IgE in subjects with allergic and non-allergic rhinitis

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ABSTRACT

Purpose: The prevalence of "local allergic rhinitis" within individuals suffering from perennial rhinitis remains uncertain, and patients usually are diagnosed with non-allergic rhinitis. The aim of this study was to evaluate the prevalence of a potential "local allergic rhinitis" in subjects suffering from non-allergic rhinitis in a non-selected group of young students.

Methods: 131 students (age 25.0 ± 5.1 years) with a possible allergic rhinitis and 25 non-allergic controls without rhinitis symptoms (age 22.0 ± 2.0 years) were recruited by public postings. 97 of 131 students with rhinitis were tested positive (≥ 3 mm) to prick testing with 17 frequent allergens at visit 1. Twenty-four 24 subjects with a house dust mite allergy, 21 subjects with a non-allergic rhinitis, and 18 non-allergic controls were further investigated at visit 2. Blood samples were taken, and nasal secretion was examined. In addition, all groups performed a nasal provocation test with house dust mite (HDM).

Results: In serum and nasal secretion, total IgE and house dust mite specific IgE significantly differed between HDM positive subjects and controls. However, no differences between non-allergic subjects and control subjects were quantifiable. Neither a nasal provocation test nor a nasal IgE to HDM allergens showed a measurable positive response in any of the non-allergic rhinitis subjects as well as the healthy controls, whilst being positive in 13 subjects with HDM allergy.

Conclusions: Nasal IgE is present in subjects with HDM allergy, but not in non-allergic rhinitis. In the investigated non-selected population, exclusive local production of IgE is absent. By implication, therefore, our findings challenge the emerging concept of local allergic rhinitis. Study identifier at ClinicalTrials.gov: NCT 02810535.

Keywords: Allergic rhinitis, House dust mite allergy, Local IgE, Local allergic rhinitis, Non-allergic rhinitis

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INTRODUCTION

Allergic rhinitis (AR), seasonal or perennial, is a very common disease in the western world. The prevalence ranges from approximately 15% as related by physicians and as high as 30% by patients reports.^{1,2} Most patients suffer from rather mild symptoms like sneezing, nasal pruritus, and congestion. Hence, only half of the patients seek medical treatment. The diagnosis of AR is based on characteristic symptoms and evidence of sensitization, measured either by skin prick tests (SPT) or the presence of allergen-specific IgE (sIgE) in serum most frequently to birch and grass pollen, mold, house dust mites (HDM), or animal dander.

Diagnosis and treatment of most patients with AR in clinical practice is not considered a major challenge for an experienced physician. However, in some patients the applicable diagnosis is difficult when physicians are faced with patients suffering from typical symptoms of AR without any objectifiable sensitization. In accordance with national and international guidelines, the differential diagnosis includes further forms of rhinitis that are non-allergic in origin such as vasomotor rhinitis, non-allergic rhinitis with eosinophilia-syndrome (NARES), and recently local allergic rhinitis (LAR).³⁻⁶

The discovery of nasal IgE defined as local production of IgE antibodies in the nasal mucosa has been widely reported. In 1947 Samter and Becker recognized that nasal secretions of individuals allergic to ragweed could be used to passively transfer a local reaction to previously non-allergic individuals. Furthermore, in 1970 ragweed specific IgE was detected in the nasal washings of ragweed allergic patients.⁷ In 1975 Huggins and Brostoff reported that in patients with symptoms indicating a possible AR, but with negative SPT, IgE antibodies to HDM could be found in nasal secretions.⁸ Sennekamp et al described a high conversion rate from negative to positive skin tests in patients with LAR.⁹

The term "LAR" was first proposed and introduced by Rondón et al.¹⁰ These authors described nasal provocation tests (NPT) with HDM being positive in 54% of patients with a diagnosis of non-allergic rhinitis in their hands.¹¹

Furthermore, in a recent review on AR, the authors stated that LAR requires further study, and the measurement of allergen-specific IgE in nasal fluid is restricted to research only.² In line with this statement, most allergy specialists and clinics do not measure nasal IgE to detect LAR in routine practice. Therefore, the diagnosis of LAR only relies on a positive nasal provocation test in everyday practice, which may show falsely positive results when not performed carefully.^{12,13}

Indeed, the prevalence of LAR has been shown in 47%–62.5% of patients in patients suffering from perennial non-allergic rhinitis (NAR).^{11,14} Similar results were recently described by Bozek et al whom described the prevalence of NAR as high as 42% in a study cohort of 621 individuals.¹⁵ Demographical differences might be attributable as a study group in China found a prevalence of LAR in only 7.7% of patients in a cohort of 195 individuals whilst Ishida et al recently published data suggesting a prevalence of LAR in 2 of 14 patients (14.3%) and HDM LAR in 5 of 21 (23.8%) in a study of 50 highly selected Japanese patients suffering from chronic rhinosinusitis.^{16,17} Contrary to these conclusions others found no prevalence of nasal IgE in patients with non-allergic rhinitis.¹⁸ Such discrepant data was obtained in selected populations of subjects suffering from rhinitis. However, the prevalence of LAR in the general population is still unexplored, and true prevalence of LAR remains still to be established. The aim of this prospective study was to evaluate the prevalence of LAR in an unselected population of young students suffering from seasonal or perennial AR.

MATERIALS AND METHODS

Subjects

Subjects were recruited by means of public posting at the university campus and advertisement on social media platforms. As a result, many students of the Goethe University Frankfurt am Main participated in the trial. The study was performed in accordance with the declarations of Good Clinical Practice (GCP) and registered by [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT 02810535).

The population consisted of 131 (91 female and 40 male) subjects with symptoms of seasonal or

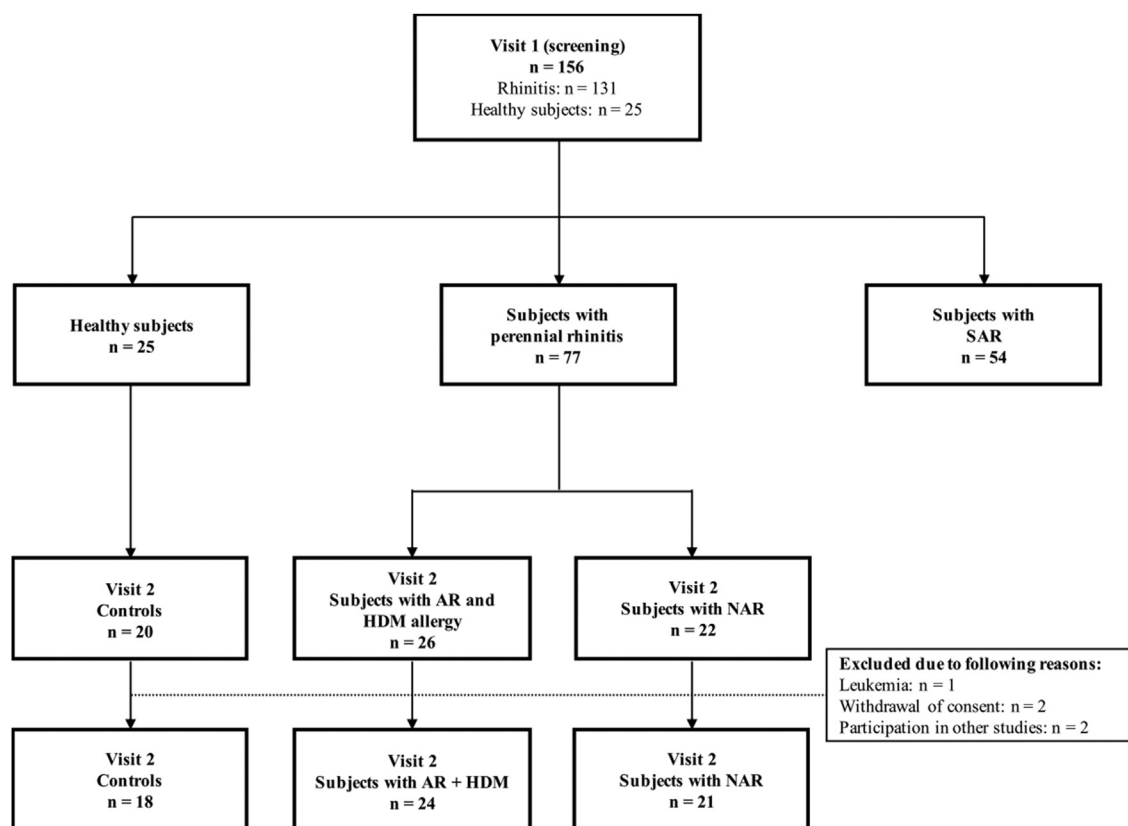


Fig. 1 Study flow chart and subject groups. Fig. 1. Study flow chart and subject groups. AR (allergic rhinitis); HDM (house dust mite); SAR (seasonal allergic rhinitis); NAR (non-allergic rhinitis)

perennial rhinitis and 25 (22 female and 3 male) healthy controls. Exclusion criteria were age <18 years, acute infections 4 weeks before study inclusion, severe diseases such as cystic fibrosis or malignant diseases, present pregnancy or lactation, participation in another clinical trial within 30 days, documented alcohol and/or drug abuse, or incapability to perform the study procedures. Furthermore, we excluded all subjects with previous allergen immunotherapy against HDM from the study. Immunotherapy against other perennial allergens was not considered an exclusion criterion since we did not expect any influence on the study.

Study design

Our study was a prospective, exploratory clinical study specifically designed to investigate the presence of local IgE in the nasal mucosa of subjects with AR to HDM allergens (AR + HDM), NAR and healthy controls. The study comprised 2 visits,

1 screening visit, and 1 visit for determination of serum IgE, nasal IgE, and NPT.

A total of 156 subjects underwent visit 1, which consisted of a physical examination, a health questionnaire, lung function testing, and SPT.

68 participants were invited to a second visit according to their clinical symptoms (perennial rhinitis) and the results of the SPT (see Fig. 1). During the second visit, nasal secretion and blood samples were taken and a NPT with HDM was performed.

Health and activity questionnaire

The subjects were asked to fill out a questionnaire that had been taken, adjusted, and modified from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (supplementary material) in order to meet our study design. It included questions on the employment situation, asked for other kinds of diseases and symptoms perennial or during pollen season, and

collected information concerning the symptoms of wheezing and dry cough. Additionally, the questionnaire evaluated medical conditions related to allergic symptoms of the nose and eyes and measured the intake of medication such as anti-histamines, rapid-acting beta-2 agonists, nasal drops, eye drops, and topical cortisone. The subjects had to rank the frequency of the intake of their before mentioned medications on a scale from 0 to 6. Whereas 0 showed no intake and 6 showed consumption over 16 times (maximum sum score was 30). Regarding nasal symptoms, the subjects had to assess the severity of the symptoms "blocked nose", "runny nose", "sneezing" and "itchy nose" on a scale from 0 (= none) to 6 (=severe) (maximum sum score was 24).

Skin prick test

A SPT using 17 standard allergens (birch pollen, alder pollen, hazelnut pollen, ash tree pollen, grass pollen, rye pollen, ragweed pollen, mugwort pollen, plantain, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, cat, and horse) (Allergopharma, Merck, Reinbek, Germany) was performed at visit 1 according to international standard.⁶ The mean of the largest diameter of the wheal and its perpendicular diameter was recorded as the response. A response of at least 3 mm and a negative saline control as well as a response to histamine as positive control was considered as positive regarding sensitization to the tested allergen.

Pulmonary function test

Baseline pulmonary function tests were performed using the plethysmograph JAEGER[®] MasterScreen Body (CareFusion Germany 234 GmbH, Hoechberg, Germany). The following parameters were recorded: forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), and FEV₁%FVC ratio (FEV₁%/FVC).

Collection of nasal secretion

After inspection of the nasal cavity with a nasal speculum, a cotton swab was placed underneath the lower turbinate and left there for at least 15 min.¹⁹ For that, cotton swabs with a diameter of

1.0 cm were used (M + W Select cotton rolls with pulp, Müller & Weygandt GmbH, Büdingen, Germany). After obtaining the nasal secretion, the swabs were sealed in a Salivette[®] (Sarstedt AG & Co. KG, Nuembrecht, Germany) and centrifuged at 3000 revolutions for 10 min. Then, the centrifuged secretion was transferred into Eppendorf tubes and frozen at -80 °C until further analysis.

Nasal provocation test

The NPT was performed according to our laboratory's standard as recently described in more detail and interpreted in concordance with international standards.^{4,5,20,21} Before starting the NPT, we made sure that no patient had used any treatment for rhinitis before. After nasal secretion collection, a NPT with HDM allergen was performed.²² First, the lyophilised HDM allergen *Dermatophagoides farinae* (Dpt. 708, Allergopharma, Merck, Reinbek, Germany) was dissolved in 5 mL of 0.9% saline, resulting in a solution with a dosage of 5000 AU/mL. The solution was transferred in a pump dosing spray of which one spray-puff equates to 0.04-0.05 mL with a dosage of 400 AU. Whereas the negative control was a physiological saline solution (0.9%) with phenolic preservation. The negative control was used to determine values prior to the provocation itself. The reaction to the NPT was measured using two different methods: Lebel symptom score scale and measurement of peak nasal inspiratory flow (PNIF).

To determine the nasal flow rate and to objectify nasal obstruction the Inspiratory Flow Meter In-Check Nasal (Clement Clarke International Ltd, Essex, UK) was used. One measurement consisted of 3 attempts whereof the highest value was selected.

The Lebel symptom score scale recorded the frequency of sneezing (0-3 points), the extent of rhinorrhea (0-2 points), the severity of nasal obstruction (0-3 points), and possible concomitant itching of the nose, palate, ear, or eye (0-3 points), as described.²³

First, the baseline scores were obtained, requiring a Lebel score <3 and a PNIF of at least

50 L/min. Then the negative control solution was applied with one spray-puff into each nostril. After 10 min the Lebel and PNIF scores were recorded. When a decrease of the PNIF from baseline score was detected and either >20% or the Lebel score had a value ≥ 3 the NPT was terminated due to an unspecific reaction. The score evaluation was followed by the application of the HDM allergen solution, one spray-puff for each nostril. After another 10 min, the scores were again evaluated. The NPT was considered to be positive if either the Lebel score after HDM provocation was ≥ 6 or a decrease of the PNIF from after saline to after HDM was >40%.

A nasal spray rescue medication with xylometazoline hydrochloride as main active substance (Otriven 0.1%, GlakoSmithKline GmbH & Co. KG, Munich, Germany) was offered to subjects with a strong nasal reaction.

Laboratory measurements

Coded blinded serum and nasal secretions on dry ice were sent to the Upper Airways Research Laboratory of the Ghent University for IgE determinations. Serum and nasal secretions were analyzed for total IgE and specific IgE to HDM (D1 = *Dermatophagoides pteronyssinus*) and

(D2 = *Dermatophagoides farinae*) by using the UniCAP system (Thermo Fisher Scientific - ImmunoDiagnostics, Groot-Bijgaarden, Belgium). Analysis was performed according to the manufacturer's instructions.

Statistical analysis

The data were analyzed using Microsoft® Excel 2016 for Mac (Microsoft Corporation, Redmond, WA, USA), GraphPad Prism 7 for Mac OS X (GraphPad Software, La Jolla, CA, USA), and SPSS Version 19.0 (IBM, Chicago, Illinois, USA). All P-values < 0.05 were considered to be statistically significant. The parameters were tested for normal distribution using the D'Agostino & Pearson normality test. Normally distributed values are indicated as mean value and standard deviation (SD), whereas not normally distributed values are indicated as median and range. The non-parametric Kruskal-Wallis test and Mann-Whitney U test were used for comparison between not normally distributed values, whereas ANOVA was used for comparison between normally distributed values. To compare nominal data, the Fisher-Freeman-Halton's exact test was used. Correlations between the PNIF values, the Lebel score, and the nasal specific IgE were calculated using the Spearman's rank correlation test.

	Controls	AR + HDM	NAR
Subjects [number]	n = 18	n = 24	n = 21
Gender [number]	f = 15, m = 3	f = 16, m = 8	f = 17, m = 4
Age [years, mean \pm SD]	22.39 \pm 1.91	23.92 \pm 3.99	24.19 \pm 3.34
FVC [%pred, mean \pm SD]	99.63 \pm 10.38	101.45 \pm 10.99	98.24 \pm 10.34
FEV ₁ [%pred, mean \pm SD]	97.94 \pm 11.66	95.77 \pm 11.92	96.62 \pm 10.60
FEV ₁ /FVC [% , mean \pm SD]	85.41 \pm 6.77	81.91 \pm 8.88	85.08 \pm 7.78
HDM SPT positivity [% , mean \pm SD]	0 \pm 0	100 \pm 0	0 \pm 0
Serum total IgE [kU/L, median and range]	24.89 (2.15-74.70)	207.56 (15.27-4868.00) ***/*****	21.93 (2.23-621.17)
Serum slgE-D1 [kUA/L, median and range]	0.05 (0.05-0.32)	27.99 (0.11-311.48) ****	0.05 (0.05-1.47)
Serum slgE-D2 [kUA/L, median and range]	0.05 (0.05-0.36)	33.22 (1.47-447.80) ****	0.05 (0.05-1.59)

Table 1. Clinical characteristics. ***/****, $P \leq 0.001$ compared to subjects with NAR and $P \leq 0.0001$ compared to controls; ****, $P \leq 0.0001$ compared with controls and subjects with NAR

	Controls	AR + HDM	NAR
Duration of perennial symptoms [years, median and range]	-	9 (2-25)	5 (0-20)
Sum score of nasal symptoms [median and range]	0 (0-5)	11 (6-21) ****	11 (6-20) ****
Sum score of medication intake [median and range]	0 (0-2)	5 (0-25) ***/n.s.	1 (0-18) *
Antihistamines	0 (0%)	9 (50.00%) ***/n.s.	2 (13.33%) ^{n.s.}
Eye drops	0 (0%)	4 (22.22%)	3 (20.00%)
Nasal drops	1 (5.56%)	9 (50.00%)	7 (46.67%)
Rapid-acting β_2 -agonists	0 (0%)	3 (16.67%)	1 (6.67%)
Topical Cortisone use	0 (0%)	2 (11.11%)	1 (6.67%)

Table 2. Symptoms and medication intake. For the separate drugs, the number of subjects using them for their allergic complaints during the last year, are listed. **** - $P \leq 0.0001$ compared to controls; ***/n.s. - $P \leq 0.001$ compared to controls/AR + HDM compared to NAR: not significant, n.s. - not significant when compared to controls

RESULTS

Subjects characteristics

We screened 156 subjects in total (82.7% students), 131 subjects with reported seasonal or perennial rhinitis, and 25 healthy controls. Five healthy controls without rhinitis symptoms were excluded due to a positive SPT against HDM, and 2 further subjects were excluded due to reaction to NaCl (negative control) in the SPT. Of the 35 subjects with perennial nasal symptoms and positive SPT against HDM (AR + HDM), 26 agreed to attend the follow up visit. Twenty-two of 33 NAR subjects, 22 and 20 of 25 healthy controls agreed to attend the follow up visit, resulting in 68 subjects willing to participate in visit 2. The 68 subjects were then invited to a second visit. Five of the 68 invited subjects were excluded due to different reasons: new diagnosed leukemia ($n = 1$), withdrawal of consent ($n = 2$), and the participation in other studies ($n = 2$), see Fig. 1. Twenty-four subjects with AR + HDM (age: 23.9 ± 4.0), 21 subjects with NAR (age: 24.2 ± 3.3), and 18 healthy control subjects with no allergic symptoms (age: 22.4 ± 1.9) fulfilled the inclusion criteria.

As shown in Table 1, groups were age-matched (ns) with a higher percentage of women in all groups (66.7%–83.3%). Even though the percentage of women was higher, there was no significant

difference regarding the distribution of female and male participants between the groups.

There was no difference regarding the FVC, FEV₁ and FEV₁/FVC ratio between groups. Subjects with AR + HDM had higher levels of total and specific IgE in serum than controls and subjects with NAR ($P < 0.0001$).

Clinical symptoms and medication

Duration of rhinitis, impairment by rhinitis symptoms, nasal symptom scores, and medication intake are shown in Table 2. Subjects with AR + HDM and subjects with NAR had a significantly higher nasal sum score than controls ($P < 0.0001$). The nasal sum score between subjects with AR + HDM and NAR (ns) did not differ. As expected, the sum score regarding the medication intake from subjects with AR + HDM ($P \leq 0.001$) and NAR ($P \leq 0.05$) differed significantly from controls.

The severity of nasal symptoms (sneezing, blocked-, runny- and itchy nose) is shown in Fig. 2. As shown, severity of nasal symptoms of subjects with AR + HDM did not differ from NAR, but significantly increased compared to controls.

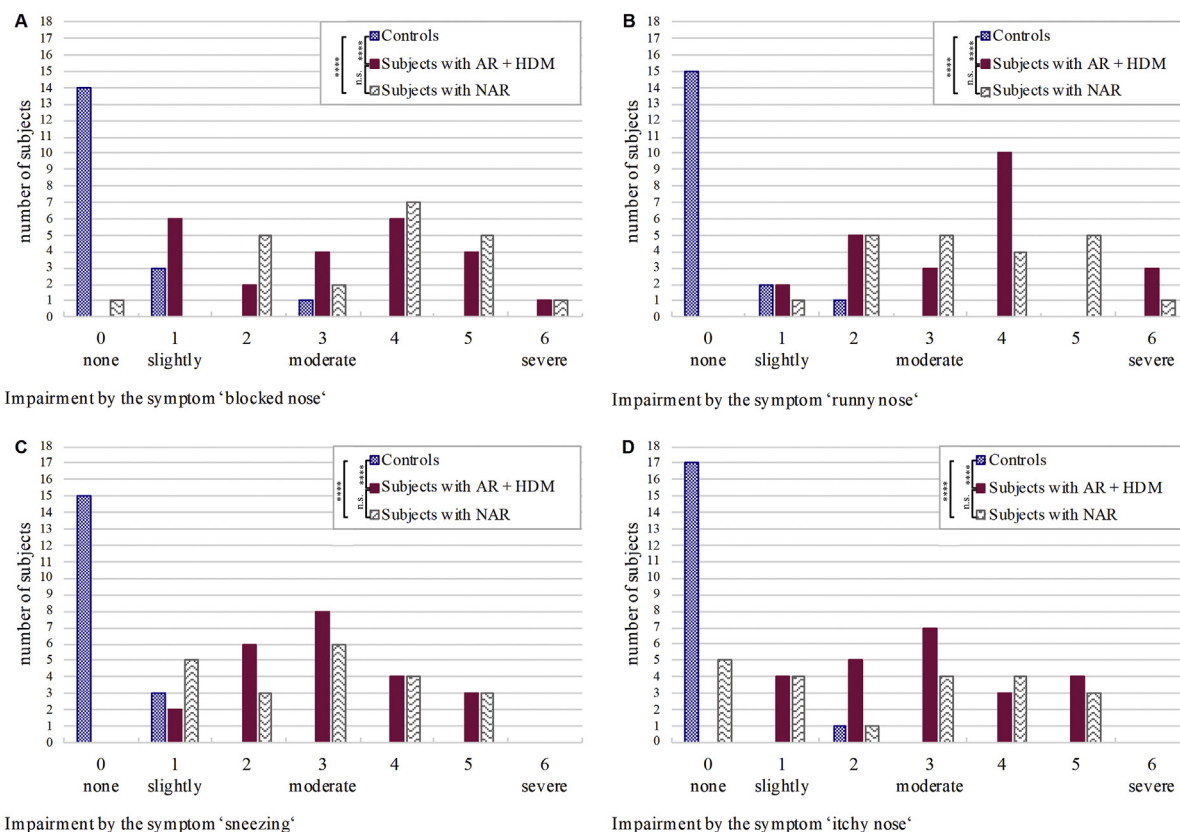


Fig. 2 Severity of nasal symptoms. Fig. 2: Severity of nasal symptoms ‘blocked nose’ (A), ‘runny nose’ (B), ‘sneezing’ (C) and ‘itchy nose’ (D). Sum scores were compared using the Kruskal-Wallis test. **** - $P \leq 0.0001$; n.s. - no significant difference

Skin prick test (SPT)

Of the 156 screened subjects, 104 (66%) showed sensitization against one of the tested antigens. Of the 131 subjects with rhinitis symptoms 97 participants, (74%) had a positive SPT. Of these subjects, 8.25% ($n = 8/97$) were mono-sensitized whilst 91.75% ($n = 89/97$) were sensitized against more than 1 antigen.

The subgroup analysis showed positive SPT in all of the AR + HDM subjects. Within this group, 95.83% were sensitized against both species of *Dermatophagoides*. Of AR + HDM subjects, 83.33% further showed sensitization against other antigens. None of the controls was positive in SPT, but 23.81% of subjects with NAR showed sensitization against seasonal allergens but not against HDM, molds, or dander whilst having perennial allergic symptoms. Of this subgroup, 1 patient showed a positive reaction to grass pollen (8 mm) whilst another individual tested positively against ash pollen (7 mm) in the SPT. All other individuals

of the NAR group showed minor reactions just above threshold ranging between 3 mm and 4 mm without any clinical significance. The control group showed no positivity in SPT against HDM or any of the further tested allergens.

Local IgE in nasal secretion

In 17 of 18 (94.4%) controls, 21 of 24 (87.5%) subjects with AR + HDM and 17 of 21 subjects with NAR (80.9%) we were able to obtain a quantitatively sufficient amount of nasal secretion which was further analyzed for IgE. As shown in Fig. 3, there were significant differences ($P < 0.0001$) in total IgE and specific IgE to D1 and D2 between groups. There were no significant differences regarding the total IgE and specific IgE between controls and subjects with NAR. None of the controls or the subjects with NAR had specific IgE to HDM expressed in nasal secretions as shown in Fig. 3.

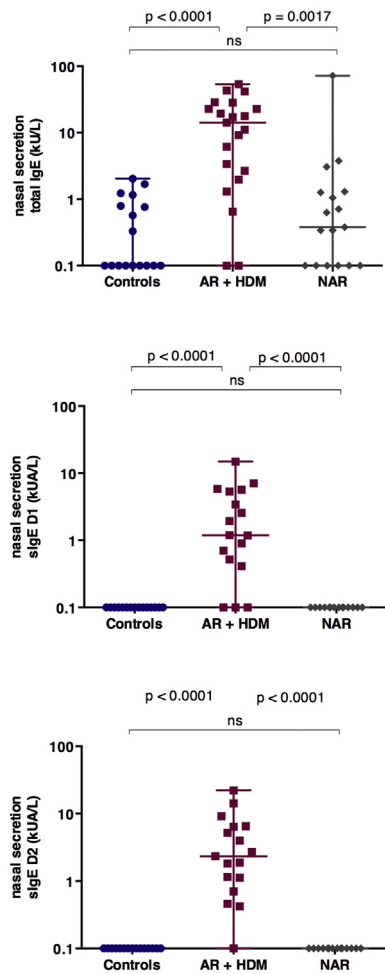


Fig. 3 Comparison of total IgE and specific IgE to D1 and D2 in nasal secretion between groups. Fig. 3. Comparison of total IgE (in kilo international units (IU) of IgE per liter (kU/L) and sIgE (in kilo international units (IU) of allergenspecific antibody per liter (kUA/L) to D1 (Dermatophagoides pteronyssinus) and D2 (Dermatophagoides farinae) in nasal secretion between groups, in log10. Kruskal-Wallis test results regarding the P-values are shown in the graphs

Nasal provocation test

The NPT was performed in all groups. Three subjects with AR + HDM and 1 subject with NAR did not start the NPT due to a Lebel baseline score ≥ 3 or a PNIF less than 50 L/min. After provocation with saline control solution, 7 subjects with AR + HDM, 1 subject with NAR, and 1 control were excluded due to an unspecific reaction with either a decrease of $>20\%$ regarding the PNIF or a Lebel score ≥ 3 . After provocation with HDM, 13 subjects with AR + HDM either had a Lebel score ≥ 6 points or a decrease in PNIF $>40\%$ which was considered to be a positive reaction. None of the controls and the subjects with NAR had a positive reaction to provocation with HDM as shown in Table 3. The PNIF decrease in percentage also differed significantly between controls and subjects with AR + HDM ($P < 0.0001$) and between subjects with AR + HDM and NAR ($P = 0.001$) but not between controls and NAR subjects (*ns*) (Table 3).

Test for correlations between NPT and nasal specific IgE

We found significant correlations between the specific IgE of D1 ($r = -0.59$, $P \leq 0.01$) and D2 ($r = -0.65$, $P \leq 0.01$) measured in nasal secretion and the reaction to provocation with HDM measured via PNIF decrease. Thus, higher sIgE D1 and D2 values were related to a higher decrease of the PNIF after HDM provocation. The values for specific IgE, D1 and D2, also correlated significantly with the Lebel symptom score, for D1 ($r = 0.62$, $P \leq 0.01$) and for D2 ($r = 0.69$, $P \leq 0.01$).

	Controls	AR + HDM	NAR
Lebel after HDM ≥ 6	0/17	11/14	0/19
PNIF decrease after HDM $> 40\%$	0/17	10/14	0/19
Lebel ≥ 6 AND PNIF decrease $> 40\%$	0/17	8/14	0/19
Lebel ≥ 6 OR PNIF decrease $> 40\%$	0/17	13/14	0/19
Lebel score	0 (0-2)	7.5 (4-10)	2 (0-5)
PNIF Reduction [L/min, median and range]	0 (+20-30)	70 (30-145)****/***	10 (+30-60) ^{ns}
PNIF Reduction [% , median and range]	0 (+20.00-15.79)	55.85 (19.05-100)****/***	7.14 (+25.00-40.00) ^{ns}

Table 3. Results of nasal provocation test with HDM allergen HDM (house dust mite), PNIF (peak nasal inspiratory flow). ****/*** - $P \leq 0.0001$ compared to controls, $P \leq 0.001$ compared to NAR; *n.s.*- no significant difference compared to controls

The higher the sIgE in nasal secretion, the higher the evaluated Lebel symptom score after HDM provocation.

All controls and subjects with NAR with a negative Radioallergosorbent Test (RAST) (<0.35 kUA/L) for D1 and D2 in nasal secretion ($n = 28$) also had a negative Lebel score and PNIF after HDM provocation.

DISCUSSION

In our study we were able to investigate a collective of non-selected adult individuals suffering from NAR and compare the findings to subjects suffering from AR + HDM as well as healthy controls. Since all subjects were recruited by public posting, no selection bias was to be expected, resulting in a better characterization of the prevalence of LAR in the field of chronic rhinitis.

In concordance with findings of previous investigations, the nasal sum score between subjects with AR + HDM and NAR did not differ significantly.^{11,24} As expected, total and sIgE was significantly elevated in the serum of subjects with AR + HDM. In addition, we were able to detect significantly elevated levels of total IgE and sIgE to HDM in nasal fluid of subjects with AR + HDM demonstrating that our technique of local IgE measurement was appropriate. In contrast, none of the subjects suffering from NAR showed elevated levels of total IgE and sIgE to HDM in the nasal fluid. In keeping with these findings none of our subjects with NAR had a positive reaction to NPT with HDM.¹¹ Since we were able to detect elevated levels of IgE and sIgE in the AR + HDM group, attribution of the negative test results to methodological errors is highly unlikely.

Our findings on sIgE are in line with the results obtained by Becker et al, who analyzed nasal secretion of subjects with NARES using a state of the art allergen chip.¹⁸ Of the 19 subjects included in their study, none showed presence of LAR in the immuno-chip-analysis. However, these findings and our results are contrary to results published by others.^{8,11} These discrepancies are difficult to explain. Rondón et al were able to detect nasal specific IgE to HDM in a substantial percentage

of subjects suffering from perennial NAR using nasal lavage.¹¹

One could speculate that the presence of very low specific IgE levels in nasal secretion could lead to false negative results in the NAR group due to a lack of sensitivity regarding the measuring method. However, the test was carried out in one of the world's most renowned allergological laboratories and that measurable and specific IgE was detected by other working groups in measurable quantities in NAR subjects.^{11,25} Furthermore, as nasal lavage actually dilutes the secretions further, it makes a specific measurement even more unlikely. In addition, a pre-selection of subjects regarding perennial and non-perennial NAR might be also relevant.

By implication, therefore, our findings challenge the concept of a LAR which has emerged in the past years and is by some authors believed to be a pathological entity on its own,²⁶ whilst others stated that LAR might be an early form of NAR developing into AR or other kinds atopic diseases like Samter Widal triad.²⁷⁻²⁹ Recently a long term follow up study of 176 patients with LAR and 115 healthy controls was published, describing that LAR is a distinct clinical entity with a low rate of development to systemic atopy.²⁶

As we were unable to obtain either local sIgE in nasal fluid nor any positive results in the NPT, the prevalence of LAR in the field of NAR has to be much lower in the investigated, non-selected population than previously reported.^{14,24} These discrepancies maybe related in part to demographic and genetic differences or technical reasons. Poor quality of SPT solution might also be attributable to negative SPT results and positive nasal IgE. However, most studies measured serum IgE to verify or dismiss systemic atopy. Of subjects with NAR, 23.81% showed sensitization against seasonal allergens in the SPT. In that regard one could argue that this subgroup of patients is not a typical NAR collective. However, all patients tested reported perineal symptoms and tests were performed outside the season for the specific pollen allergen. As none of the NAR subjects showed any sensitization to molds or dander attributing the findings to other allergens seems unlikely.

Some studies used nasal lavage for local IgE detection. Therefore, attribution of the high prevalence of local sIgE to the used collection technique seems unlikely, as the dilution effect of nasal lavage has been shown to alter sensitivity compared to obtaining nasal fluid straight from the nasal cavity.³⁰⁻³²

In contrast to other studies, our population was not highly selected by an otorhinolaryngology center. Therefore, we truly believe that our study is representative of the normal population in Germany. Due to the public posting, our study group consisted of individuals with nasal symptoms. As study recruitment was done in a metropolitan area of Frankfurt, the subjects recruited had a diverse geographical and ethnical background. In addition, the subjects' age and health profile are similar to individuals investigated by other working groups.^{11,18}

Biopsies from nasal mucosa would maybe help to further investigate the prevalence of nasal IgE and would give a more detailed insight into the immunopathological changes present in NAR as previously described.^{33,34} As obtaining biopsies are invasive, new techniques for immunological analysis present an appealing concept.^{30,35}

CONCLUSION

Nasal IgE is present in a substantial amount in subjects with AR + HDM allergy, but not in NAR. In a non-selected population with NAR, exclusive local production of IgE is absent. Therefore, our findings challenge the emerging concept of LAR.

Abbreviations

AR: allergic rhinitis; SPT: skin prick test; sIgE: allergen-specific IgE; HDM: house dust mite; NARES: non-allergic rhinitis with eosinophilia-syndrome; LAR: local allergic rhinitis; NPT: nasal provocation tests; GCP: Good Clinical Practice; D1: Dermatophagoides pteronyssinus; D2: Dermatophagoides farinae; AR + HDM: allergic rhinitis with house dust mite allergy; ISAAC: International Study of Asthma and Allergies in Childhood questionnaire; FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; PNIF: peak nasal inspiratory flow; SD: standard deviation; RAST: Radioallergosorbent Test

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Consent for publication

All authors verified their approval with the publication of the manuscript by providing a written consent for publication.

Consent to participate

A written informed consent was obtained by all participants.

Ethics approval

The study was approved by the Frankfurt ethics committee and performed in accordance with the declarations of Good Clinical Practice (GCP). Furthermore, the study was registered on [ClinicalTrials.gov](https://clinicaltrials.gov) NCT02810535.

Availability of data and materials

Raw data of this study are not available for public disclosure.

Authors' contributions

J. Eckrich and J. Hinkel made substantial contributions regarding the design of the work as well as the acquisition, analysis, and interpretation of data for the work. They were substantially involved in the drafting of the manuscript and the revision process. Both approved the manuscript upon submission and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Since J. Eckrich and J. Hinkel equally contributed to this work they are considered both as first authors.

A. Fischl made substantial contributions regarding the analysis, and interpretation of data for the work. Furthermore she was involved in the drafting of the manuscript and the revision process. She approved the manuscript upon submission and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

E. Herrmann made substantial contributions regarding the study design and was substantially involved in statistical analysis, and interpretation of data for the work. Furthermore she was involved in the drafting of the manuscript and the revision process, and approved the manuscript upon submission and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

G. Holtappels and C. Bachert made substantial contributions in the field of data acquisition, analysis, and interpretation of data for the work. Furthermore they were involved in the drafting of the manuscript and the revision process. Both approved the manuscript upon submission and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

S. Zielen: Made substantial contributions regarding the conception and design of the work and was involved in the acquisition, analysis, and interpretation of data for the manuscript. Furthermore he contributed substantially to the drafting of the manuscript and the revision process. He approved the manuscript upon submission and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of competing Interest

The authors report no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.waojou.2020.100129>.

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REFERENCES

- Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J*. 2004;24(5):758-764.
- Wheatley LM, Togias A. Clinical practice. Allergic rhinitis. *N Engl J Med*. 2015;372(5):456-463.
- Eifan AO, Durham SR. Pathogenesis of rhinitis. *Clin Exp Allergy*. 2016;46(9):1139-1151.
- Ellis AK, Soliman M, Steacy L, et al. The Allergic Rhinitis - clinical Investigator Collaborative (AR-CIC): nasal allergen challenge protocol optimization for studying AR pathophysiology and evaluating novel therapies. *Allergy Asthma Clin Immunol*. 2015;11(1):16.
- Scadding G, Hellings P, Alobid I, et al. Diagnostic tools in Rhinology EAACI position paper. *Clin Transl Allergy*. 2011;1(1):2.
- Scadding GK, Kariyawasam HH, Scadding G, et al. BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis. *Clin Exp Allergy*. 2017;47(7):856-889 (Revised Edition 2017; First edition 2007).
- Samter M, Becker EL. Ragweed reagins in nasal secretion. *PSEBM (Proc Soc Exp Biol Med)*. 1947;65(1):140-141.
- Huggins KG, Brostoff J. Local production of specific ige antibodies in allergic-rhinitis patients with negative skin-tests. *Lancet*. 1975;2(7926):148-150.
- Sennekamp J, Noldeke H, Berdel D. Positive nasal provocation tests with negative skin-tests. *Allergologie*. 1987;10(5):167-172.
- Rondon C, Campo P, Togias A, et al. Local allergic rhinitis: concept, pathophysiology, and management. *J Allergy Clin Immunol*. 2012;129(6):1460-1467.
- Rondon C, Romero JJ, Lopez S, et al. Local IgE production and positive nasal provocation test in patients with persistent nonallergic rhinitis. *J Allergy Clin Immunol*. 2007;119(4):899-905.
- Auge J, Vent J, Agache I, et al. EAACI Position Paper on the Standardization of Nasal Allergen Challenges. *Allergy*. 2018;73(8):1597-1608. <https://doi.org/10.1111/all.13416>.
- Litvyakova LI, Baraniuk JN. Nasal provocation testing: a review. *Ann Allergy Asthma Immunol*. 2001;86(4):355-364. quiz 364-5, 386.
- Carney AS, Powe DG, Huskisson RS, Jones NS. Atypical nasal challenges in patients with idiopathic rhinitis: more evidence for the existence of allergy in the absence of atopy? *Clin Exp Allergy*. 2002;32(10):1436-1440.
- Bozek A, Scierski W, Ignasiak B, Jarzab J, Misiolek M. The prevalence and characteristics of local allergic rhinitis in Poland. *Rhinology*. 2019;57(3):213-218.
- Ishida M, Matsune S, Wakayama N, Ohashi R, Okubo K. Possibility of local allergic rhinitis in Japan. *Am J Rhinol Allergy*. 2020;34(1):26-34.
- Tao XY, Ng CL, Chen D, et al. Clinical characteristics and allergen sensitization patterns of patients with local allergic rhinitis in southern China. *Int Arch Allergy Immunol*. 2018;175(1-2):107-113.
- Becker S, Rasp J, Eder K, Berghaus A, Kramer MF, Groger M. Non-allergic rhinitis with eosinophilia syndrome is not associated with local production of specific IgE in nasal mucosa. *Eur Arch Oto-Rhino-Laryngol*. 2016;273(6):1469-1475.
- Bez C, Schubert R, Kopp M, et al. Effect of anti-immunoglobulin E on nasal inflammation in patients with seasonal allergic rhinoconjunctivitis. *Clin Exp Allergy*. 2004;34(7):1079-1085.
- Fischl A, Eckrich J, Passlack V, et al. Comparison of bronchial and nasal allergen provocation in children and adolescents with bronchial asthma and house dust mite sensitization. *Pediatr Allergy Immunol*. 2020;31(2):143-149.
- Auge J, Vent J, Agache I, et al. EAACI Position paper on the standardization of nasal allergen challenges. *Allergy*. 2018;73(8):1597-1608.
- Riechelmann H, Bachert C, Goldschmidt O, et al. Nasal provocation tests in diseases of the upper airways. *Allergologie*. 2002;25(9):489-496.
- Lebel B, Bousquet J, Morel A, Chanal I, Godard P, Michel FB. Correlation between symptoms and the threshold for release of mediators in nasal secretions during nasal challenge with grass-pollen grains. *J Allergy Clin Immunol*. 1988;82(5 Pt 1):869-877.
- Rondon C, Campo P, Galindo L, et al. Prevalence and clinical relevance of local allergic rhinitis. *Allergy*. 2012;67(10):1282-1288.

25. Colavita L, Catalano N, Sposito G, et al. Local allergic rhinitis in pediatric patients: is IgE dosage in nasal lavage fluid a useful diagnostic method in children? *Int J Mol Cell Med*. 2017;6(3):174-182.
26. 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.
27. Moneret-Vautrin DA, Hsieh V, Wayoff M, Guyot JL, Mouton C, Maria Y. Nonallergic rhinitis with eosinophilia syndrome a precursor of the triad: nasal polyposis, intrinsic asthma, and intolerance to aspirin. *Ann Allergy*. 1990;64(6):513-518.
28. Sennekamp J, Joest I, Filipiak-Pittroff B, von Berg A, Berdel D. Local allergic nasal reactions convert to classic systemic allergic reactions: a long-term follow-up. *Int Arch Allergy Immunol*. 2015;166(2):154-160.
29. Bachert C, Wahl R, Bousquet J, et al. Determination of IgE-specificities in nasal secretions and sera of allergic subjects by crossed radio-immunoelectrophoresis. *Clin Exp Allergy*. 1990;20(3):305-309.
30. Campo P, Del Carmen Plaza-Seron M, Eguiluz-Gracia I, et al. Direct intranasal application of the solid phase of ImmunoCAP(R) increases nasal specific immunoglobulin E detection in local allergic rhinitis patients. *Int Forum Allergy Rhinol*. 2018;8(1):15-19.
31. Watelet JB, Gevaert P, Holtappels G, et al. Collection of nasal secretions for immunological analysis. *Eur Arch Oto-Rhino-Laryngol*. 2004;261(5):242-246.
32. Campo P, Rondon C, Gould HJ, Barrionuevo E, Gevaert P, Blanca M. Local IgE in non-allergic rhinitis. *Clin Exp Allergy*. 2015;45(5):872-881.
33. Powe DG, Huskisson RS, Carney AS, Jenkins D, Jones NS. Evidence for an inflammatory pathophysiology in idiopathic rhinitis. *Clin Exp Allergy*. 2001;31(6):864-872.
34. Song J, Wang H, Zhang YN, et al. Ectopic lymphoid tissues support local immunoglobulin production in patients with chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol*. 2018;141(3):927-937.
35. Hamizan AW, Rimmer J, Alvarado R, et al. Turbinate-specific IgE in normal and rhinitic patients. *Am J Rhinol Allergy*. 2019;33(2):178-183.