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Potential Differences between Local and Systemic Allergic Rhinitis Induced by Birch Pollen

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Allergic rhinitis · IgE · Basophil activation test · FeNO · Aeroallergen

Abstract
Introduction: Different endotypes of rhinitis are known, but its pathomechanism has not been conclusively established. For example, the precise difference between systemic allergic rhinitis (SAR) and local allergic rhinitis (LAR) is still being checked. Comparison of patients with LAR and with allergies to birch of those with intermittent allergic rhinitis, same allergy, or with non-allergic rhinitis (NAR) was the purpose of this study. ***Methods:*** Twenty-six patients with LAR, 18 with SAR and allergy to birch, and 21 with NAR were included. Patients who met the inclusion criteria were selected to undergo the following procedures at baseline: medical examinations, nasal provocation test (NPT), detection of nasal-specific IgE to birch as well as basophil activation test (BAT). All immunological parameters were detected before and after NPT. ***Results:*** Concentration of nasal IgE to Bet v1 increased comparably in the LAR and SAR groups after NPT to birch as follows: in 21 (81%) patients with LAR, 14 (78%) with SAR, and in everyone in the NAR group. Serum concentration of allergen-specific IgE to Bet v1 increased significantly from a median of 20.7 (25–75% interval: 11.2–35.6) IU/mL to 29.9 (13.6–44.1) ($p = 0.028$) after NPT in patients with SAR. Allergen-specific IgE to Bet v1 was absent in all patients with LAR and NAR before and after NPT. BAT with Bet v1 was positive in 22 (85%) patients with LAR, in 14 (78%) with SAR, and 2 (9.5%) with NAR. ***Conclusion:*** These obtained data suggest there are no potential mechanisms that could explain LAR compared to SAR.

Introduction

Rhinitis is a serious problem throughout the world. It is typically classified as either allergic or non-allergic based on the medical history, skin prick tests (SPTs), and concentration of serum-specific IgE (sIgE) to allergens [1]. There are different endotypes of rhinitis, and the dif-

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ferences between them are not always obvious, for example, between systemic allergic rhinitis (SAR) and local allergic rhinitis (LAR). LAR is characterized by the local production of IgE in the nasal mucosa during natural exposure to aeroallergens. Typically, these patients have negative SPTs and sIgE results but have a positive response to the nasal provocation test (NPT) to aeroallergens [2, 3]. As in SAR, IgE-dependent pathomechanism is also present in patients with LAR. However, there is much doubt as to whether the local IgE mechanism is present in all patients [3, 4]. Moreover, there is a question about the difference between SAR and LAR mechanism regardless of the obvious systemic production of allergen-specific IgE in the latter case. Therefore, the local immunological reactions in the nasal mucosa in LAR patients are still under investigation, and the final mechanism is not completely known, just as the LAR effect on the whole body has not been determined. Therefore, we asked whether a systemic effect produced by LAR is possible. Such a systemic effect may be more or less specific than a local effect and may relate, for example, to oxidative stress. It is known that highly reactive oxygen species may cause toxic effects. Oxidative stress is defined as an imbalance between the level of reactive oxygen species and antioxidant molecules. Compared with its role in asthma, the role of oxidative stress in allergic rhinitis (AR) has received little attention. AR can occur as a result of many factors: allergic inflammation and exposure to allergens, air pollution, and smoking [5]. The specific localization of antioxidant enzymes in the respiratory tract and the rapid reaction of nitric oxide with reactive oxygen species, such as superoxide, suggest that antioxidant enzymes might also function as cell-signalling agents or regulators of cell signalling [6]. However, there is not much information about the role of this system in patients with different LARs. The investigation of the mechanism of LAR in patients with allergies to birch in comparison to those with intermittent AR with the same allergy or with non-allergic rhinitis (NAR) was the purpose of the study.

Material and Methods

It was an observational prospective study. We included adult patients: 26 with LAR, 18 with SAR with a monovalent allergy to birch pollen, and 21 with NAR. The inclusion criteria included the following: >18 years old; well-documented symptoms of moderate or severe intermittent rhinitis according to the Allergic Rhinitis and its Impact on Asthma [1]; a positive NPT to birch, negative SPT results for common inhalant allergens, including *D. pteronyssinus*, *D. farinae*, grass pollen, hazel, alder, *Alternaria*, and cats; total negative serum and allergen-specific IgE results against the mentioned allergens; and provided consent to participate in the study.

Patients had confirmed LAR if they had a positive NPT to birch and/or positive nasal-specific IgE (nsIgE) production to birch and a negative SPT, and allergen-specific IgE (sIgE) to all common inhalant allergens including birch. The control group included patients with intermittent AR induced by birch with positive SPT and sIgE to birch pollen as well as patients with NAR. The exclusion criteria included the following: chronic rhinosinusitis and/or nasal polyposis, bronchial asthma, and respiratory infections within 4 weeks before the initiation of the study.

Diagnostic Procedures

Patients who met the inclusion criteria were selected to undergo further procedures at baseline as follows: medical examination, NPT, detection of nsIgE as well as basophil activation test (BAT) and sIgE, and IgG4 antibody to Bet v1, nasal fractional exhaled nitric oxide (FeNO), and the analysis of a panel of antioxidants in the blood serum. All immunological parameters and antioxidants were also measured after NPT as described below.

Examination

A full rhinolaryngological examination was performed using anterior and posterior rhinoscopy, and in some patients, endoscopy and CT scans were performed. Rhinitis was classified according to the following Allergic Rhinitis and its Impact on Asthma guidelines: Rhinitis is considered persistent when symptoms are present for >4 days/week or persist for >4 consecutive weeks. The rhinitis severity was based on estimations of activity impairment (sleep, daily activities, work/school performance, and troublesome behaviour) and was classified as severe, moderate, or mild [1].

Serum-Specific IgE

Total sIgE antibody levels to the same aeroallergens as used in the SPT panel were determined using ELISA (Thermo Fisher, Uppsala, Sweden). The positive cut-off value for sIgE levels was >0.1 kU/L. Separately, IgE and IgG4 production in response to Bet v1 was analysed at baseline and after therapy.

Nasal Provocation Test

NPTs were performed using acoustic rhinometry with an acoustic rhinometer A1 (GM Instruments, Kilwinning, UK) between November and December. These tests were performed according to the guidelines of the Standardization Committee on Acoustic Rhinometry and the EAACI position paper [7, 8]. NPTs were performed when the concentrations of the examined allergens were low in Poland. First, using a metered pump spray, the patients were intranasally challenged with saline to exclude nasal hyper-reactivity. If the NPT was negative, it was performed again 1 week later with another provocation with saline as the negative control and then with the NPT with extracts of birch at 100,000 SQ (Aquagen, ALK-Abelló). A total of 100 μL of the allergen solution was applied to each nostril. The total volume of both nasal cavities was determined to be 2–6 mL using acoustic rhinometry, and the results were compared with those of the baseline test. The immediate reaction was analysed at 15 min, 1 h, and 6 h according to the protocol based on the EAACI position paper [7].

Nasal Lavage

The nsIgE and specific IgG4 to Bet v1 were examined similarly by the use of immunoassay (ImmunoCAP 100, Thermo Fisher Scientific, Uppsala, Sweden). These measurements were performed at baseline, immediately (30 s) after allergen provocation, and at 15 min, 1 h, and 6 h after the NPTs.

Bilateral nasal lavage was performed according to Nacleiro et al. [9]. First, 6 mL of room temperature physiological saline was added dropwise into each nostril. The mucus and saline sample was expelled after 10 s and stored on ice. The fluid was centrifuged at 4°C for 15 min at 1,500 *g*, and the solid phase was separated. The samples were stored at −80°C before further analysis. For analysis, 25 µL samples were incubated for 90 min at room temperature, after which a biotin-labelled goat anti-human IgE antibody (1:1,000, Vector Lab, Burlingame, CA, USA) was added and incubated to detect specific IgE antibodies. After being washed, the plates were incubated with streptavidin peroxidase (1:1,000) and anti-goat–AP (1:10,000) for 1 h at room temperature. After subsequent washing, 0-phenylenediamine was added as a substrate solute, and the optical densities were measured using an ELISA reader (Metertech S-960, Metretech Inc., Taipei, Taiwan). Additionally, 3 mL of normal saline was added to each sample, and the concentrations of local antibodies were recalculated using the total protein concentration for each measurement to correct for the dilution effect of the samples (Bradford protein analysis). All the values are provided as a calculated protein ratio.

Basophil Activation Test

Blood samples were obtained before and 1 h after NPT and were analysed according to the Rentzos protocol [10]. Birch (Betula verrucosa) allergen was used (Soluprick, ALK-Abelló, Hørsholm, Denmark). Basophils were stimulated with Bet v1 at concentrations of 10,000, 1,000, 100, 10, and 1 ng/mL (Euroimmune AG Germany). Basophil activation was measured based on the upregulation of CD63 on CD203c + basophils observed by flow cytometry of blood samples collected in heparinized tubes (Becton-Dickinson Biosciences). All tests were carried out within 2 h of blood sampling. The cut-off for determining a positive test was set at 15% CD63-positive basophils. To determine the final results, the stimulation index was calculated as the ratio between the percentage of activated basophils in the presence and absence of allergens.

Panel of Antioxidant Agents

Blood samples were obtained before and 1 h after NPT. The following factors were measured.

Determination of Protein Sulfhydryl Groups

The protein sulfhydryl concentration was determined as described by Koster et al. [11] using DTNB, which undergoes reduction by compounds containing sulfhydryl groups, yielding the yellow anion derivative, 5-thio-2-nitrobenzoate, which absorbs at a wavelength of 412 nm using an automated analyser Perkin Elmer. The results are shown in µmol/L.

Determination of Total Antioxidant Capacity

Total antioxidant capacity was measured according to Erel [12]. In this colorimetric assay, radicals are generated, and the antioxidant activity of the serum reduces radical formation. The change in colour of ABTS + ions (2,2′-azinobis [3-ethylbenzothiazoline-6-sulfonate]) is measured as the change in absorbance at 660 nm. This assay was conducted on an automated Perkin Elmer analyser calibrated with Trolox. Data are shown in mmol/L.

Determination of Total Oxidation Status

Total oxidant status was measured according to Erel [13] in seminal plasma. The assay is based on the oxidation of ferrous ions to ferric ions in the presence of various oxidant species in acidic medium. The change in colour of the ferric ion by xylenol orange is measured as a change in the absorbance at 560 nm. This process was analysed using an automated analyser Perkin Elmer calibrated with hydrogen peroxide. Data are shown in µmol/L.

Determination of Malondialdehyde

Malondialdehyde, a product of lipid peroxidation, was measured fluorometrically as 2-thiobarbituric acid-reactive substance in serum according to Ohkawa et al. [14] with modifications. Samples were mixed with 8.1% sodium dodecyl sulphate, 20% acetic acid, and 0.8% 2-thiobarbituric acid. After being vortexed, the samples were incubated for 1 h at 95°C, and butanol-pyridine 15:1 (v/v) was added. The mixture was shaken for 10 min and then centrifuged. The butanol-pyridine layer was measured fluorometrically at 552 and 515 nm excitation (Perkin Elmer, Waltham, MA, USA). 2-Thiobarbituric acid-reactive substance values are expressed as malondialdehyde equivalents. Tetraethoxypropane was used as the standard. Concentrations are given in µmol/L plasma.

Determination of Superoxide Dismutase Activity

The method of Oyanagui [15] was used to measure the activity of superoxide dismutase (SOD) in serum. In this method, xanthine oxidase produces superoxide anions that react with hydroxylamine to form nitric ions. These ions react with naphthalene diamine and sulfanilic acid, generating a coloured product. The concentration of this product is proportional to the number of superoxide anions produced and negatively proportional to the activity of SOD. The absorbance was measured using an automated analyser Perkin Elmer at a wavelength of 550 nm. The enzymatic activity of SOD was expressed in nitric units. SOD activity in the serum was expressed in NU/mL.

Measurements of Nitric Oxide

Measurements of the nasal FeNO level were obtained using a hand-held chemiluminescence analyser (NIOX MINO Airway Inflammation Monitor, Aerocrine AB, Solna, Sweden) and were performed according to Maniscalco et al. [16]. The instrument was calibrated with a nitric oxide calibration gas mixture. Nasal steroids, nasal decongestants, and antihistamine drugs were not applied within 2 weeks before the examinations. A single measurement was made both during nasal exhalation and after 10 s of breath-holding against an expiratory resistance of 5–25 cm H_2O with a flow of 50 mL/s using a nasal mask. Measurements were performed before and after 1 h of NPT. All measurements were repeated the following day at the same time. Three acceptable FeNO results and mean values were included in the analysis. The detection limit was 1 part per billion. The measurement range was 5–400 part per billion.

Statistical Analysis

A descriptive analysis was performed, and the results are presented as the median and 25–75% interval. ANOVA test was used

Table 1. Characteristics of patients with allergies to birch

	LAR, *n* = 26	SAR, *n* = 18	NAR, *n* = 21
Age, median with 25–75% interval, years	27.5 (21.3–30.4)	24.5 (20.9–28.7)	26.1 (22.7–29.6)
Time of nasal symptoms, median with 25–75% interval, s	3.5 (2.9–3.8)	3.9 (3–4.2)	4.4 (3.8–4.7)
Moderate rhinitis, *n* (%)	14 (54)	9 (50)	11 (53)
Severe rhinitis, *n* (%)	12 (46)	9 (50)	10 (48)
Female, *n* (%)	14 (54)	10 (56)	12 (57)
Smoking, *n* (%)	4 (15)	3 (17)	4 (19)
Positive family history of atopy, *n* (%)	6 (23)	11 (61)	4 (19)
Total IgE, median with 25–75% interval, IU/L	38.5 (27.5–49.5)	172 (128–214)	43 (29.5–60.4)
Serum allergen-specific IgE to Bet v1	–	20.7 (11.2–35.6)	–
Positive NPT to birch, *n* (%)	26 (100)	17 (89)	–

LAR, local allergic rhinitis; SAR, systemic allergic rhinitis; NAR, non-allergic rhinitis; NPT, nasal provocation test.

Table 2. Results of mean FeNO levels in the studied groups before and 15 min after NPT

Median FeNO, 25–75%, ppb	LAR	SAR	NAR	LAR vs. SAR	LAR vs. NAR	SAR vs. NAR
Before NPT, ppb	39 (27–43)	45 (32–58)	40 (29–48)	$p = 0.72$	$p = 0.52$	$p = 0.14$
15 min after NPT, ppb	67 (54–77)	72 (61–83)	46 (39–58)	$p = 0.07$	$p = 0.05$	$p = 0.05$
p	0.02	0.02	0.18			

LAR, local allergic rhinitis; SAR, systemic allergic rhinitis; NAR, non-allergic rhinitis; NPT, nasal provocation test; FeNO, fractional exhaled nitric oxide; ppb, part per billion.

to compare the characteristic parameters of the study subgroups. Additionally, the χ^2 test was used to compare other parameters and Student's *t* test was used for parametric variables. Differences were considered significant at $p < 0.05$.

A logistic multiple regression analysis was performed to identify independent risk factors for LAR diagnosis. First, a univariate analysis was carried out to assess how each potential variable (positive detection of nasal IgE, IgG4 to Bet v1, the presence of allergen-specific IgE and IgG4 to Bet v1 in the serum, a significant increase in FeNO between baseline and 15 min after NPT, positive BAT to Bet v1 for any analysed concentration of studied allergen, and significant changes in antioxidant parameters between baseline and 1 h after NPT) affected the probability of a positive NPT response to birch. Variables that were not significant in this analysis were excluded. In the second step, variables found to be statistically significant were tested in a combined analysis that indicated a poor or good influence on LAR diagnosis. The results are presented as odds ratios and 95% confidence intervals. An odds ratio of 1 for a given variable means that this variable did not influence the final diagnosis.

Results

The characteristics of the patients are presented in Table 1.

Nasal Lavage

Nasal IgE produced in response to Bet v1, and the concentration increased in response to the birch NPT comparably in the LAR and SAR groups as follows: in 18 (69%) patients with LAR, and 14 (78%) with SAR, and everyone in the NAR group. The results are presented in Figure 1 and Table 2. The maximum increase in nsIgE to Bet v1 was observed 1 h after NPT in both patient groups. In 4 patients with LAR, the presence of IgG4 was detectable (shown in Fig. 1).

Blood Serum

The serum concentration of allergen-specific IgE to Bet v1 increased significantly from a median of 20.7 (25–75% interval: 11.2–35.6) IU/mL to 29.9 (13.6–44.1) ($p = 0.028$) after 1 h and to 33.6 (19.2–49.5) and after 6 h in 11 (42%) patients with SAR. Allergen-specific IgE to Bet v1 was absent in all patients with LAR and NAR.

Allergen-specific IgG4 to Bet v1 in the serum were detected in 2 patients with LAR before and after NPT at the same level and in 13 (72%) patients with SAR without

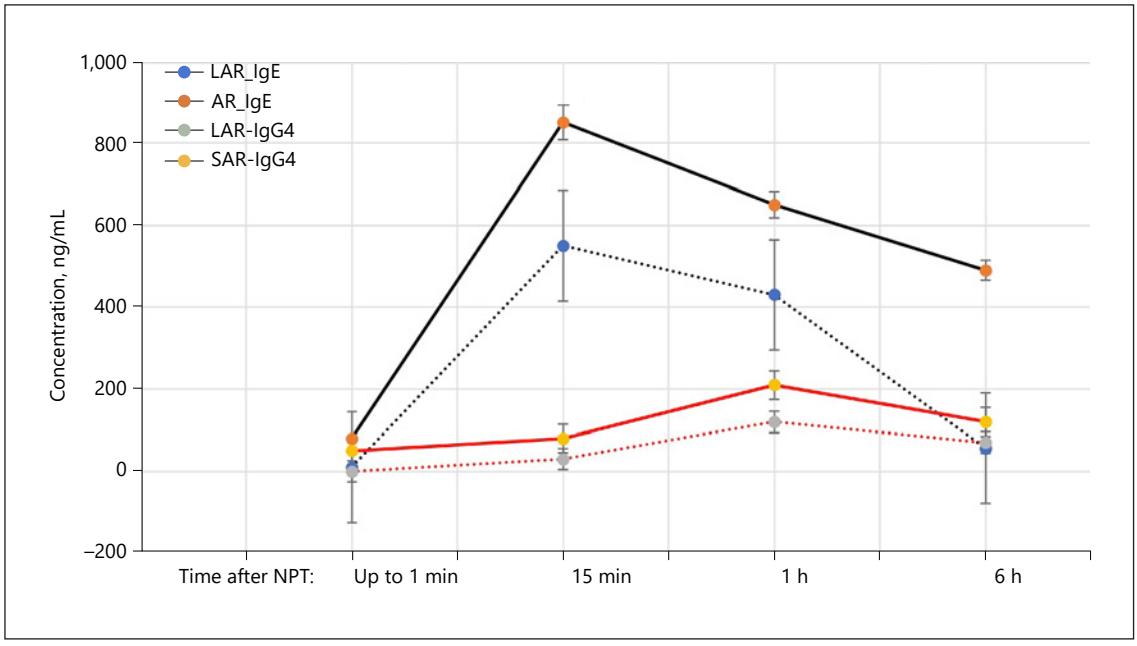

Fig. 1. Changes in nasal levels of IgE and IgG_4 in the nasal lavage produced in response to the Bet v1 NPT in patients with LAR and SAR and an allergy to birch. The significant increase in median specific IgE to Bet v1 in the SAR group compared with the LAR group at 15 min, 1 h, and 6 h after NPT. NPT, nasal provocation test; LAR, local allergic rhinitis; SAR, systemic allergic rhinitis; AR, allergic rhinitis.

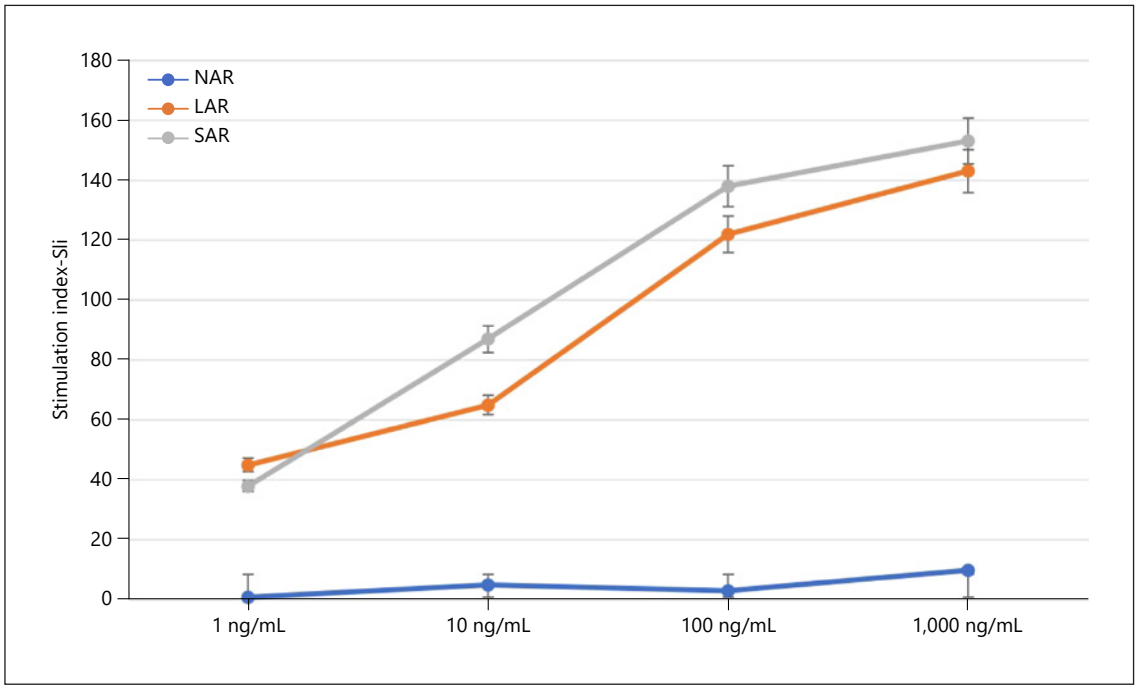

Fig. 2. SI; the horizontal line indicates the cut-off point of the assay. SI, stimulation index; LAR, local allergic rhinitis; SAR, systemic allergic rhinitis; NAR, non-allergic rhinitis.

Table 3. Results of the antioxidant parameters in the serum before and 1 h after the provocation test

Parameters	SH, μmol/dL	TAC, mmol/L	TOS, μmol/L	MDA, μmol/L	SOD, NU/mL
LAR	215 (176–286)	1.5 (1.1–1.9)	132 (105–176)	18 (11–24)	19 (13–21)
LAR_{NPT}	221 (115–291)	0.6 (0.3–1.1)	122 (98–143)	20 (9–26)	14 (8–19)
p values	>0.05	**0.002**[a]	>0.05	>0.05	>0.05
SAR	203 (154–245)	1.9 (1.4–2.2)	154 (128–192)	17 (10–23)	18 (8–29)
SAR_{NPT}	173 (145–219)	1.2 (0.8–1.5)	142 (119–201)	15 (9–21)	17 (8–25)
p values	>0.05	**0.001**[a]	>0.05	>0.05	>0.05
NAR	288 (152–341)	1.2 (0.5–1.5)	161 (132–204)	11 (7–19)	15 (9–21)
NAR_{NPT}	307 (265–351)	1.2 (0.7–1.4)	151 (112–192)	13 (8–17)	17 (9–20)
p values	>0.05	>0.05	>0.05	>0.05	>0.05

Results were shown as median with 25–75% interval. LAR, local allergic rhinitis; SAR, systemic allergic rhinitis; NAR, non-allergic rhinitis; SH, protein sulfhydryl groups; TAC, total antioxidant capacity; TOS, total oxidation status; MDA, malondialdehyde; SOD, superoxide dismutase; NPT, 1 h after nasal provocation test with birch allergen. [a] Significant difference between mean value of TAC, before and after NPT, in LAR and SAR patients.

Table 4. Multiple logistic regression analysis for the diagnosis of LAR in all analysed patients

Variables	LAR diagnosis[a]	
	OR (95% CI)	*p* values
Positive nasal detection of IgE Bet v1	**1.48 (0.99–1.61)**	**0.03**
Presence of sIgE Bet v1 in serum after NPT	0.87 (0.81–1.01)	>0.05
Positive nasal detection of IgG_4 Bet v1 after NPT	0.67 (0.52–0.80)	>0.05
Positive nasal detection of Bet v1 after NPT	1.11 (0.97–1.42)	>0.05
Positive BAT to Bet v1	**2.15 (1.87–2.39)**	**0.01**
Increase in FeNO after NPT^	0.34 (1.09–1.85)	>0.05
Decrease in TAC beyond 1 h after NPT	0.86 (0.54–1.39)	>0.05

LAR, local allergic rhinitis; TAC, total antioxidant capacity; OR, odds ratio, NPT, nasal provocation test; BAT, basophil activation test; FeNO, fractional exhaled nitric oxide; SPT, skin prick test; sIgE, serum-specific IgE. [a] LAR, diagnosis based on negative SPT sIgE and positive NPT, to birch.

changes to NPT. Allergen-specific IgG4 to Bet v1 was absent in patients with NAR.

Basophil Activation Test

Forty-six patients were tested; 4 were non-responders in the LAR group (15%), 4 (9.5%) were non-responders in the SAR group (13%), and most were non-responders in the NAR group (19; 90%). The results are presented in Figure 2. The BAT results were positive in 22 (85%) patients with LAR, in 14 (78%) with SAR, and 2 (9.5%) with NAR.

Nasal Nitric Oxide

The test-retest reliability with the intra-class correlation coefficient was assessed in all patients. The mean nasal NO level was 0.89 (range 0.68–0.98).

Compared to those in the NAR group, patients in the LAR and SAR groups had significantly higher FeNO levels after NPT, which peaked (in both groups) 15 min after allergen exposure (as shown in Table 2). Then, FeNO decreased to baseline values up to 1 h after NPT in most patients with LAR and SAR without significant differences. In 2 (10%) patients with NAR, a significant increase in the mean FeNO level was observed at 15 min, 1 h, and 6 h after NPT without any clinical symptoms. In 2 (11%) patients with SAR and 5 (19%) patients with LAR, there were no significant changes in the values between baseline and 15 min, 1 h, and 6 h after NPT. There were no significant correlations between nasal symptom scores and nasal FeNO in any of the analysed allergic patients ($p > 0.01$).

Antioxidant

The results of the analysed antioxidant parameters are presented in Table 3. In 15 (58%) patients with LAR and 13 (72%) with SAR, total antioxidant capacity decreased after NPT. Patients with NAR showed no similar trend. There were no other changes in the other parameters tested.

The multivariate analysis was performed with independent variables, which are described in the methods. The presence of nsIgE to Bet v1 after provocation in the nasal mucosa or the positive BAT response to Bet v1 was significantly increased in patients with an LAR diagnosis (is shown in Table 3).

Fourteen (54%) patients with LAR had positive results for both, nsIgE to Bet v1 and BAT test, the remaining 8 (31%) patients had only positive BAT test. In this last subgroup, a significant increase in FeNO and changes in antioxidants after NPT were noticed.

In patients with SAR, there was no similar trend; most patients had nasal-positive IgE to Bet v1 after NPT, positive BAT to Bet v1, and positive serum IgE and IgG4 to Bet v1. There were significant changes in antioxidant parameters in 11 patients (61%).

Patients with NAR had negative results in all immunological parameters concerning Bet v1. The FeNO trends are presented above. The antioxidant parameters did not change after NPT. Based on the multiple logistic regression analysis, patients were diagnosed with LAR if they had a positive nasal IgE Bet v1 response and/or positive BAT production to Bet v1 (as shown in Table 4).

Discussion

The presented results suggest that a large group of patients with LAR had a positive allergen-specific IgE response in the nose, but not everyone, as was the case for patients with SAR. This evidenced that the analysis method was not sensitive enough and that the dose of the allergen was too low in some patients or specific IgE does not appear in some forms of LAR. This finding is consistent with other authors' observations that some patients with LAR do not develop the typical IgE-dependent response [17]. However, if this response occurs, it develops differently without switching IgG + B to IgE according to other authors' observations [17].

The BAT was positive in most of the studied subjects, excluding patients with NAR. This observation is in line with those of other authors [17, 18]. The authors suggest that BAT is more sensitive than IgE [18]. To compare patients with LAR and SAR, these mechanisms are present in a similar way. However, it is possible that local mechanisms underlying the specific response to an allergen in the nose of LAR may be more numerous than those underlying SAR and involve IgE reactions. IgE-dependent reactions may not be the only reactions. Other authors have similar doubts [17]. Multivariate analysis revealed that IgE or BAT can play an equivalent role in recognizing LAR but also in SAR. Despite the obvious similarities, LAR seems not to be the first stage of SAR. There are data that only about 6% of patients whose LAR goes into SAR [19].

The increase in mean nasal FeNO after NPT in patients with SAR and LAR (but not in those with NAR) confirms the induction of an allergen-specific inflammatory response, and it does not differentiate patients with LAR from SAR. This is consistent with observations in patients with SAR, but the value of FeNO in LAR patients has not been confirmed [20].

There is little information on how the antioxidant system behaves in patients with LAR symptoms. A decrease in TAP after NPT in patients with LAR and SAR but not in those with NAR was observed. Most likely, this is the first observation that the induction of LAR symptoms may produce a systemic antioxidant response. There is evidence that oxidative stress plays a significant role in atopic disease, for example, in AR [21, 22]. The decrease in antioxidant enzymes in patients with SAR was also observed in the present study. Some reports have also confirmed that oxidative stress plays a significant role in the maintenance of the chronic inflammatory process that occurs, for example, in AR [23]. Also, the specific role of oxidative stress in the induction and exacerbation of inflammation of the airways is increasingly considered an important element in the asthma pathogenesis [24, 25]. However, the obtained results herein showed a decrease in only the total antioxidant capacity in some patients with LAR and SAR. Moreover, the oxidative stress response seems not to differ between LAR and SAR.

No other significant changes in the analysed antioxidant system parameters were noted. This result may be associated, for example, with a lower allergen exposure during NPT than in the pollen season. Therefore, the generalizability of this observation may be limited.

There were some limitations to this study. First, the number of patients was relatively small. This is due to the strict inclusion criteria and type of protocol. However, these quantities are comparable with those of other similar studies. Another limitation is the lack of a similar analysis in the natural birch pollen season. However, this analysis is planned. An important limitation may also be

the inclusion criteria for the group with LAR. Positive NPT results have limited sensitivity and specificity in the diagnosis of LAR, but this is currently the most important diagnostic tool.

Conclusion

These obtained data suggest there are no potential mechanisms that could explain LAR compared to SAR except for systemic IgE production. Despite its local nature, LAR can induce oxidative stress. Further research is needed.

Statement of Ethics

The local ethics committee approved the study (Medical University of Silesia, Katowice, Poland), and all participants gave informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Medical University of Silesia, Poland.

Author Contributions

Andrzej Bozek: performed study procedures, analysed and interpreted the patients data, statistical analysis, and a major contributor in writing the manuscript. Jolanta Zalejska Fiolka: performed study procedures and contributed in writing the manuscript. Beata Galuszka: analysed data and performed study procedures. Anna Krajewska Wojtys: performed study procedures. Anna Cudak: performed study procedures and analysed data. Beata Galuszka: performed study procedures and contributed in writing the manuscript. All authors read and approved the final manuscript.

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