

Original article

Seasonal idiopathic rhinitis with local inflammatory response and specific IgE in absence of systemic response

Background: Patients with idiopathic rhinitis (IR) are considered to be nonallergic because they have a negative skin prick test (SPT) and allergen specific-IgE in serum. The concept of localized mucosal allergy in the absence of atopy has recently been proposed. The immunological mechanisms involved in seasonal IR have not been sufficiently studied. We examined nasal mucosa inflammation, the presence of nasal specific-IgE and the response to nasal allergen provocation test (NAPT) in patients with seasonal IR who presented symptoms only in spring.

Methods: We evaluated 32 patients with seasonal IR and 35 with persistent allergic rhinitis to pollen (PAR-P) and compared these with healthy controls and persons with PAR to house dust mite during the pollen season, as well as by NAPT out-of-season with grass and *Olea europea*. We measured the nasal leukocyte-lymphocyte phenotype (CD45, CD33, CD16, CD3, CD4 and CD8), eosinophil-cationic-protein, and total and specific-IgE to grass and olive pollen in serum and nasal lavage and performed NAPT.

Results: In the IR group, 62.5% had a positive NAPT (IR-PosNAPT), 20/32 to grass, with four of these having a positive NAPT to olive pollen as well. IR-PosNAPT patients showed a similar nasal leukocyte-lymphocyte profile to the PAR-P patients and different to controls. We detected nasal specific-IgE in 35% of IR-PosNAPT patients.

Conclusions: These results support the hypothesis that a subgroup of patients with IR have seasonal symptoms with evidence of a nasal allergic immune reaction in the absence of a positive SPT or serum specific IgE.

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Key words: allergic rhinitis; flow cytometry; idiopathic rhinitis; local IgE production; nasal allergen provocation test.

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Idiopathic rhinitis (IR) comprises a group of nasal diseases of unknown etiology, usually diagnosed by exclusion (1, 2). IR is also referred to as 'vasomotor rhinitis', 'nonallergic, noninfectious rhinitis', or 'perennial nonallergic rhinitis' (1). Although the aetiopathology is poorly understood, immunological, neurogenic or other mechanisms may participate (2, 3). Patients with IR are considered to be nonallergic because they have a negative skin prick test (SPT), absence of specific IgE (sIgE) to aeroallergens and normal IgE levels in serum (3, 4). However, many of these patients have clinical criteria for allergic rhinitis (1). The concept that it could be a form of localized allergy in the absence of systemic atopy has been proposed (4–6). Patients with allergic rhinitis have an

IgE-mediated response (7) involving a Th2 immunological pattern (8, 9). Re-exposure to aeroallergens induces symptoms because of mast cell activation (7, 10), with release of inflammatory mediators and local recruitment of inflammatory cells (7).

In a previous study, we identified subjects with persistent nonallergic rhinitis who develop symptoms throughout the year, more intense in autumn and winter, and despite being negative to conventional allergological tests they show evidence of local sIgE production to perennial allergens (4). This observation can also be extended to subjects with seasonal symptoms. Well-defined cases with repeated symptoms of rhinitis just in the spring and who improve with topical nasal corticosteroids and oral antihistamine therapy have been found, sometimes accompanied by ocular and bronchial symptoms but with negative allergy skin and *in vitro* tests for sIgE antibodies.

The aim of this work was to study nasal inflammation, the presence of nasal sIgE and the nasal allergen provocation test (NAPT) response to grass and *Olea europea* pollen, two common environmental seasonal allergens in Spain, in patients with IR who reported seasonal symptoms only during the spring.

Abbreviations: DP, *Dermatophagoides pteronyssinus*; ECP, eosinophil cationic protein; IR, idiopathic rhinitis; IR-NegNAPT, IR with negative NAPT; IR-PosNAPT, IR with positive NAPT; NAPT, nasal allergen provocation test; PAR, persistent allergic rhinitis; PAR-HDM, PAR to house dust mite; PAR-P, PAR to pollen; sIgE, specific IgE; SPT, skin prick test; VAS, visual analog scale; VAS-NAPT, total range of the VAS during NAPT; VOL 2–6 cm, volume of the nasal cavity from 2 to 6 cm.

Methods

Study subjects

Over a 10-month period we recruited consecutively 147 non-smoking subjects, aged 18–70 years, divided into four groups: 32 subjects with seasonal IR, 35 with persistent allergic rhinitis to pollens (PAR-P) with symptoms also occurring only in the spring, 30 with persistent allergic rhinitis to house dust mite (PAR-HDM) with symptoms occurring most of the year, and 50 healthy non-atopic subjects as a healthy control (HC) group. The IR and PAR-P subjects were studied both during and outside the pollen season. The following inclusion criteria were applied:

- 1 General inclusion criteria for rhinitis subjects: no evidence of other immunologic disease, chronic rhinosinusitis and/or nasal polyposis (CT scanning), vasomotor rhinitis (clear rhinorrhea and response to ipratropium bromide) or respiratory infection for 4 weeks; no treatment with systemic or nasal corticosteroids for 4 months or systemic antihistamines or nasal vasoconstrictors for 2 weeks. No patient was pregnant or breast feeding.
 - a IR group: patients with IR (3) with symptoms exclusively during the pollen season (April–June) for at least 2 years and good response to topical nasal corticosteroids and oral antihistamines. Negative SPT and serum sIgE to common environmental aeroallergens, and negative intradermal skin test to grass and *O. europea* pollen.
 - b PAR-P group: patients with PAR-P for at least 2 years, positive SPT and/or positive serum sIgE to grass or *O. europea*, positive NAPT with grass and/or *O. europea*, and no specific immunotherapy for 10 years.
 - c PAR-HDM group: patients with PAR-HDM with positive SPT, serum sIgE and NAPT to *Dermatophagoides pteronyssinus* (DP) and negative to grass/olive pollen. No specific immunotherapy for 10 years.
- 2 HC group: healthy; no allergic, nasal or bronchial diseases; no pregnancy or lactation; negative SPT, serum sIgE to aeroallergens and NAPT with grass or *O. europea*.

The study was approved by the institutional review board.

Natural exposure to pollen (April–June)

The SPT was performed with a panel of the most prevalent inhalant allergens, including house dust mite, pollens, molds, latex and animal epithelia (4) (ALK-Abelló, Spain). The intradermal skin test was performed in the IR patients with grass pollen mixture (0.01 and 0.1 µg/ml) and *O. europea Ole e1* (0.06 and 0.6 µg/ml) (ALK-Abelló).

All the subjects used a visual analog scale (VAS) (11) with a total range of 0–700 mm to record symptoms of obstruction, posterior rhinorrhea, anterior rhinorrhea, itching, sneezing, loss of smell and ocular symptoms during the week prior to the nasal lavage. The severity of each symptom was categorized as mild (VAS 0–30), moderate (VAS 31–70) and severe (VAS 71–100).

Nasal lavage and flow cytometry

Nasal lavage was performed as described (12, 13), with 10 ml of physiologic saline. The supernatant was stored at –20°C. The pellet was studied by flow cytometry (4) after incubation with fluoresceinated monoclonal antibodies and their isotype controls. The cells were acquired using a FACSCalibur (Becton Dickinson, San Jose, CA, USA) and results depicted on a graph that included the side scatter and CD45-APC (Caltag Laboratories, Burlingame, CA, USA) marker selecting the different cell populations, neutrophils, eosinophils, basophil-mast cells and lymphocytes (Fig. 1). From the lymphocyte population we characterized the following subpopulations: myeloid series when positive for CD33-PE (BD Biosciences, Pharmingen, San Diego, CA, USA), NK cells when positive for CD16-FITC and negative for CD3-PerCP (both from Pharmingen), T cells when positive for CD3-PerCP, helper T cells when positive for CD3-PerCP and CD4-PE (Pharmingen) and cytotoxic T cells when positive for CD3-PerCP and CD8-FITC (Pharmingen).

Inflammatory mediators, total and sIgE in serum and nasal lavage

Eosinophil cationic protein (ECP), total IgE and sIgE were determined by immunoassay (UniCAP, Phadia, Uppsala, Sweden). For serum sIgE we used the same allergens as for the SPT. In nasal lavage we measured sIgE to grass and *O. europea*. The cut-off value for sIgE was 0.35 kU/l.

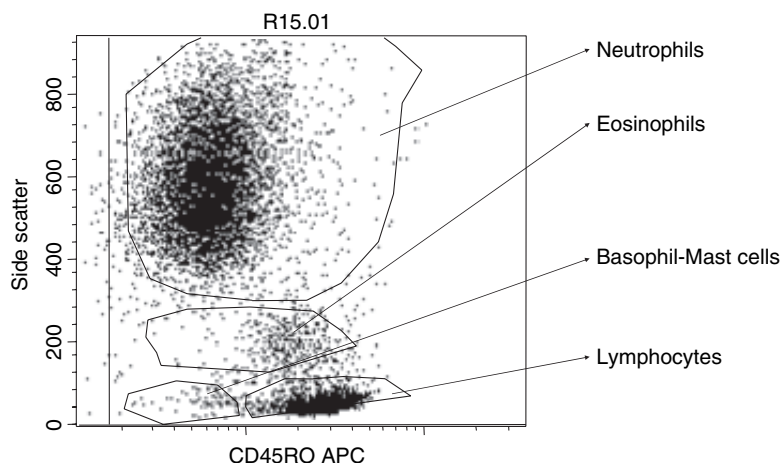


Figure 1. Representative dot plot showing the nasal flow cytometry gate strategy for selecting neutrophils, eosinophils, basophil-mast cells and lymphocytes based on side scatter (SSC) and CD45-APC marker expression.

NAPT outside the pollen season (October–November)

Saline challenge was performed to exclude nasal hyperactivity. If negative, NAPT (4) was performed after 1 and 2 weeks with freshly reconstituted grass (0.001–0.01–0.05–0.1 µg/ml) and *O. europea* [*Ole e1* (0.006–0.06–0.03–0.6 µg/ml)] extracts (ALK-Abelló) in 32 asymptomatic IR patients and in 30 symptomatic PAR-HDM patients, to exclude a nonspecific response to pollen. The specificity of the response was verified in subjects with IR performing intra-nasal challenge with DP.

Before NAPT, each 15 min during NAPT, and 15 min, 1, 6 and 24 h afterwards, nasal obstruction, rhinorrhea, itching, sneezing and ocular symptoms were recorded by VAS and the volume of the nasal cavity from 2 to 6 cm (VOL 2–6 cm) was assessed by acoustic rhinometry (14) (SRE 2000 rhinometer. Rhinometrics, Lynge, Denmark). The total range of the VAS during NAPT (VAS-NAPT) was 0–500 mm. A positive NAPT was considered to be an increase >30% in the total VAS-NAPT and a decrease >30% in the VOL 2–6 cm (%VOL 2–6 cm) in acoustic rhinometry compared with the baseline test. Positive responses were categorized as immediate (<1 h after NAPT), late (≥6 h after NAPT) or dual (both immediate and late). The IR patients were divided into two groups: those with a positive response to NAPT (IR-PosNAPT) and those with a negative response (IR-NegNAPT).

Statistical analysis

Differences in percentages between the groups were compared by chi-squared analysis, demographic data by Student *t*-test, and the flow cytometry, total and sIgE, and ECP results by the Mann–Whitney *U*-test. Associations between symptom score, eosinophils and ECP values were made by Spearman correlation. We used the software package SPSS for Windows 11.5.1 (SPSS Corporation, Chicago, IL, USA). A *P* < 0.05 was considered significant.

Results

Study groups

Of 156 subjects initially evaluated, nine patients with IR and symptoms of vasomotor rhinitis were excluded from the study. Clinical and epidemiological data are shown in Table 1. No differences existed concerning a family history of atopy, years of symptoms and city dwelling. Conjunctivitis was the most frequent presentation in IR and PAR-P, and the most frequent accompanying disease in all groups of rhinitis subjects. Asthma was present in 30% of IR and in 10% of PAR-P patients (*P* = 0.009).

Determinations made during natural exposure to pollen (April–June)

SPT. In the PAR-P group the SPT was positive to grass pollen in 17/35 (49%) and to *O. europea* in 10/35 (28%), with 8/35 subjects positive to both (23%). In all cases the SPT was positive to a least one of the pollens tested. The SPT was negative in all the IR patients.

Symptom score. Posterior rhinorrhea was the most common symptom in IR (96%) and sneezing in PAR-P

Table 1. Epidemiological and clinical data of the study subjects

Groups	IR	PAR-P	PAR-HDM	HC
Subjects (<i>n</i>)	32	35	30	50
Age (year)	41 ± 18	28 ± 11	31 ± 12	37 ± 12
Disease duration (year)	7 ± 7	6 ± 5	8 ± 6	NA
Sex, <i>n</i> (%)				
Male	13 (41)	14 (40)	11 (37)	19 (38)
Female	19 (59)	21 (60)	19 (63)	31 (62)
FHA, <i>n</i> (%)	15 (46)	15 (43)	13 (43)	14 (28)
Dwelling, <i>n</i> (%)				
City	20 (62)	22 (63)	20 (67)	31 (62)
Country	12 (38)	13 (37)	10 (33)	19 (38)
Co-morbidity, <i>n</i> (%)				
Conjunctivitis	20 (62)	23 (65)	13 (43)	NA
Asthma	10 (31)	4 (11)	9 (30)	

Data expressed as mean ± standard deviation.

IR = idiopathic rhinitis, PAR-P = persistent allergic rhinitis to pollen, PAR-HDM = persistent allergic rhinitis to house dust mite, HC = healthy control group, *n* = number of subjects, FHA = family history of atopy, NA = not applicable.

(80%). Hyposmia was present in 34% of the IR and 26% of the PAR-P patients. These differences were not significant.

Comparison of severity showed that ocular symptoms received the highest score in both IR and PAR-P patients (37% and 31%, respectively, *P* > 0.05). The IR patients presented a greater severity in sneezing (*P* < 0.05) and anterior and posterior rhinorrhea (*P* < 0.002) than the PAR-P patients (Table 2).

Flow cytometry. Similar values of CD45⁺ cells, neutrophils, eosinophils and basophil-mast cells were found between the PAR-P and the IR patients, including the nine patients with IR and bronchial asthma. The PAR-P group had significantly higher values of total lymphocytes (*P* = 0.008), CD3⁺ T cells (*P* = 0.02) and CD4⁺ T cells (*P* = 0.04). No differences were observed for the CD8⁺ T cells among the three groups. The CD45⁺ cells and eosinophils were significantly higher in the IR group compared with the controls (*P* < 0.05 and *P* = 0.007 respectively) (Table 3).

Total IgE, sIgE and ECP in serum and nasal fluid. In the IR group serum total IgE values were similar to the controls and lower than the PAR-P group (*P* = 0.02). Serum sIgE was positive to grass and/or *O. europea* in 27/35 patients with PAR-P (77%). All IR and control subjects had negative serum sIgE. The serum ECP values were lower in IR than PAR-P (*P* = 0.04). The IR and control groups had similar ECP values (Table 3).

Although the nasal levels of total IgE were higher in the PAR-P compared to the IR and control groups, significant differences were only found between PAR-P and controls (*P* = 0.04). The nasal sIgE showed higher values

Table 2. Frequency and severity of symptoms during the pollen season

Symptom	IR (n = 32)	PAR-P (n = 35)	IR vs PAR-P P value	HC (n = 50)
Itching				
Frequency, %	24 (75)	23 (65)	NS	—
Mild, %	8 (25)	7 (20)		—
Moderate, %	12 (37)	11 (31)		—
Severe, %	4 (13)	5 (14)	NS	—
Sneezing				
Frequency, %	25 (78)	28 (80)	NS	2 (4)
Mild, %	6 (19)	9 (26)		2 (4)
Moderate, %	11 (34)	16 (46)		—
Severe, %	8 (25)	3 (8)	<0.05	—
Anterior rhinorrhea				
Frequency, %	28 (88)	27 (77)	NS	3 (6)
Mild, %	3 (9)	7 (20)		3 (6)
Moderate, %	15 (48)	19 (54)		—
Severe, %	10 (31)	1 (3)	0.002	—
Posterior rhinorrhea				
Frequency, %	30 (96)	27 (77)	0.001	—
Mild, %	4 (13)	7 (20)		—
Moderate, %	15 (48)	19 (54)		—
Severe, %	11 (35)	1 (3)	0.002	—
Nasal obstruction				
Frequency, %	20 (62)	24 (68)	NS	1 (2)
Mild, %	—	12 (34)		1 (2)
Moderate, %	12 (38)	7 (20)		—
Severe, %	8 (25)	5 (14)	NS	—
Hyposmia				
Frequency, %	11 (34)	9 (26)	NS	—
Mild, %	5 (15)	9 (26)		—
Moderate, %	6 (19)	—		—
Severe, %	—	—	NS	—
Ocular symptoms				
Frequency, %	20 (62)	21 (60)	NS	—
Mild, %	—	—		—
Moderate, %	8 (25)	10 (29)		—
Severe, %	12 (37)	11 (31)	NS	—

Values in parentheses are percentages.

IR = idiopathic rhinitis, PAR-P = persistent allergic rhinitis to pollen, HC = healthy control group, NS = not significant.

to grass pollen in the PAR-P group than the IR and the control groups ($P = 0.04$ and $P = 0.007$, respectively). No differences were found in nasal sIgE to *O. europea*. The PAR-P group had more cases with sIgE in nasal fluid than in peripheral blood: 20/25 cases (80%) to grass and 15/18 (83%) to *O. europea*.

In the IR group we detected selective nasal sIgE in 7/32 cases (21.8%), all seven to grass pollen (0.64, 0.76, 0.91, 1.08, 1.15, 1.31, 1.42 kU/l) and two to *O. europea* (0.58 and 0.67 kU/l). Only one of these local sIgE positive patients had bronchial asthma. In all cases nasal total IgE was lower than 18 IU/ml.

Nasal ECP values were higher in the IR and PAR-P groups than in the control group ($P = 0.007$ and

Table 3. Laboratory data during the pollen season in seasonal IR subjects regardless of response to NAPT

	IR	PAR-P	HC
Serum			
ECP, µg/l	23 ± 12*	38 ± 18†	18 ± 13
Total IgE, IU/ml	143 ± 178*	430 ± 507†	47 ± 59
sIgE grass, kU/l	<0.35*	24 ± 43†	<0.35
sIgE olive, kU/l	<0.35*	12 ± 18†	<0.35
Nasal lavage			
Supernatant			
ECP, µg/l	12 ± 17†	48 ± 63†	2 ± 2
Total IgE, IU/ml	21 ± 28	23 ± 16†	8 ± 19
sIgE grass	0.62 ± 0.40*	0.69 ± 0.86†	<0.35
sIgE olive, kU/l	0.21 ± 0.37	0.28 ± 0.46	<0.35
Flow cytometry			
TCC	9218 ± 1766	9369 ± 1588	8758 ± 2316
CD45 ⁺	85 ± 16†	80 ± 19†	57 ± 29
N, %	16 ± 8	12 ± 10	17 ± 23
E, %	44 ± 25†	52 ± 22†	14 ± 8
B-MC, %	1.39 ± 1.20	1.47 ± 1.23†	0.77 ± 0.91
L, %	0.45 ± 0.42*	1.01 ± 0.64†	0.29 ± 0.34
CD3 ⁺ T cells, %	0.04 ± 0.04*	0.22 ± 0.26†	0.12 ± 0.25
CD4 ⁺ T cells, %	14 ± 22*	30 ± 29†	7 ± 13
CD8 ⁺ T cells, %	16 ± 26	32 ± 31	26 ± 32

Data represent mean ± standard deviation.

IR = idiopathic rhinitis, PAR-P = persistent allergic rhinitis to pollen, HC = healthy control group, sIgE = specific IgE, ECP = eosinophil cationic protein, TCC = total cell count, N = neutrophils, E = eosinophils, B-MC = basophils-mast cells, L = lymphocytes.

*Significant differences between IR and PAR-P patients.

†Significant differences with HC.

$P = 0.006$, respectively), with no differences between IR and PAR-P (Table 3).

Determinations made outside the pollen season (October–November)

Nasal provocation test. No subject in any group responded to control saline. In the IR group 20 subjects had a positive NAPT to grass (62.5%) and five to *O. europea* (15.62%). All cases with nasal sIgE had a positive NAPT.

In all cases, the response was immediate or dual; no isolated late responses were observed. Most of the subjects developed a bilateral response in acoustic rhinometry (Fig. 2), and responded to low concentrations of allergens (0.001 and 0.01 µg/ml of grass, and 0.006 and 0.6 µg/ml of Ole e1) (Fig. 3). In the PAR and HC group, NAPT with both grass and olive pollen was negative. In the IR and PAR-P groups challenge with DP was negative.

Immunological markers in the IR-PosNAPT. This group showed a similar inflammatory response to the PAR-P patients (Table 4). Nasal ECP values were higher in the PAR-P group ($P < 0.05$), and the basophil-mast cells and the CD3⁺ cells were higher in the IR-PosNAPT

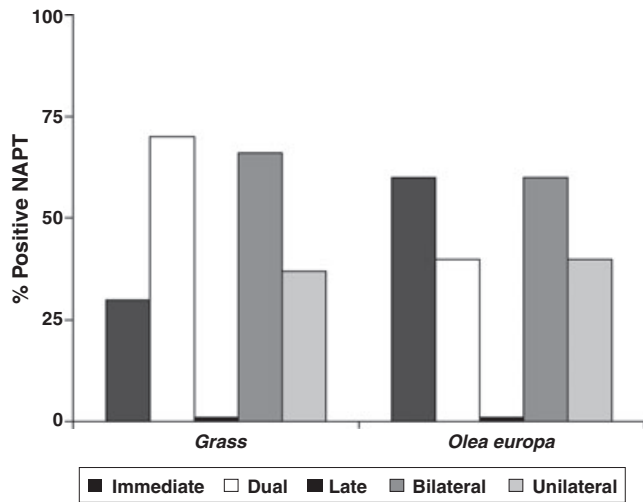


Figure 2. Positive responses to nasal allergen provocation test with grass (left bars) and *Olea europaea* pollen (right bars) in idiopathic rhinitis group. The immediate response (black bars) was considered to be that occurring < 1 h after challenge. Late response (gray bars) was considered to be that occurring ≥ 6 h after challenge. Dual response (white bars) was considered when both immediate and late responses occurred in the same patient. The nasal challenge was considered to be unilateral or bilateral depending on whether, after local application of the allergen, the positive response occurred on one side or both sides.

group ($P = 0.02$ for both). The IR-PosNAPT group had a significant positive association between nasal sIgE to grass pollen and nasal ECP ($Rho = 0.836$, $P < 0.05$), and between ECP and percentage of eosinophils in nasal lavage ($Rho = 0.813$, $P < 0.05$). Compared to the control group, the IR-PosNAPT group showed significant differences in nasal ECP ($P = 0.009$), eosinophils ($P = 0.008$), basophils ($P < 0.01$), and total lymphocytes and CD3⁺ cells ($P < 0.05$ for both). No differences were found in the other values.

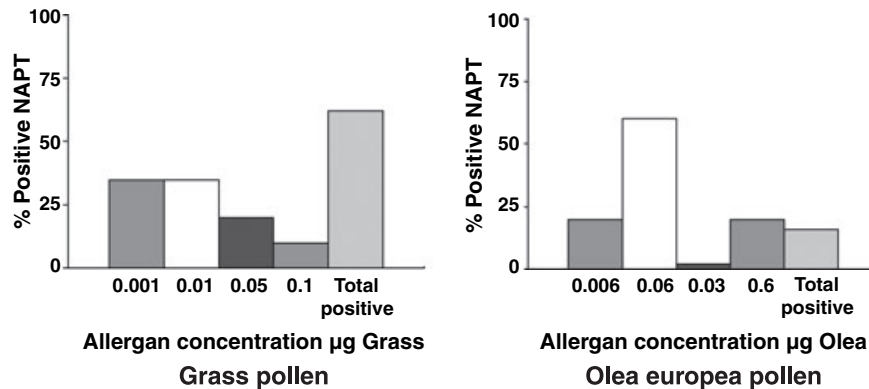


Figure 3. Allergen concentration and positive response to nasal allergen provocation test in the idiopathic rhinitis group. Nasal challenge with grass pollen is shown on the left. Four 10-fold increasing concentrations (0.001–0.1 µg/ml) of grass pollen were used. The total positive bar represents the percentage of cases with a positive nasal challenge (20 out of 20 cases). Each bar represents the percentage of cases in this group of 20 cases. The same experiments were made with *Olea europaea* pollen allergen. Concentrations ranged from 0.006 to 0.6 µg/ml. The total positive bar also represents the percentage of cases with a positive nasal challenge with olive pollen (four out of 32 cases).

Table 4. Laboratory data during the pollen season in seasonal IR subjects with positive or negative response to NAPT

	IR-PosNAPT	PAR-P	IR-NegNAPT	HC
Serum				
ECP, µg/l	25 ± 12	38 ± 18†	22 ± 10*	18 ± 13
Nasal lavage				
Supernatant				
ECP, µg/l	19 ± 24*†	48 ± 63†	14 ± 21*	2 ± 2
Flow cytometry				
TCC	8638 ± 2725	9369 ± 1588	9354 ± 1130	8758 ± 2316
CD45 ⁺	80 ± 20†	80 ± 19†	86 ± 13†	57 ± 29
N, %	12 ± 5	12 ± 10	16 ± 9	17 ± 23
E, %	56 ± 24†	52 ± 22†	40 ± 24†	14 ± 8
B-MC, %	2.64 ± 0.69*†	1.47 ± 1.23†	1.11 ± 1.07	0.77 ± 0.91
L, %	0.78 ± 0.51	1.01 ± 0.64†	0.39 ± 0.42*	0.29 ± 0.34
CD3 ⁺ T cells, %	0.50 ± 0.30*†‡	0.22 ± 0.26†	0.02 ± 0.04*	0.12 ± 0.25
CD4 ⁺ T cells, %	33 ± 38	30 ± 29†	11 ± 17	7 ± 13
CD8 ⁺ T cells, %	52 ± 14‡	32 ± 31	19 ± 30	26 ± 32

Data represent mean ± standard deviation.
IR = idiopathic rhinitis, NAPT = nasal allergen provocation test, IR-PosNAPT = IR with positive response to NAPT, IR-NegNAPT = IR with negative response to NAPT, PAR-P = persistent allergic rhinitis to pollen, HC = healthy control group, TCC = total cell count, N = neutrophils, E = eosinophils, B-MC = basophils-mast cells, L = total lymphocytes.
*Significant differences with PAR-P patients.
†Significant differences with HC.
‡Significant with IR-NegNAPT.

Immunological markers in the IR-NegNAPT. IR-NegNAPT patients showed similar levels to the PAR-P group in CD45⁺ T cells, neutrophils, eosinophils and basophils-mast cell; and significantly lower levels of serum and nasal ECP ($P < 0.05$), nasal total lymphocytes ($P = 0.01$) and CD3⁺ T cells ($P = 0.002$). Compared with the control group, the IR-NegNAPT group had significantly higher levels of CD45⁺ T cells ($P = 0.009$) and eosinophils ($P = 0.02$) in nasal lavage. IR-NegNAPT patients had significantly lower nasal levels of CD3⁺ ($P = 0.007$)

and CD8⁺ T cells ($P = 0.008$) compared with the IR-PosNAPT group (Table 4).

Discussion

Local IgE production may occur in nasal mucosa of allergic and IR patients (5, 15). Several studies have found expression of epsilon germline transcripts and mRNA for the epsilon heavy chain of IgE in nasal and bronchial mucosa (16–18). Specific local IgE antibodies that recognize allergens, with subsequent induction of symptoms can be produced (18–20).

We studied subjects who showed typical symptoms to those associated with PAR with seasonal occurrence, but with negative allergy tests. These patients are usually diagnosed as having nonallergic rhinitis and are often included within the IR group (1, 2, 21). The prevalence of IR is unknown but it appears to be common, occurring in approximately 19 million in the United States (22). According to Bachert, nonallergic noninfectious rhinitis occurs in 9.6% of subjects with rhinitis when compared with 29.8% of subjects with allergic rhinitis (23).

Although there is increasing evidence to support an inflammatory disorder with local production of IgE in IR (4–6), this concept is not universally accepted; Van Rijswijk et al. (21) found no evidence to support the involvement of inflammatory cells in patients with IR. These differences may be explained by the fact that the studies included patients with different pathophysiological mechanisms of IR [inflammatory disorders, neurogenetic mechanisms (3) and changes in the permeability of the mucosa (2)].

We have shown that an important number of subjects with persistent rhinitis with symptoms occurring most of the year but with negative skin and serum allergy tests presented positive responses to nasal challenge with DP and had sIgE antibodies that were only detectable in the nasal fluid (4). On the basis of these observations, we undertook a study in a well-defined group of 32 subjects with IR who experienced symptoms only during the spring, with negative skin tests and no evidence of sIgE in serum to inhalant allergens. Persons with vasomotor rhinitis were excluded from our study to concentrate on subjects who could, *a priori*, present a local inflammatory response.

The clinical symptoms were very similar between the IR and PAR-P patients concerning the frequency of itching, sneezing, anterior rhinorrhea, nasal obstruction, hyposmia and ocular symptoms. The only significant difference found was posterior rhinorrhea, more frequent in the IR group. Regarding severity, sneezing and rhinorrhea were also more important in the IR group. Mild to moderate hyposmia was observed in a low percentage of subjects from both the groups. Similarities were found in the history of atopy, years of evolution and the presence of concomitant ocular symptoms. However,

a marked difference was found in the presence of asthma, significantly higher in the IR group. The reason for this was not investigated, and whether local sIgE is also produced in the lung of IR patients needs to be determined in further studies.

Wedback et al. (24), detected a lower rate of positive response to NAPT-pollen (7/15) in seasonal nonallergic rhinitis patients challenged with high concentrations of allergens, with no immediate isolated responses, four late responses, and three dual responses. Nevertheless, in the IR group in our study, the NAPT showed a positive immediate or dual response but no late response in 62.5% of cases to grass pollen and 15% of cases to *O. europea* pollen (the IR-PosNAPT group). All the IR-PosNAPT patients presented a negative NAPT to Der p1, the main allergen of DP, indicating that this was a specific response. It is important to mention that 35% of these IR-PosNAPT patients (7/20) had nasal sIgE antibodies to grass and two to both grass and olive. All cases with nasal local sIgE had a positive NAPT to grass or olive. These results support an IgE mechanism. To our knowledge this has not been reported previously.

The reason for finding no positive nasal sIgE antibodies in the other cases with IR-PosNAPT may be either a limitation in the sensitivity of the method for nasal detection of sIgE or the involvement of another mechanism. The dilutional effect of nasal lavage may imply a lower sensitivity. Direct interaction between allergen and mast cells has been proposed (6), although no evidence supporting a nonIgE mechanism has yet been shown.

A detailed study of the IR-PosNAPT group revealed an inflammatory pattern in the nasal fluid during the seasonal exposure, with increased nasal values of eosinophils, total lymphocytes and ECP that was similar to those of the PAR-P group. Basophil-mast cells and CD3⁺ T cells were significantly higher in the IR-PosNAPT group. Similar data were found by Powe et al. in IR patients (25, 26). The IR-NegNAPT group also showed a nasal inflammatory pattern compared with HCs, but only with increased levels of eosinophils and nasal ECP.

The results of this study suggest the presence of three IR groups: one group with positive NAPT and nasal sIgE to pollen; a second group, where despite seasonal symptoms and positive NAPT, no sIgE antibodies were detected; and a third group resembling nonallergic rhinitis with eosinophilia syndrome. However, further studies are required to define these groups better. Whether the second group can be incorporated into the first group by improving the detection method of specific antibodies in nasal fluids also needs to be examined.

Comparing these results with a previous study with persistent nonallergic rhinitis (4), the IR-PosNAPT patients showed a stronger inflammatory response, with higher levels of eosinophils, basophil-mast cells and CD3⁺ T cells in nasal fluid. This may be because these patients could be exposed to a greater concentration of pollen allergen than those exposed to house dust mite,

although no properly designed comparative studies have examined this question.

In summary, we present evidence indicating that patients with IR who develop well-defined symptoms during the pollen season show an inflammatory pattern equivalent to that existing in PAR-P patients produced by pollen, with an important percentage having a positive NAPT response and sIgE antibodies. Whether other allergens were also implicated and/or other mechanisms involved is currently under study. These

findings should be taken into account when evaluating patients with typical symptoms, either persistent or intermittent.

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