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Immunoglobulin concentrations in nasal secretions differ between patients with an IgE-mediated rhinopathy and a non-IgE-mediated rhinopathy

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Nasal secretions from patients with an IgE-mediated rhinopathy, patients with a non-IgE-mediated rhinopathy, and healthy control subjects were collected with a newly developed direct aspiration system. Total protein, albumin, secretory IgA (sIgA), IgE, IgG, and IgM concentrations were measured in the nasal secretions to detect whether the nasal pathology is reflected in nasal secretion protein concentrations. It was found that protein and immunoglobulin concentrations in nasal secretions were inversely related to amount of secretion in the nasal cavity. Both patients' groups had a significantly higher sIgA to protein ratio than the healthy control subjects. Furthermore, patients with an IgE-mediated rhinopathy had significantly higher sIgA and IgM to total protein ratios in their nasal secretions than patients with a non-IgE-mediated rhinopathy. Probably these differences are due to changes in immunoregulation. (J ALLERGY CLIN IMMUNOL 1991;88:612-19.)

Key words: IgE-mediated rhinopathy, non-IgE-mediated rhinopathy, nasal secretion, immunoglobulins

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Abbreviations used

SPT: Skin prick test
sIgA: Secretory IgA
Ab: Antibody
AR: Allergic rhinitis
HRP: Horseradish peroxidase

Immune and inflammatory reactions in the upper respiratory tract are reflected in protein and immunoglobulin composition of nasal secretions.¹ However, the results of nasal secretion analysis in patients with

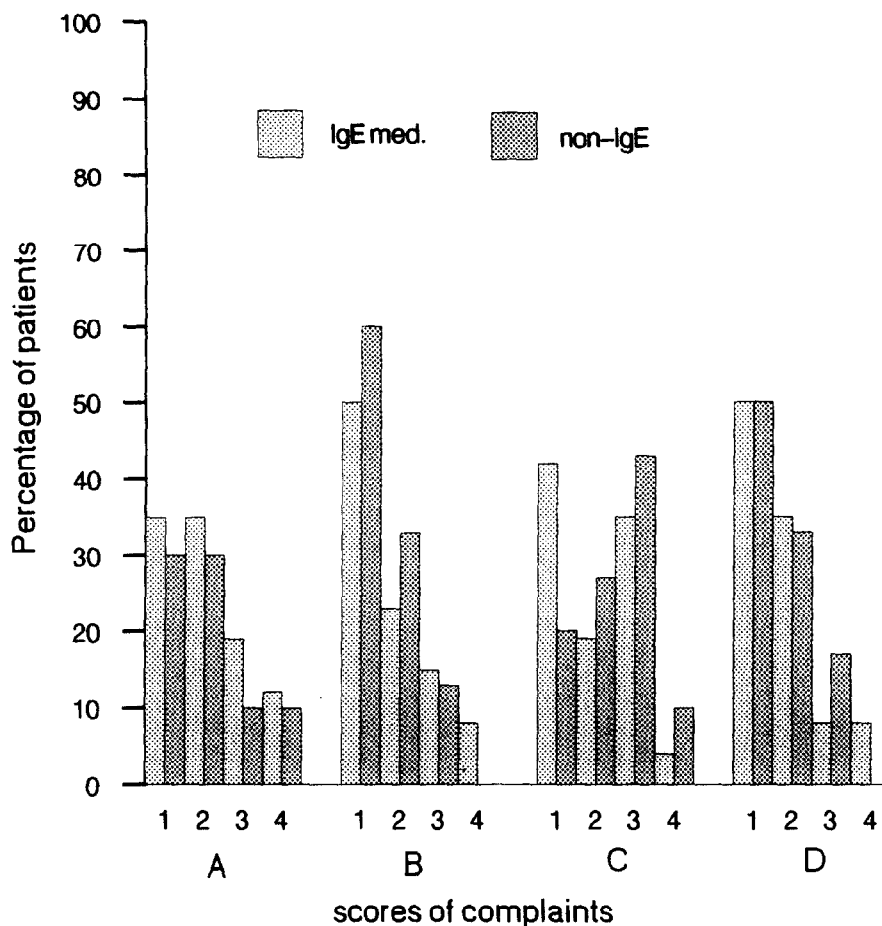


FIG. 1. Comparison of clinical data of the patients with an IgE-mediated rhinopathy and a non-IgE-mediated rhinopathy. A, sneezing; B, itching in the nose; C, obstruction; D, rhinorrhea. Scoring: 1, no complaints; 2, few complaints; 3, serious complaints; 4, severe complaints.

respiratory complaints have been variable. At least one of the reasons is the difficulty of collecting a representative sample. Throughout the years, most of the studies were performed on nasal secretions obtained by nasal lavages.²⁻⁴ Also, other, irritative methods have been used.^{5, 6} Using a filter paper method for the collection of nasal secretions, Illum and Balle⁷ found that patients with perennial rhinitis had higher albumin, IgE, and IgM concentrations in nasal secretions than healthy control subjects. In nasal lavage fluids of patients with AR, Pulido and Garcia-Calderon⁸ measured significantly higher concentrations of IgA, IgE, IgG, and IgM than in control subjects. In patients with rhinitis vasomotorica, this was found only for IgA and IgG.

In the present study, nasal secretions were collected from patients with an IgE-mediated rhinopathy, from patients with a non-IgE-mediated rhinopathy, and from healthy control subjects. A newly developed, rather nonirritative direct aspiration system was used.⁹

The secretions were analyzed for total protein, albumin, sIgA, IgE, IgG, and IgM to detect whether the two groups differ in nasal immunoglobulin levels and to what extent nasal pathology is reflected in nasal secretion protein concentrations.

MATERIAL AND METHODS

Patients

The study patients (N = 59) were first observed in the outpatient department of the Ear, Nose, and Throat clinic of the Vrije Universiteit in Amsterdam and were suspected of having an IgE-mediated rhinopathy on the basis of their medical history. Patients with nasal polyps or medication for nasal complaints were excluded from the study. Allergy screening for common inhalation allergens was performed with percutaneous SPTs (Phazet, Pharmacia Diagnostics, Uppsala, Sweden) and the determination of allergen-specific IgE (IgE FAST Plus test, 3M Diagnostic Systems, Santa Clara, Calif.). The criteria for allergy were a wheal >2 mm for the SPT and/or serum RAST class ≥ 2 (>0.70 PRU/ml) for any of the allergens tested. A positive hista-

TABLE IA. Clinical data of patients with IgE-mediated rhinopathy

No.	Sex	Age (yr)	Skin test	RAST	Total IgE
1	M	39	Ti, Ry, Mi	Mi	42
2	F	25	Ryg, Ti, Ry, Yo, Bi, Ho	Ryg, Ti	94
3	M	25	Ryg, Ti, Ry, Yo	Ryg, Ti, Mi	1770
4	M	30	Ryg, Ti, Ry, Yo	Ryg, Ti, Bi	198
5	F	19	Ti, Ry, Yo, Mi	Ti	251
6	F	28	Mi, Ca	Mi	207
7	F	43	Mi	—	121
8	F	30	Ti, Ry, Yo	—	19
9	F	21	Bi	—	67
10	M	18	Mi	—	19
11	M	30	Ryg, Ti, Ry, Yo, Al, Bi, Mi, Ca, Do	Ryg, Ti, Mi, Mo	749
12	M	38	Ryg, Ti, Ry, Yo, Mi, Ca, Ho	Ryg, Mi	374
13	F	33	Ryg, Ti, Ry, Yo	Ryg	30
14	M	40	Ryg, Ti, Ry, Yo	Ryg	340
15	M	20	Ryg, Ti, Ry, Yo	Ryg	178
16	M	23	Ti, Mi	Mi	153
17	F	25	Ryg, Ti, Ry, Yo, Bi, Mi, Ca	Ryg, Mi	288
18	M	43	Ryg, Ti, Ry, Yo, Al, Bi, Oa, Mi	Ryg, Ti, Mi	285
19	F	24	Ryg, Ti, Ry, Yo, Mi	—	250
20	F	43	Ryg, Ti, Ry, Yo, Al, Bi, Wa	Ryg, Ti	95
21	F	29	Ho, Do	—	106
22	M	45	Ryg, Ti, Ry, Yo, Mi	Ryg, Ti, Mi	51
23	F	23	Ti, Ry, Yo, Mi, Do	Mi	291
24	M	39	Ti, Ry, Yo, Ho, Do	—	729
25	F	33	Mi	Mi	185
26	M	19	Ryg, Ti, Ry, Yo	Ryg, Mi	670

Al, Alder; Bi, birch; Ca, cat hair; Do, dog hair; Ho, horse hair; Mi, mite; Mo, mold; Oa, oak; Ry, rye; Ryg, ryegrass; Ti, timothy; Wa, waybread; Yo, yorkshire fog.

TABLE IB. Clinical data of patients with a non-IgE-mediated rhinopathy

Symptoms	No.
A specific hyperreactivity of nasal mucosa	12
Nose obstruction	12
Allergy screening because of ear complaints	6
Cyst in sinus maxillaris	1
Recurrent sinusitis	2

mine control was performed routinely with each SPT. According to these criteria, 26 patients (13 female and 13 male patients, aged 19 to 44 years; mean age, 30 years) were classified as having an IgE-mediated rhinopathy (Table IA) and 33 patients (19 female and 14 male patients, aged 17 to 80 years; mean age, 30 years) as having a non-IgE-mediated rhinopathy (Table IB). Serum levels of IgA, IgG, and IgM of all these patients were within the normal range, 0.6 to 4.5 gm/L, 6.4 to 19.2 gm/L, and 0.4 to 3.6 gm/L, respectively. The results of symptom scoring for sneezing, itching in the nose, nose obstruction, and rhinorrhea for both groups of patients are illustrated in Fig. 1, and the results of allergy screening are presented in Table IA. The

group of 26 healthy control individuals (12 female and 14 male subjects, aged 19 to 38 years; mean age, 25 years) had no medical history of respiratory tract allergy and had not received any medication or had any symptoms of respiratory tract disease for at least 1 month before the collection of nasal secretion.

Collection and analysis of nasal secretions

Nasal secretions were collected for a period of about 1 minute between 10 AM and 3 PM by aspiration from the nonstimulated middle meatus and the medial surface of the inferior turbinate (twice) of each nasal cavity with the aspiration system described previously.⁹ Briefly, nasal secretions were aspirated with an outside siliconized metal aspiration tube into a disposable collection tube. The aspiration tube was washed with 0.5 ml of phosphate-buffered saline (0.1 mol/L of phosphate and 0.15 mol/L of NaCl, pH 7.4), which was added to the sample. Samples were obtained between August 1989 and February 1990. The aspiration procedure was well tolerated by the patients. Sample weights were determined from the weights of the collection tubes before and after sampling and the weights of added phosphate-buffered saline. The samples were cooled on ice immediately after collection, then homogenized on

TABLE II. Total protein, albumin, IgG, IgM, and sIgA concentrations in nasal secretions of patients with an IgE-mediated rhinopathy, patients with a non-IgE-mediated rhinopathy, and healthy control subjects*

	Weight of secretion (mg)	Total protein (mg/g)	Albumin (μ g/g)	IgG (μ g/g)	IgM (μ g/g)	sIgA (μ g/g)
IgE-mediated rhinopathy (N = 26)						
Range	19-147	2.67-27.44	4-11236	6-1685	15-342	337-6576
Median	70	9.27	735	383	66	1352
Non-IgE-mediated rhinopathy (N = 33)						
Range	7-168	2.75-35.92	105-2869	11-4530	20-335	132-4690
Median	71	8.23	556	350	43	1377
Control subjects (N = 26)						
Range	11-176	3.35-35.71	309-4804	51-3358	14-447	310-1617
Median	46	10.7	1093	540	66	640
Significance	NS	NS	NS†	NS	NS/ND	NS

NS, Nonsignificant among the three groups; ND, not defined because of nonparallel regression curves.

*Differences among the three populations were determined with multiple regression methods.

†Nonsignificant after weighted regression.

a vortex mixer (Cenco Instrumenten BV, Breda, The Netherlands) for at least 2 minutes, and centrifuged at 120 g. The supernatant was collected and centrifuged at 1500 g to remove any cell debris. The final supernatant was stored at -20°C until analysis. Cytospin preparations were prepared from the sediment of the first centrifugation step after resuspension in the standard cell culture medium, RPMI 1640 (Gibco Europa, Breda, The Netherlands), containing 1% bovine serum albumin. Cytospin preparations were stained with May-Grünwald/Giemsa. Samples with more than an occasional erythrocyte in the cytospin preparation were excluded from the study, since this could indicate that the mucosa was damaged during sampling. Thus, samples from six patients and one control subject were excluded.

Protein measurements

Total protein, IgG, IgM, and sIgA concentrations were measured by standard methods. Briefly, total protein was determined by the bichinchonic acid method (Pierce Chemical Co., Rockford, Ill.). IgG concentrations were determined by radial immunodiffusion on low concentration plates (LC-Partigen IgG, Behringwerke AG, Marburg, Germany). IgM was measured by ELISA.¹⁰ Microtiter plates (Nunc GMB, Roskilde, Denmark) were coated with swine antihuman IgM Ab (Orion Diagnostics, Espoo, Finland). Bound IgM was detected with HRP-conjugated rabbit antihuman IgM (Dako P 215, Dakopatts, Copenhagen, Denmark). sIgA was also measured by ELISA. The plates were coated with monoclonal antisecretory component Abs (purified H 194-4.1, kindly donated by J. J. Haaijman and J. Radl, Rijswijk, The Netherlands). Bound sIgA was detected with HRP-conjugated rabbit antihuman IgA (Dako P 216) to which unlabeled sheep antihuman sIgA (Red Cross Blood Transfusion Service, Amsterdam, The Netherlands) was added to reduce the slope of the standard curve and thus increase the detection range. Staining was performed

with o-phenylenediamine dihydrochloride (Sigma Chemical Co., St. Louis, Mo.). Albumin was measured by a competitive ELISA.¹¹ Plates were coated with albumin (Behringwerke AG, OHRA 04/05) and incubated with purified rabbit antihuman albumin (Dako P 001) that was preincubated with the samples. Binding of residual Ab was detected with HRP-conjugated swine antirabbit immunoglobulin (Dako P 217). IgE concentrations were determined with the IgE FAST test according to the manufacturers' instructions.

Evaluation and statistics

Concentrations were expressed in milligrams (for total protein) or micrograms (for albumin and immunoglobulins) per gram of secretion and relative to total protein in micrograms per milligrams of protein. The values were plotted against the weights of the collected secretions. Concentrations were compared between groups with multiple regression analysis; p values < 0.05 were considered significant. The smaller sample weights were least reliable because of the multiple weighing procedure. Therefore, samples with a weight < 15 mg were excluded from the statistics in which concentrations per gram of secretion were evaluated.

RESULTS

The protein concentrations per gram of secretion are summarized in Table II. For each parameter in each group, an inverse relationship was found between protein concentrations per gram of secretion and the weight of the secretions, which is illustrated for total protein and sIgA in Fig. 2. For total protein, albumin, IgG, and IgM, the regression curves for the control group fell between those for the group with IgE-mediated rhinopathy (upper curve) and the group with non-IgE-mediated rhinopathy (lower curve). Only for sIgA was the regression curve for the latter between

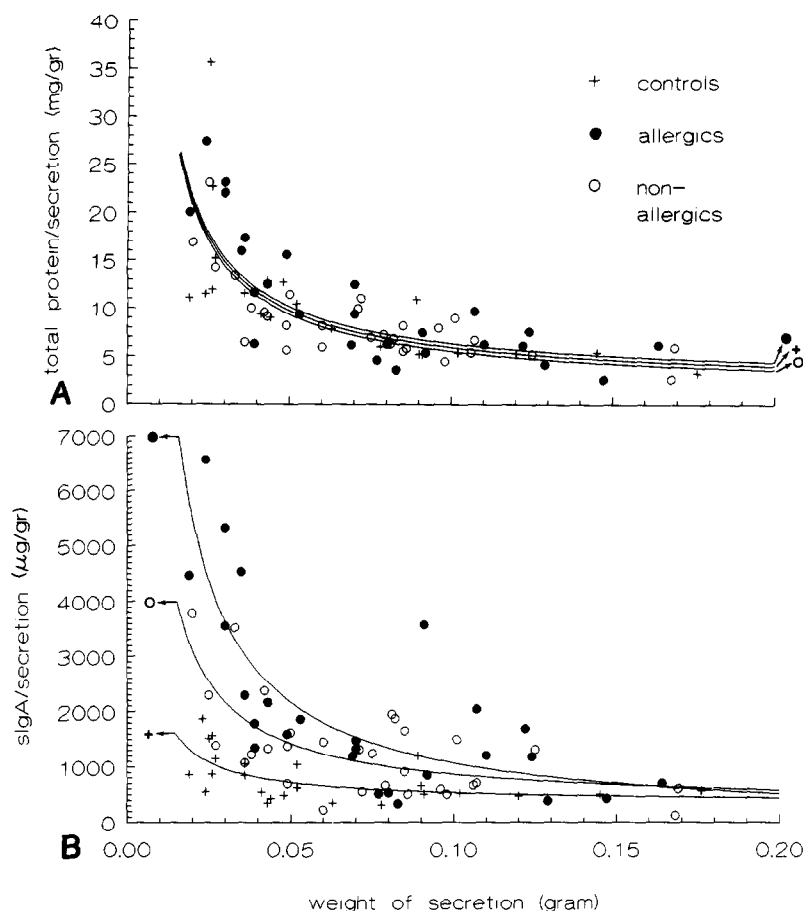


FIG. 2. A, Total protein. B, Total sIgA. Concentrations in nasal secretions from patients with an IgE-mediated rhinopathy, patients with a non-IgE-mediated rhinopathy, and from healthy control subjects plotted against the weights of the secretions.

a lower curve for the control group and a higher curve for the group with IgE-mediated rhinopathy. For IgG and total protein, no significant differences between the fitted regression curves (and thus between groups) were found. This finding implies that for each level of secretion weight, the IgG and total protein concentrations are, on average, the same for each of the three groups. Initially, the regression curve for albumin in the group with IgE-mediated rhinopathy was significantly higher than curves for the other groups. However, this result could be totally ascribed to two samples of low weight with very high concentrations (secretion weights, 0.036 and 0.024 gm; albumin concentrations, 5793 and 11236 $\mu\text{g/gm}$). If weighted regression analysis was performed,¹² such that concentrations with a higher secretion weight contributed more to the fitted curves than concentrations with a lower weight, no differences among the three groups were found. For the sIgA concentrations, the relationship with the weights of the secretions differed significantly between groups. This relationship is

weak for the control group, intermediate for the group with non-IgE-mediated rhinopathy, and strong for the group with IgE-mediated rhinopathy (Fig. 2, B). Because of the difference in dependency of sIgA concentrations on the weight of the secretion, differences among the groups cannot be defined uniquely nor tested for significance. For IgM the relationship with the weight of the secretion was the same for the control group and the group with non-IgE-mediated rhinopathy, but differed significantly between the group with IgE-mediated rhinopathy and both other groups. The regression curve for the group with IgE-mediated rhinopathy cut the curves for the control group and the group with non-IgE-mediated rhinopathy at sample weights of 0.07 and 0.12 gm, respectively. Thus, only the difference between the control group and the group with non-IgE-mediated rhinopathy could be tested and was found not significant (Table II).

The sIgA, IgG, and IgM to total protein ratios were independent of the weights of the secretions, which is illustrated for sIgA (Fig. 3, B). Comparisons among

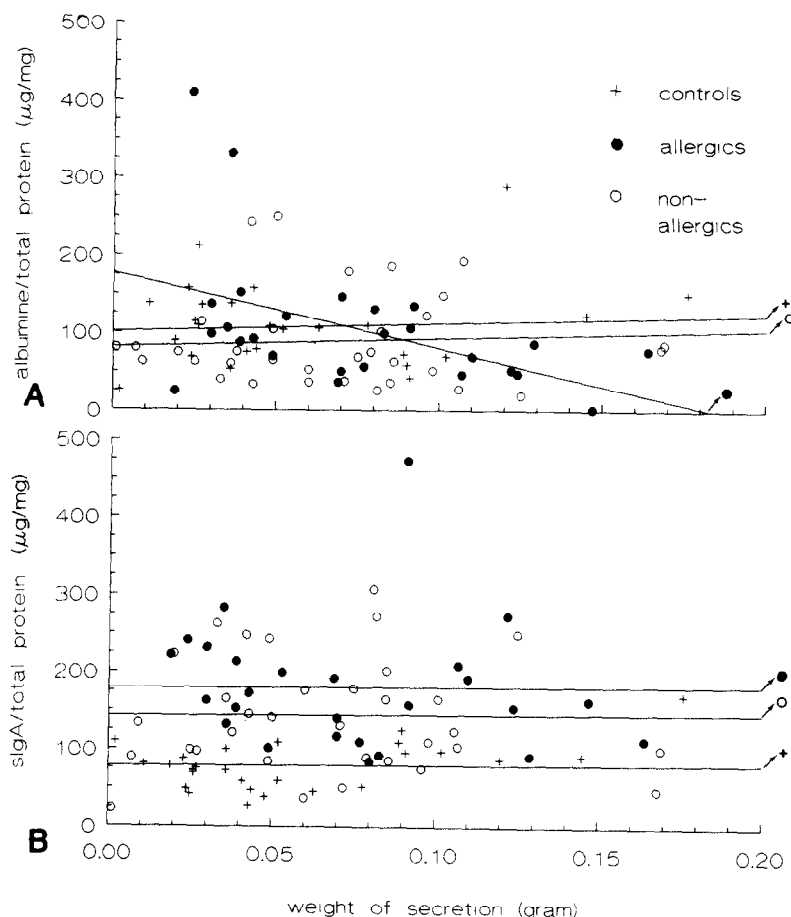


FIG. 3. A, Albumin, and **B,** sIgA to total protein ratios in nasal secretions from patients with an IgE-mediated rhinopathy, patients with a non-IgE-mediated rhinopathy, and from healthy control subjects plotted against the weights of the secretions.

the three groups elicited the following results (Fig. 4): for sIgA, the ratios differed significantly among groups (Table III); on average, the sIgA to protein ratio was highest for the group with IgE-mediated rhinopathy and lowest for the control group. For IgM, the ratios differed significantly only between the group with IgE-mediated rhinopathy and the group with non-IgE-mediated rhinopathy. For IgG, the ratios did not differ among groups. For the group with IgE-mediated rhinopathy, the albumin to protein ratio demonstrated a dependency on the weight of secretion (Fig. 3, A). This dependency remained significant, even after ignoring the two aforementioned extreme values. Such a dependency was not found for the control group and the group with non-IgE-mediated rhinopathy, nor did the albumin to total protein ratios differ significantly between these two groups. In the group with IgE-mediated rhinopathy, 23.1% of the patients had detectable IgE in the diluted nasal secretions. In the group with non-IgE-mediated rhinopathy and the control group, detectable IgE was found in 6.1% and

7.7% of the diluted nasal secretions, respectively. These percentages were not significantly different ($p = 0.1$, chi-square test).

DISCUSSION

The finding of higher nasal secretion protein concentrations at lower sample weights is in agreement with the suggestion that variations in nasal secretion protein concentrations are due to changes in secretory activity.^{5, 13} Thus, in the case of nasal hypersecretion, lower protein concentrations are expected at higher sample weights. These data (Table II) demonstrate that the three groups have comparable nasal secretion weight ranges and do not differ significantly in total protein, albumin, and IgG concentrations in nasal secretions. This finding indicates that as far as differences in nasal secretion protein concentrations occur between the groups of patients, differences are not caused by changes in secretory activity of the nasal mucosa or leakage of serum proteins. At lower secretion weights, both groups of patients had higher

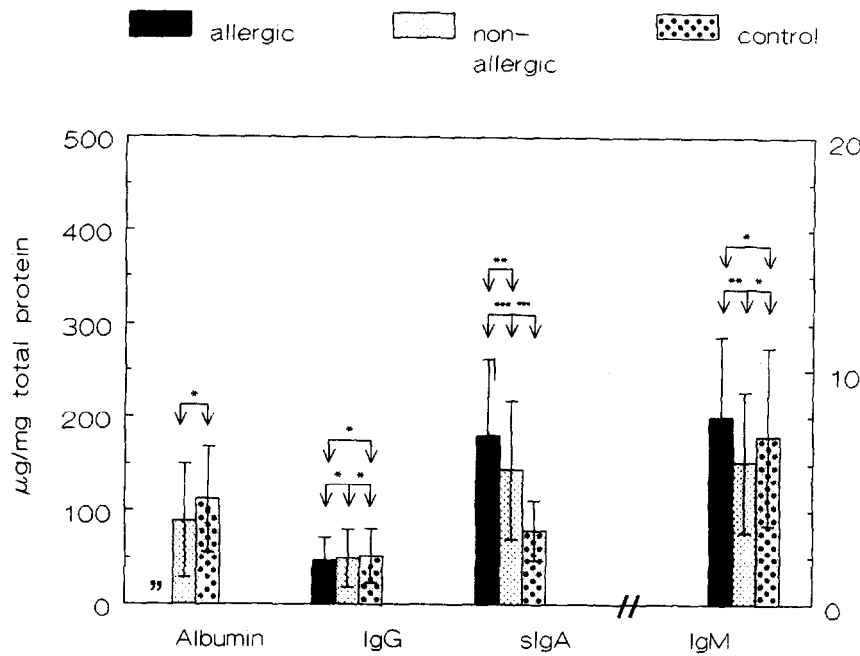


FIG. 4. Albumin, IgG, IgM, and sIgA levels in nasal secretions of patients with an IgE-mediated rhinopathy, patients with a non-IgE-mediated rhinopathy, and from healthy control subjects. Significance (p) is expressed to the distance between the fitted curves, *not significant; ** $p < 0.05$; *** $p < 0.0001$; "not defined because of nonparallel regression curves (see Fig. 3, A).

TABLE III. Concentrations of albumin, IgG, IgM, and sIgA relative to total protein concentration in nasal secretions of patients with an IgE-mediated rhinopathy, patients with a non-IgE-mediated rhinopathy, and healthy control subjects

Subjects	Albumin ($\mu\text{g}/\text{mg}$)	IgG ($\mu\text{g}/\text{mg}$)	IgM ($\mu\text{g}/\text{mg}$)	sIgA ($\mu\text{g}/\text{mg}$)
Allergic (N = 26)				
Mean		46	8.0	180
SD	*	26	3.5	82
Median		49	7.2	163
Nonallergic (N = 33)				
Mean	89	49	6.1	144
SD	61	31	3.0	74
Median	75	47	5.8	131
Control (N = 26)†				
Mean	112	52	7.2	79
SD	56	29	3.8	32
Median	108	49	7.3	77
Significance of the differences between the ratios				
Controls vs allergic	ND	$p = 0.57$	$p = 0.40$	$p < 0.0001$
Controls vs nonallergic	$p = 0.28$	$p = 0.81$	$p = 0.23$	$p < 0.0001$
Allergic vs nonallergic	ND	$p = 0.71$	$p < 0.05$	$p < 0.05$

p , Significance of the distance between the fitted curves; ND, not defined because of nonparallel regression curves.

*Not defined because of dependency on the weight of secretion.

†One of the control samples was only available for sIgA measurement.

sIgA concentrations in nasal secretion than the control group (Fig. 2, B), which suggests an increased IgA synthesis in the nasal mucosa of the patients.

Immunoglobulin to total protein ratios was independent on the weight of the secretions. Albumin to total protein ratios in the allergic patients, however, may depend on the weight of the secretions. The sIgA to protein ratios in both groups of patients were significantly higher than in the healthy control group (Figs. 3, B and 4). These data indicate that in patients, on average, more sIgA is produced in the nasal mucosa than in the control group, which is in agreement with previous studies on (adult) patients with AR and rhinitis vasomotorica.^{8, 14} However, in children with asthma and children with recurrent infections of the upper respiratory tract,^{15, 16} an increase in nasal (s)IgA concentration was not found. In the group with IgE-mediated rhinopathy, the sIgA and IgM to total protein ratios were significantly higher than in the group with non-IgE-mediated rhinopathy. Together with IgM, sIgA has an important function in the first line of defense in the respiratory mucosa.^{17, 18} Our data (Fig. 4) indicate that, especially in patients with an IgE-mediated rhinopathy, this "first line of defence" is stimulated. Apparently, this is not sufficient to prevent AR, despite the fact that (s)IgA can agglutinate antigens and inhibit antigen absorption.¹⁹ Histologic data suggest that, when IgA synthesis is impaired, for example, in patients with selective IgA deficiency, a compensatory secretory IgM response can occur.²⁰ Whether the observed relative increase in IgM secretion in the group with IgE-mediated rhinopathy is a compensation for a nonadequate sIgA response can not be excluded. Leakage through the mucosa, as suggested by Illum and Balle,⁷ is not likely, as mentioned earlier. For IgE, evaluation of nasal secretion analysis is limited because most samples had an IgE concentration lower than the detection level (2 IU/ml), and the dilution factor differed between the samples.

In conclusion, the present study has demonstrated that nasal sIgA production is higher in patients with rhinopathy than in healthy control subjects. In addition, nasal secretion total protein, albumin, and immunoglobulin concentrations are inversely related to the amount of secretion in the nasal cavity. Furthermore, patients with an IgE-mediated rhinopathy have higher nasal secretion sIgA and IgM to total protein ratios than patients with a non-IgE-mediated rhinopathy. Most likely, these differences reflect changes in local immune regulation.

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