Contribution of In Vivo and In Vitro Testing for The Diagnosis of Local Allergic Rhinitis

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Local allergic rhinitis (LAR) is characterized by an allergen-specific, IgE-mediated inflammatory response limited to the nasal mucosa [1]. This local production of IgE (entopy) is not associated with measurable specific IgE (sIgE) in peripheral blood or with positivity in skin prick testing (SPT) for the culprit allergen. In southern Europe, LAR is estimated to account for 26% of all cases of rhinitis and up to 70% of all cases of nonallergic rhinitis (NAR) [2]. Despite similar disease mechanisms, LAR seems to be distinct from classic allergic rhinitis and not its precursor [3].

LAR should be suspected when the patient's symptoms are suggestive and triggered by allergen exposure, despite negative findings in a conventional allergological work-up. Patients are frequently misdiagnosed with idiopathic NAR, and distinguishing between both entities is difficult without specific diagnostic tests, which may not be available in all centers [4]. Underdiagnosis of LAR has implications for the management of these patients, as they are deprived of allergen immunotherapy (AIT), an effective approach in such cases [5].

The nasal provocation test (NPT) is considered the gold-standard for diagnosis, although it can be time-consuming [6]. Given the limited experience using the basophil activation test (BAT) as part of a comprehensive diagnostic approach to LAR [7,8], we re-evaluated the relative contribution of this test in patients with suspected LAR and determined whether it would help to avoid in vivo testing.

We report data from 20 patients with rhinitis symptoms triggered by exposure to house dust mites (mean and median age, 45.5 years; 80% female; mean age at time of diagnosis, 31 years; median age, 30.2 years). We also evaluated 4 healthy controls and 4 allergic rhinitis patients (mean age, 33.4 years; median age, 31.5 years).

All patients had negative SPT results and sIgE for dust mites—as did the healthy controls—and underwent NPT with a dust mite extract (Laboratorios LETI). An extract of *Dermatophagoides pteronyssinus* (100 HEP/mL) or *Lepidoglyphus destructor* (30 HEP/mL) was selected according to the patient's clinical history and/or occupational exposure. The provocation test was performed with 1/1000, 1/100, and 1/10 dilutions of mite extract applied nasally using a metered pump at 15-minute intervals. The result of the NPT was determined using clinical and/or rhinomanometric criteria. The clinical *D pteronyssinus* criteria included triggered symptoms, such as sneezing, nasal pruritus, obstruction, anterior or posterior rhinorrhea, and tearing. A visual analog scale was used for each symptom, and an increase >30% for the sum of all 5 parameters was considered positive [6]. A baseline and post-NPT rhinomanometric evaluation was performed (MasterScreen Body, Jaeger), and a 50% increase in resistance was considered positive [9].

sIgE was quantified in nasal secretions before the NPT (T0), at the end of the NPT (T1), and 1 hour later (T2) (ImmunoCAP, Thermo Fisher Scientific). A BAT (Buhlmann) was performed according to the manufacturer's instructions with mite extracts (LETI, see above) in 17 of the 20 patients and in the controls. The *D pteronyssinus* extract was run with the commercially available concentration of 1.19 mg/mL (100 HEP/mL) and with concentrations of 0.595, 0.298, 0.0595, 0.029, and 0.019 mg/mL. For *L destructor*, the BAT was performed with the commercially available concentration of 5 mg/mL (30 HEP/mL) and with concentrations of 1.4, 0.35, and 0.025 mg/mL. Basophils were identified as $CCR3^+$ cells, and CD63 expression was used as a marker of basophil activation. The study was approved by the local ethics committee. Informed consent was obtained from all participants.

Seventeen of the 20 NPTs (85%) were positive. Fourteen NPTs were performed with *D pteronyssinus* (13 positive) and 6 with *L destructor* (4 positive). Four NPTs were positive only by clinical criteria, 7 only by rhinomanometric criteria, and another 6 by both (Table). There were no significant differences in the quantification of sIgE (kU/L) in nasal secretions between patients with positive or negative NPT results, or between the different collection times of nasal secretions (T0, median [IQR], 0.125 [0.113-0.138], mean, 0.130; T1, median, 0.130 [0.110-0.130], mean, 0.125; T2, median, 0.125 [0.113-0.130], mean, 0.120).

The BAT was performed in 17 patients, of whom 15 had positive NPT results. The results were all negative for healthy

Table. Nasal Provocation Test and Basophil Activation Test Results

Subject	Extract	NPT Result[a]	ΔVAS >30%, cm	Rhinomanometry ΔRes ≥50%	Nasal sIgE, kU/L (T0, T1, T2)	BAT results (SI)
F, 60	LD	+ (0.50)	Yes (7.2→15.7)	Yes (152%→289%)	0.11, 0.11, 0.11	+ (45.86)
F, 29	DP	+ (0.12)	Yes (3.7→12.7)	Yes (151%→268%)	0.12, 0.13, 0.12	– (1)
F, 39	DP	+ (0.01)	Yes (1.7→3.3)	Yes (50%→170%)	0.13, 0.13, 0.13	+ (6.49)
M, 46	DP	+ (0.12)	Yes (3.1→6.2)	Yes (77%→187%)	0.13, 0.13, 0.12	– (0.73)
F, 47	DP	+ (0.12)	Yes (3.6→4.8)	Yes (132%→235%)	0.13, 0.13, 0.13	– (0)
F, 54	DP	+ (0.12)	Yes (0→28.3)	Yes (51%→139%)	0.14, 0.13, 0.12	+ (3.39)
F, 35	LD	+ (0.05)	Yes (22.6→30.9)	No (62%→102%)	0.11, 0.11, 0.12	+ (5.44)
F, 27	DP	+ (0.12)	Yes (5.7→14)	No (130%→149%)	0.22, 0.15, 0.13	NP
F, 40	DP	+ (0.12)	Yes (0→8)	No (75%→102%)	0.16, 0.15, 0.14	– (0)
M, 43	DP	+ (0.12)	Yes (3.3→6.3)	No (45%→70%)	0.12, 0.13, 0.13	+ (2.95)
F, 53	LD	+ (0.5)	No (20→20.4)	Yes (63%→117%)	0.12, 0.11, 0.10	+ (9.72)
F, 64	LD	+ (0.5)	No (3.3→4.1)	Yes (44%→116%)	0.10, 0.11, 0.10	+ (82.88)
F, 22	DP	+ (0.12)	No (7.9→6.6)	Yes (69%→119%)	0.15, 0.15, 0.15	NP
F, 43	DP	+ (0.12)	No (3.7→1.9)	Yes (65%→214%)	0.12, 0.13, 0.14	– (1.65)
F, 47	DP	+ (0.12)	No (0.7→0)	Yes (110%→229%)	0.13, 0.11, 0.13	– (0)
F, 55	DP	+ (0.12)	No (0→0)	Yes (58%→255%)	0.13, 0.13, 0.13	+ (2.30)
F, 58	DP	+ (0.12)	No (33.2→1.5)	Yes (114%→245%)	0.12, 0.12, 0.13	NR
F, 43	LD	-	No (1.8→2)	No (48%→69%)	0.10, 0.11, 0.10	– (0)
F, 45	LD	-	No (11.6→14)	No (69%→83%)	0.11, 0.10, 0.10	NP
F, 60	DP	-	No (1→0)	No (298%→180%)	0.14, 0.12, 0.12	– (0)
Allergic (Positive) Controls						
M, 18	DP	+ (0.01)	Yes (6.1→16.8)	Yes (149%→277%)	0.13, 0.12, 0.14	+ (33.62)
F, 41	DP	+ (0.12)	Yes (5.2→17.7)	Yes (124%→292%)	0.11, 0.11, 0.12	+ (66.37)
F, 26	LD	+ (0.5)	Yes (0→9.1)	Yes (71%→134%)	0.12, 0.13, 0.13	+ (58.09)
F, 35	LD	+ (0.5)	No (16→16.7)	Yes (67%→205%)	0.10, 0.12, 0.14	+ (87.57)
Healthy (Negative) Controls						
M, 20	DP	-	No (3→2.5)	No (53%→88%)	0.10, 0.10, 0.10	– (0)
M, 47	DP	-	No (11→12.7)	No (61%→89%)	0.11, 0.11, 0.10	– (0)
F, 28	LD	-	No (0→0)	No (158%→180%)	0.11, 0.12, 0.14	– (0)
F, 52	LD	-	No (1→0)	No (104%→99%)	0.10, 0.12, 0.12	– (0)

Abbreviations: BAT, basophil activation test; DP, *Dermatophagoides pteronyssinus*; LD, *Lepidoglyphus destructor;* NP, not performed; NR, nonresponder; SI, stimulation index; ΔRes, variation in measured resistance; ΔVAS, variation in the result of the visual analog scale.
[a]Allergen concentration with positive response in mg/mL.

controls and all positive for allergic rhinitis controls. The BAT was positive (stimulation index, ≥2) in 8 of the 15 patients with a positive NPT result (53.3%) and negative in 8 patients, 2 of whom had a negative NPT result. One patient was a nonresponder. In 6 patients with a positive NPT result, the result of the BAT was negative.

Despite the small sample, a diagnosis of LAR (positive NPT result) was established in 85% of participants. This large percentage emphasizes the importance of further investigation in these patients, for whom current evidence supports treatment with AIT. In one study, AIT improved symptoms and increased allergen tolerance, as measured by NPT [5].

The positivity criteria for NPT varied in the literature until the recent publication of unified guidelines [10]. Clinical symptoms are insufficient for interpreting NPT results, as further evidenced in our study, where 41.2% of NPTs were considered positive solely by rhinomanometric criteria.

We observed no significant variation in sIgE levels. Determination of sIgE in nasal secretions is very specific, although less sensitive than NPT, probably because of a dilution effect of nasal lavage [4].

In LAR, BAT has been shown to have a sensitivity of 50.0%-66.6% and a specificity of 90.0%-91.7% [7,8]. In our study, BAT and NPT results agreed in 10 out of 16 patients (62.5%). There were no false positives. The sensitivity of BAT obtained in the present study (53.3%) reproduces the results of previous studies [7,8] and reinforces the usefulness of BAT in the first steps of a rational diagnostic approach in LAR and when NPT is not available.

NPT is a time-consuming procedure. Our findings and the high specificity of BAT obtained in previous studies performed in LAR patients suggest that a positive BAT result could confirm a diagnosis of LAR. We propose that, where possible, the various available diagnostic methods should be combined to maximize diagnostic accuracy.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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