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AIRWAYS DISEASE

IgE antibody repertoire in nasal secretions of children and adults with seasonal allergic rhinitis: A molecular analysis

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Editor: Ömer Kalaycı**Abstract**

Background: There is growing interest both in testing IgE in nasal secretions (NS) and in molecular diagnosis of seasonal allergic rhinitis (SAR). Yet, the reliability of nasal IgE detection with the newest molecular assays has never been assessed in a large cohort of pollen allergic patients.

Objective: To investigate with microarray technology and compare the repertoires of specific IgE (sIgE) antibodies in NS and sera of a large population of children and adults with SAR.

Methods: Nasal secretions were collected with an absorbent device (Merozel 2000[®], Medtronic) and a minimal dilution procedure from 90 children and 71 adults with SAR. Total IgE (tIgE) (ImmunoCAP, Thermo Fisher Scientific (TFS)) and sIgE antibodies against 112 allergen molecules (ISAC-112, TFS) were measured in NS and serum.

Results: Nasal sIgE was detectable in 68.3% of the patients. The detected nasal sIgE antibodies recognized airborne (88%), vegetable (10%), and animal food or other (<1%) allergen molecules. The prevalence and average levels of sIgE in NS and serum were highly interrelated at population level. A positive nasal sIgE antibody to a given molecule predicted the detection of the same antibody in the patient's serum with a specificity of 99.7% and a sensitivity of 40%.

Conclusions: The concentration of sIgE is much lower in nasal secretions than in the serum. sIgE assays with very high analytical sensitivity and sampling methods with minimal dilution will be therefore needed to validate nasal secretions as alternative to serum in testing the sIgE repertoire.

Abbreviations: AR, Allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; CI, Confidence interval; FEIA, Fluorescent enzyme immunoassay; GINA, Global Initiative for Asthma; HDM, House dust mite; ICC, Intraclass correlation; IgE, Immunoglobulin E; ImmunoCAP, Immunoassay capture test; ISAC, ImmunoCAP Solid-Phase Allergen Chip; ISU, ISAC Standardized Units; kUA/L, Kilounits/liter; NS, Nasal secretions; N-sIgE, Nasal specific IgE; Pe, Pooled estimated; SAR, Seasonal allergic rhinitis; SD, Standard deviation; sIgE, Specific Immunoglobulin E; SPT, skin prick test; tIgE, Total IgE; TPC, Total protein concentration; WNS, Weight of collected nasal secretions.

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KEYWORDS

allergen molecules, allergic rhinitis, diagnosis, immunoglobulin E, microarray, nasal secretions, pollen allergy

1 | INTRODUCTION

There is growing interest in the examination of nasal secretions (NS) in patients affected by allergic rhinitis (AR).¹ Evidence of a local production of immunoglobulin E (IgE), the key mediator in allergic diseases, in the nasal mucosa, was first discovered in the 1970s²⁻⁴ and further investigated since then.⁵⁻⁸ More recently, the analysis of NS has been proposed as a useful non-invasive approach to AR diagnosis,⁹⁻¹¹ for definition and diagnosis of allergic rhinitis in children¹² and adults^{13,14} with no systemic IgE sensitization ("local allergic rhinitis [LAR]"), and to establish an endotype for non-allergic rhinitis (NAR).^{15,16} Moreover, nasal specific IgE (N-sIgE) has been proposed as a control parameter for the efficacy of allergen-specific immunotherapy (AIT).¹⁷⁻¹⁹ IgE testing in NS has been also suggested as a potentially beneficial non-invasive tool to identify the local onset of IgE production in small children.^{20,21}

Many efforts have been made to standardize the methodology of NS collection.¹ The list includes the collection of secretions from the nasal cavity through aspiration devices,⁹ nasal washing,⁴ and absorbent materials.^{3,10,22,23} Major targets in NS sampling are preventing dilution artefacts and minimize the patient's discomfort.¹ However, there is still no international consensus on optimal validated standards for collection, procession, and evaluation of NS.¹ Studies testing N-sIgE in AR often differ in procedures and have small population numbers. The most used extract-based singleplex IgE assays have the disadvantageous need of high sample volumes, leading to higher dilution. IgE in NS is present at quite low concentrations,²⁴ so that sample dilution often pushes them below the detection limits of classic IgE assays.²⁵

The development of microarray technologies provided a highly sensitive immunologic assay requiring only microliters of sample to test IgE specificities against large panels of allergenic molecules.²⁶ In a preliminary work, we have successfully applied this technology on NS for sIgE detection against mite molecules in patients with AR.¹⁰

We aimed the present study to investigate the repertoire of antigen-specific IgE antibodies in NS with biochip technology. We intended to characterize the local IgE reactivity profiles of allergic patients on larger scale and compare them to their serum IgE responses. To these ends, we have examined NS and sera of 161 pediatric and adult patients affected by seasonal allergic rhinitis (SAR), participating in a broader study on pollen allergy in Italy.²⁷ In more detail, we tested specific IgE reactivity to 112 allergenic molecules present on a microarray (ISAC-112TM; TFS) in their NS and sera. To our knowledge, this is the first time that local allergen-specific IgE antibodies have been assessed in NS of such a large population of AR patients using biochip technology.

Key Message

We investigated the allergen specific IgE repertoire in nasal secretions (NS) of children and adults with seasonal allergic rhinitis (SAR) with biochip technology. As a non-invasive method, IgE testing in NS could become very interesting in the diagnostic work-up of SAR, especially in pediatrics. Nasal secretions are a suitable medium for IgE-testing and reflect at population level the systemic sensitization profiles. Testing nasal IgE to allergen molecules predicted with a high specificity but low sensitivity the serum sensitization profile of a large population of SAR patients. Development of biochips with higher sensitivity could validate NS as an alternative to serum in the diagnostic of pollen allergy.

2 | METHODS

2.1 | Study design and population

Subjects were participants of an observational longitudinal clinical study, recruited in 2016 among patients affected by SAR due to pollen. Children (10-18 years) were enrolled in the Department of Pediatrics of "Sandro Pertini" Hospital in Rome (Italy), and adults (19-60 years) were enrolled in the Hospital "S. Maria degli Angeli" of Pordenone (Italy).²⁷ The recruited patients underwent interviews with standardized questionnaires, skin prick test (SPT), and blood drawing, followed by a second visit, including NS collection. A subset of patients underwent a second blood drawing, performed the same day as the NS sampling (for further details, see Methods in Appendix S1). The local ethic committees have approved the study design and procedures.

2.2 | Collection and processing of NS

Nasal secretions were collected with a sponge ("Meroceol 2000[®] Kennedy Laminated Sinustent", 3.5 cm × 0.6 cm × 1.2 cm, Medtronic Xomed) (for further details, see Methods in Appendix S1).¹⁰ A novelty of this study consists in the dilution process of the NS samples. We designed a "minimal dilution method," based on the application of a different, personalized dilution factor inversely proportional to the volume of the NS collected in the individual patient, thereby getting enough sample volume for the envisaged analyses and to create a large biobank of nasal secretions from well-phenotyped AR

patients, while keeping the dilution at a minimum and maximizing test sensitivity. The dilution factors ranged from 2× (WNS \geq 700 μ L) to 10× (WNS \leq 140 μ L). We derived the concentration of proteins and IgE in the collected samples by multiplying the values measured in the diluted samples available for testing by their respective dilution factor.

2.3 | Total and specific IgE

Total IgE (tIgE) levels were measured in serum and NS with single ImmunoCAP fluorescent enzyme immunoassay (FEIA) (TFS). Specific IgE to 112 allergenic molecules was measured with a multiplex microarray (ISAC-112™, TFS) in NS and serum (for further details, see Methods in Appendix S1).

2.4 | Statistics

Statistical analyses were performed using STATA v 14 (StataCorp). A P -value $<$.05 was considered as statistically significant. Data were presented as mean (standard deviation, SD), as median (interquartile range, IQR; or min-max range, range) when continuous, and as numbers and percentage when categorical. The association between two continuous variables was established by Pearson's linear correlation coefficient or, when appropriate, by non-parametric Spearman's rho coefficient. IgE responses and levels to a given allergenic source were defined by the presence of nasal sIgE antibodies against one or more of its examined species-specific molecules (see Methods in Appendix S1).

3 | RESULTS

3.1 | Study population

We examined 161 patients with SAR: 90 children (aged 10 years–18 years) recruited in Rome and 71 adults (aged 18 years–65 years) recruited in Pordenone. About 2/3 of the patients were affected by a moderate/severe, persistent SAR in both age groups (70% and 66.7% for children and adults, respectively). Most children and a considerable proportion of adults were highly polysensitized. Timothy grass (96.7%), olive tree (90.0%), and cypress (87.8%) in Rome, and timothy grass (83.1%), Birch (56.3%), and cypress (38.0%) in Pordenone were the most frequently sensitizing pollens, tested by SPT. Since the pediatric and the adult population were recruited in two different areas, one in the center and one in the northeast of Italy, with different variety of plants and pollination seasons and concentrations, this may have affected some differences between the two population groups. Most of the children and about half of the adults were also sensitized to indoor airborne allergens (see Table S1 in Appendix S1).

TABLE 1 Characteristics of nasal secretion samples (n = 161)

	Mean	SD	Median	Range
Volume (μ L)	643	344.9	600	50-2233
Dilution factor	3.2	2.0	2.3	2-10
Total protein (mg/mL) ^b	9.2 ^a	1.7	8.8	0.5-91.7
Total IgE (kU/L)	26.9 ^a	2.1	24.1	8.1-211.8

^aGeometric mean.

^b5% of missing values.

3.2 | Characteristics of NS samples

The collected samples of NS broadly varied with regard to their volume. Based on our "minimal dilution method," the applied dilution factor changed accordingly (see Figure S1A in Appendix S1). The concentration of total protein and tIgE in NS was highly heterogeneous (Table 1). Total protein concentration (TPC) and tIgE showed both an inverse relationship with the collected volume (see Figure S1B,C and Results in Appendix S1).

3.3 | Specific IgE in NS and sera

sIgE was detected in the NS of 110/161 patients (68.3%), with a broad range of recognized molecules (1-26). By contrast, sIgE was found in the serum of all the patients except one (99.4%). The number of recognized molecules in the serum ranged from 2 to 59. Most of the detected N-sIgE antibodies were directed to airborne molecules, the most frequent being Phl p 1 (47%), Phl p 5 (33%), Cup a 1 (27%), Cyn d 1 (25.5%), and Der p 2 (25.5%), while N-sIgE antibodies to food animal molecules were detected in only one patient (Figure 1, left). The average levels of N-sIgE toward each molecule ranged between 0.2 ISU (Api m 4) and 11.5 ISU (Bet v 1) and were unrelated to the prevalence of detected responses to the respective molecule (Figure 1, right). Reflecting the trends at the molecular level, the IgE responses to airborne sources were the most frequently detected in the population, with timothy grass ranking first (51.55%), followed by house dust mites (31.06%), cypress (27.33%), bermuda grass (25.47%), and birch (22.98%) (Figure 2). The prevalence of N-sIgE against vegetable foods was below 10% for all tested molecules, N-sIgE against animal foods was sporadic (Figure 2). The overall prevalence of IgE reactivity was highest to airborne, intermediate to vegetable food, and lowest to animal food allergens, both in NS and in serum (see Table S2 in Appendix S1).

3.4 | Relationship of local vs systemic sensitization

At *population* level, the prevalence (Spearman's rho = 0.906, $P <$.001) (Figure 3A) and average levels (Spearman's rho = 0.726, $P <$.001) (Figure 3B) of the IgE responses to each of the examined 112 molecules in the 161 NS samples were highly correlated with the IgE responses observed in the 161 sera, but lower. We examined the relationship of local vs systemic sensitization *at source level*, by using

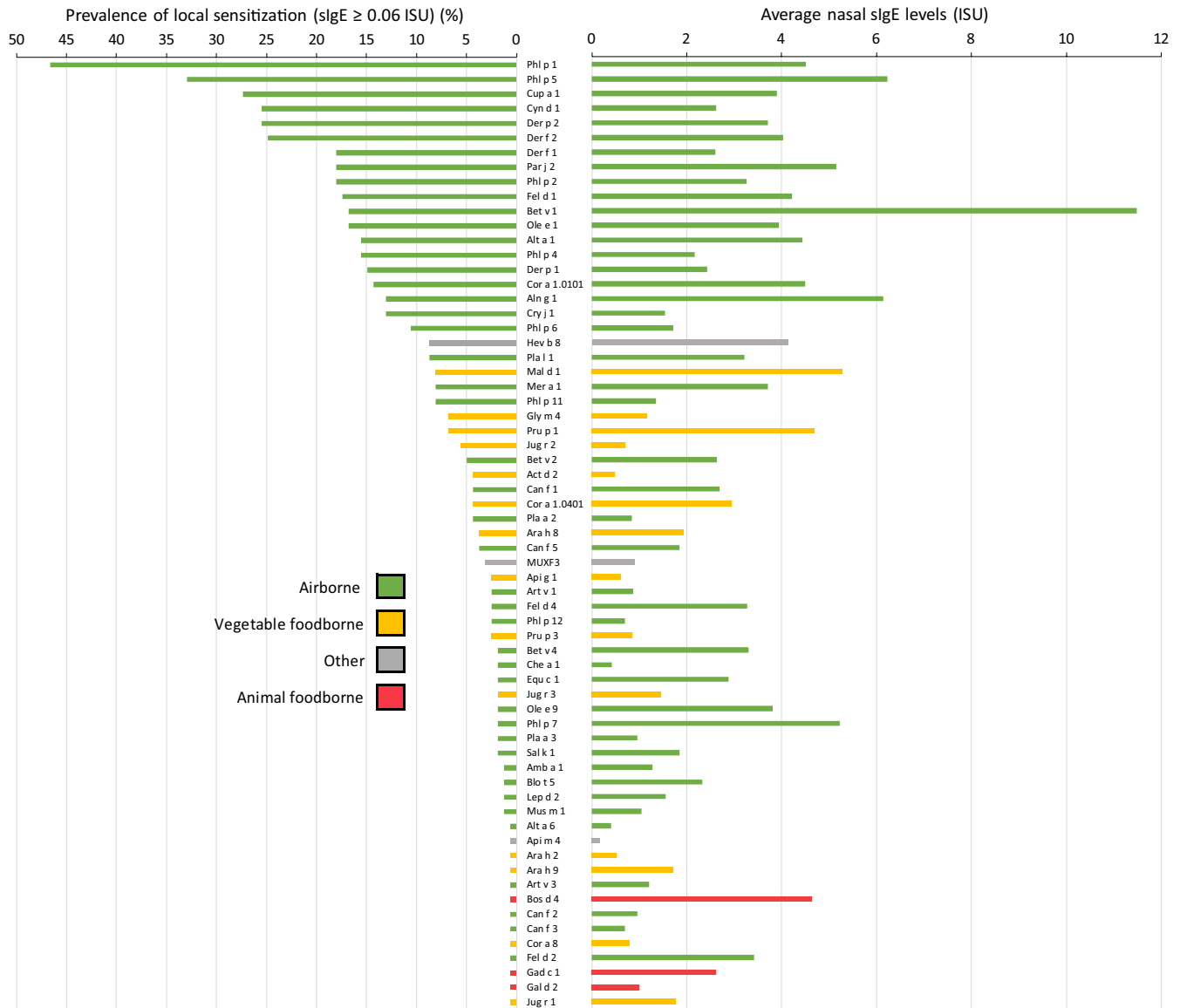


FIGURE 1 Prevalence (left) and average levels (right) of sIgE to allergen molecules in nasal secretions of 161 SAR patients. The results of molecules with at least 1 positive IgE value (≥ 0.06 ISU) are shown. Colors show the most relevant exposure route for each molecule (airborne [green], vegetable food [orange], animal food [red], other [gray])

SPT outcomes to compare NS and sera sIgE testing (see Results and Figure S2 in Appendix S1).

3.5 | Prediction of sIgE in the serum by testing sIgE in NS

When examined at *individual* level, the presence of sIgE to major allergenic molecules in NS predicted with extremely high specificity (pooled estimated (pe) = 99.7%) but with low sensitivity (pe = 40.0%) the presence in the serum of sIgE to the same molecule (Table 2). When this analysis was repeated after increasing the cutoff of serum sIgE positivity from 0.1 ISU to 3 ISU, the sensitivity of N-sIgE determination increased (pe = 53.2%), while its specificity remained extremely high (pe = 96.1%) (see Table S3 in Appendix S1). The best

performance, in terms of combination of sensitivity and specificity, of testing N-sIgE was observed at the cutoff point for serum sIgE positivity of 3 ISU (see Figure S5 in Appendix S1).

4 | DISCUSSION

We used the state of the art allergen chip technology to investigate the allergen-specific IgE repertoire in NS of adults and children with SAR. This approach could be particularly beneficial in children because of its non-invasive procedure. We found that NS, if collected and processed with the lowest possible dilution, are a suitable medium for IgE testing and reflect at population level the systemic sensitization profiles. We also found that the detection of N-sIgE antibodies to an allergen molecule predicts with absolute confidence

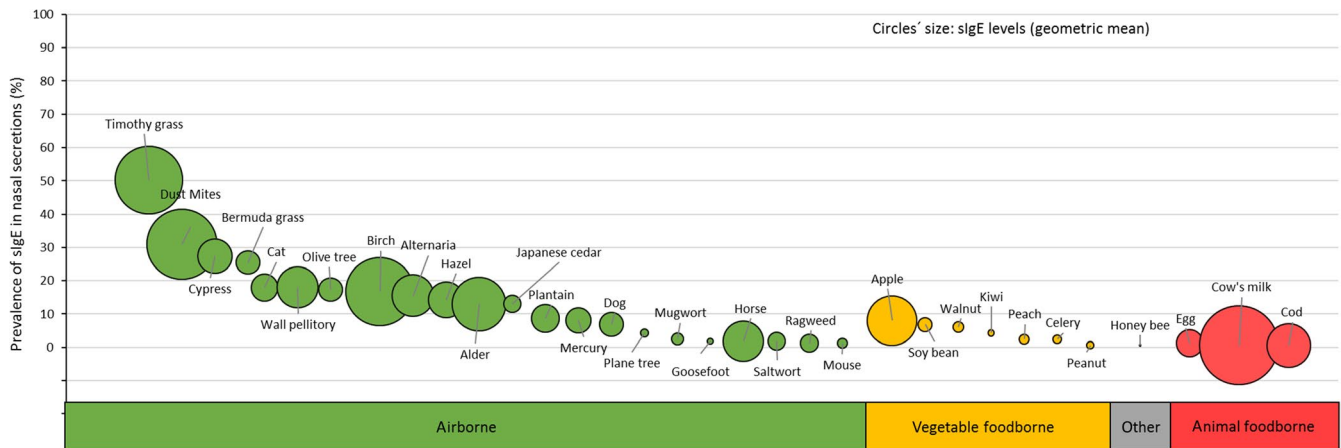


FIGURE 2 Prevalence and levels of sIgE responses to allergenic sources in the NS of 161 SAR patients. Circles show the prevalence (y-axis) and levels (diameter) of detectable sIgE responses (≥ 0.06 ISU) to allergenic sources (see Methods for definition). The exposure category to which the allergenic sources of individual molecules belong is specified: airborne (green), vegetable food (orange), animal food (red), other (gray). The values are ordered from left to right according to the prevalence in each exposure category

the presence of those antibodies in the serum. Notwithstanding, our data also suggest that sIgE detection in diluted nasal secretions with the current biochip technology is not sensitive enough to provide us with a valid and reliable substitute to the serum sIgE measurements. To our knowledge, this is the first study describing the nasal IgE repertoire to a broad range of allergenic molecules in such a large population of patients suffering from SAR.

4.1 | NS for IgE testing

Nasal IgE originate mainly from the spillover from blood, but evidence has been given that the nasal mucosa itself is a capable primary site for sIgE production.²⁴ Therefore, methods to measure allergen-specific IgE at a nasal level in patients with AR are of great interest.¹ An effective local IgE assessment could provide a non-invasive diagnostic tool for AR that would be especially advantageous in pediatrics.^{20,21} The NS collection with sinus sponges has already been successfully assessed on younger children²⁰; however, the systematic assessment of the tolerance of the procedure and the compliance of children compared to other techniques has never been done. Local sIgE detection in NS could also be an important non-invasive way to differentiate between non-allergic rhinitis and allergic rhinitis,^{15,16} especially in the absence of systemic sensitization.¹²⁻¹⁴ In our study, NS were collected from children and adults easily and without complications using an absorptive device already tested and validated.²³ We succeeded in measuring tIgE and TPC in each of the 161 samples. This outcome was facilitated by avoiding excessive dilution, which could reduce the concentration of IgE below the detection limits of immunoassays.²³ Because of the rhinorrhea characteristic of the inflammatory disease, a natural dilution is already occurring and sample dilution is not limited to the one applied by the operator during procession.²² Accordingly, the original TPC in our samples was inversely related to the amount of secretion collected, and so was the tIgE concentration (see Figure S1 in Appendix S1).

4.2 | IgE repertoire in NS and in serum

In southern Europe, patients are exposed to the simultaneous pollination of a rich variety of allergenic plants.²⁷ Hence, polysensitization to many different pollen sources is typical in patients with SAR living in these areas.²⁷ This characteristic emerged also in our study population. The repertoire of allergens recognized by IgE in the patients' secretions at a molecular (Figure 1) and source level (Figure 2) confirmed a predominance of airborne-specific molecules. This scenario was almost identical when the sera of our study population were examined (see Figures S3 and S4 in Appendix S1). The overall prevalence values (Figure 3A) and average levels (Figure 3B) of N-sIgE, respectively, showed a very good correlation with those found in the sera, although both were consistently lower in the NS. Similarly, the prevalence of IgE antibodies to allergen sources in the NS was highly related, although at lower values, to that of positive SPT to the same sources (see Figure S2 in Appendix S1). Interestingly, a few patients showed moderate to high levels of IgE to milk, egg, or cod fish molecules, indicating that the IgE repertoire of the NS is not limited to airborne molecules. We are prompted to speculate that the IgE repertoire of NS of young infants with cow milk, egg, or other food allergies is mostly dominated by those animal food allergens. The presence of IgE to animal foods has been already described in the nasal mucosa,²⁸ but this aspect remains quite open for further investigations.

4.3 | Testing sIgE in NS

No sIgE was detected with the ISAC test in nasal secretions of almost 1/3 (31.3%) of our pollen allergic patients, while their sera were positive to the same ISAC test. Accordingly, the sensitivity of testing IgE in the NS in predicting the presence of IgE to the respective molecule in the serum was quite low for all the examined molecules (overall estimate of sensitivity = 40%). However, the specificity and the positive predictive value were extremely high. Data about the N-sIgE presence among patients

TABLE 2 Prediction of serum IgE responses by testing IgE in nasal secretions in 161 patients with SAR with a serum cutoff of 0.1 ISU

	Sensitivity	Specificity	Accuracy	PPV	NPV
	%	%	%	%	%
Allergen molecules ^a					
Phl p 1	51	100	55	100	15
Phl p 5	58	100	76	100	64
Cup a 1	38	100	55	100	38
Cyn d 1	33	100	49	100	32
Der p 2	66	99	86	98	82
Der f 2	62	98	84	95	81
Par j 2	58	100	87	100	84
Fel d 1	30	100	60	100	51
Phl p 2	36	99	68	97	62
Der f 1	49	100	81	100	77
Ole e 1	30	100	60	100	52
Bet v 1	30	83	53	100	43
Alt a 1	55	99	87	96	85
Phl p 4	25	98	55	96	47
Der p 1	42	100	80	100	76
Cor a 1.0101	41	100	80	100	76
Cry j 1	22	100	52	100	44
Aln g 1	45	100	84	100	81
Phl p 6	23	100	65	100	61
Pla l 1	35	100	84	100	82
Hev b 8	37	100	85	100	84
Mal d 1	26	100	77	100	75
Mer a 1	33	100	84	100	82
Phl p 11	34	99	85	92	84
Gly m 4	28	98	84	82	85
Pru p 1	21	99	76	91	75
Pooled estimate	40	99.7			

^aOnly molecules with at least 10 subjects who had a molecule-specific IgE response were considered for this analysis.

of NS collection in a nested study of 21 patients were highly related to those obtained at the recruitment visit (Pearson's $r = .92$, $P < .001$; and ICC = 0.79, 95% CI = 0.77-0.81, respectively) and had a similar predictive capacity in relation to the serum sIgE outcomes (see Table S4 in Appendix S1). Second, since the local IgE detection can be highly influenced by environmental condition, and the moment of the NS collection did not always cover all the pollination seasons or peaks of the allergens the patients where sensitized to, this could have affected the results. Third, we used one single microarray commercial method to test sIgE antibodies and cannot extend our conclusions to all other techniques currently available.

4.5 | Conclusions

Our study shows that the concentration of sIgE is much lower in nasal secretions than in the serum. Consequently, sIgE assays with

very high analytical sensitivity and sampling methods with minimal dilution will be therefore needed before nasal secretions can be validated as alternative to serum in testing the sIgE repertoire in patients with seasonal allergic rhinitis.

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CONFLICT OF INTEREST

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Scientific, Stallergenes-Greer, and HAL Allergy. The rest of the authors declare that they have no relevant conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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