

Persistent Allergic Rhinitis Has a Moderate Impact on the Sense of Smell, Depending on both Nasal Congestion and Inflammation

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Objectives/Hypothesis: A degree of smell disturbance has been found in seasonal and perennial allergic rhinitis, but alterations in olfaction in patients with persistent allergic rhinitis (PER) have not yet been evaluated. The aims of the study were to evaluate the impact of PER on the sense of smell, and to characterize this impact based on self-reported hyposmia (SRH) and PER severity.

Study Design/Methods: A prospective controlled study was performed on 49 consecutive patients with PER. PER patients were subclassified depending on severity and the presence of SRH. Olfactory function was evaluated by the Barcelona Smell Test-24 (BAST-24) olfactometry for smell detection, identification, and forced choice for first and fifth cranial nerve (CN) dependent odors in comparison to a group of 60 healthy volunteers. In patients with SRH, obstruction was evaluated by peak nasal inspiratory flow (PNIF) and acoustic rhinometry; and nasal inflammation was evaluated by nasal nitric oxide (nNO).

Results: Most patients with PER (67%) presented SRH. Moderate/severe PER (84.8%) predominated among patients with SRH, while mild PER (75%) predominated among patients without SRH. Smell detection, identification, and forced choice tests were significantly worse in PER patients ($P < .05$) than in healthy controls for the odors related to the first and fifth CN. Among subgroups, patients with moderate/severe PER and/or with SRH presented a significant reduction in smell

detection ($P < .05$) compared to healthy controls. Nasal NO correlated ($R: 0.4$; $P < .05$) with loss of smell.

Conclusions: Patients with PER have a moderate loss of smell (BAST-24) with a higher impairment in those with self-reported hyposmia and moderate-to-severe PER. These results suggest that the sense of smell should be further investigated in all patients with allergic rhinitis, both in a clinical setting and in clinical trials.

Key Words: Hyposmia, olfaction, persistent allergic rhinitis, smell disorders.

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INTRODUCTION

An estimated 10% to 25% of the worldwide general population suffer from allergic rhinitis (AR).¹ Allergic rhinitis, an inflammatory disease that affects the nasal mucosa, has a significant impact on a patient's quality of life with respect to work, school, home, and leisure activities. Classically, the AR was divided into seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). Nowadays, using Allergic Rhinitis and its Impact in Asthma (ARIA) criteria, AR is currently divided into duration: persistent (PER) or intermittent (IAR); whereas in terms of severity it is classified as mild or moderate/severe.^{2,3} In Spain, AR affects 21.5% of the population,⁴ with 29% of these being classified as having PER.⁵

It is well-known that the association between AR and chronic rhinosinusitis has an important impact on smell disturbances.^{6,7} Smell disorders are present in 21% to 23% of patients with AR.^{8,9} Although medical literature has reported smell disorders associated with SAR,^{10–16} few studies have addressed the potential alterations in olfaction in patients with PAR,^{15,16} and none in those with PER. One study has documented moderate worsening of smell (15%) with 70% of nasal narrowing measured by acoustic rhinometry after allergen exposure.¹¹ In addition, it has been reported that 31% of patients with AR have taste disorders.⁹

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Odor-identification tests for clinical use have been developed in different countries and cultures. The University of Pennsylvania Smell Identification Test (UPSIT)¹⁷ and the Connecticut Chemosensory Clinical Research Center identification test (CCCRC)¹⁸ have been developed in the USA, while the “sniffin’ sticks” test¹⁹ and the Smell Diskettes Test²⁰ have been used in Europe. However, the nature of odor identification, closely related to familiar and cultural aromatic items, usually limits the use of olfactory tests to the country or region where they have been developed and validated. In the present study, the Barcelona Smell Test-24 (BAST-24), a smell test validated for the Spanish and Mediterranean population, has been used to evaluate the loss of smell²¹ in PER patients.

The aim of this study was to assess the impact of persistent allergic rhinitis (PER) on the different characteristics of the sense of smell (detection, identification, and forced choice), as well as to characterize it on the basis of SRH and PER severity.

MATERIAL AND METHODS

Population and Design

Study population: Forty-nine consecutive patients aged 18 years or older (21 women and 28 men, mean age: 32 years, and range: 21–56 years) with PER were included in this prospective controlled study. The control group consisted of 60 healthy subjects age-matched (20–50 years) with no SRH, no acute or chronic nasal or sinus complaints. Inclusion criteria for the patients were a history of PER for at least 2 years, based on ARIA criteria,² and skin prick test positivity to clinically relevant aeroallergens (house dust mites, pollens, animal danders, or molds).

Exclusion criteria were the existence of any nasal disease other than PER (IAR or acute or chronic paranasal sinus diseases), upper respiratory tract infection during the previous 15 days, specific immunotherapy during the last 3 years, steroid or antileukotriene medication in the last 4 weeks, antihistamines in the last 3 days, and pregnancy.

Study design: To characterize the patients with PER the following diagnostic outcomes were studied: nasal symptoms, nasal endoscopy, skin prick test, and BAST-24 olfactometry. Patients were allowed to use nasal saline washes during the washout period for oral and intranasal steroids and antihistamines. Patients with PER were evaluated for duration (symptoms present for more than 4 days a week and for more than 4 consecutive weeks) and severity following the ARIA guidelines.² PER patients were classified depending on their self-reported hyposmia (SRH) and on PER severity. The control group consisted of 60 healthy volunteers (30 women and 30 men, mean age 35 years, range: 20–50 years) without nasal symptoms.

To analyze the impact of PER severity on patients with SRH, nasal patency (peak nasal inspiratory flow [PNIF], acoustic rhinometry) and nasal inflammation were also assessed by means of nasal nitric oxide (nNO).

The Ethical Committee of our institution approved the study and signed informed consent was obtained from all patients and healthy volunteers.

Outcomes Assessment

1. **Allergy study:** Skin prick tests using commercial extracts to the 20 most common airborne allergens present in our geographic area (Barcelona) were performed in all patients and

controls.

2. **Nasal endoscopy:** Mucopurulent discharge from middle meatus, oedema/mucosal obstruction primarily in middle meatus, and nasal polyps were evaluated to reject the possibility of an acute or chronic paranasal sinus disease in all patients and controls.
3. **Nasal symptoms:** Nasal congestion, loss of the sense of smell, and patient's reported global rhinitis score (GRS) were assessed using a visual analogical scale (VAS) from 0 to 100 mm.
4. **Olfactometry:** Olfactory function was analyzed by means of BAST-24, assessing twenty odors for the first cranial nerve and four odors for the fifth cranial nerve.²¹ The smell test was performed in a quiet, noise isolated, well-ventilated room, with controlled humidity (%) and temperature (21–23°C). Neither the examiner nor the patients and controls were allowed to apply any perfumes, lotions, or creams beforehand. All the odorants were located in hermetic glass jars. Once open, the odorant jars were located at 1 cm from the nose with no contact between the explorer's finger and patient's face. Patients were studied for the different smell characteristics: detection, identification, and forced choice (4 options).
5. **Nasal function:** Nasal airflow was measured by peak nasal inspiratory flow (PNIF, l/min.). The nasal volume (cm³) within the distance of 0 and 6 cm from the nostrils and the minimum cross-sectional area (MCA, cm²) were measured from each nasal cavity using acoustic rhinometry.
6. **Nasal inflammation:** To evaluate nNO (ppb), a nasal sample was obtained from one nostril using a negative pressure pump with a flow rate of 3 l/min. The patients were instructed to blow out their cheeks to raise mouth pressure, in order to lift up the palate and isolate the nasal cavity from the rest of respiratory system.

Statistical analysis was performed using SPSS for Windows (SPSS 11.0, Chicago, IL). All analyses were performed using two-tailed test significance at the $P < .05$ level. The data are presented as mean $\pm$ SEM (standard error of the mean). Comparisons for differences in olfactory detection, identification, and forced choice between groups were performed using a Student t test. Pearson correlation coefficients were used to examine the association between nasal symptoms, BAST-24, nasal patency, and nNO.

RESULTS

Demographic data: Most of PER patients (65.3%) had moderate/severe PER, while 34.7% had mild PER (Table I). Patients with SRH (67%) presented a significant ($P < .05$) increased prevalence of moderate/severe PER compared to no SRH patients. (Table I).

Allergy study: All PER patients (100%) had a positive prick test to house dust mites. Other positivities were found to animal danders (30.7%), and pollens (27%). All healthy controls presented a negative skin prick test.

Nasal endoscopy: No mucopurulent discharge from middle meatus, oedema/mucosal obstruction primarily in middle meatus, or nasal polyps was observed in patients and healthy controls.

Nasal symptoms: All patients satisfied the ARIA criteria for PER. At the time of inclusion 76% of patients reported nasal symptoms, 97% of these reporting nasal congestion with a VAS score of 56.3 ± 3 (symptom history: 8.12 ± 1 years). SRH was reported by 89% of patients with a VAS score of 54.8 ± 3.4 (symptom history: 5.25 ± 0.6 years). In moderate/severe PER, the

TABLE I.
Demographic Characteristics of PER Patients and Healthy Controls Included in the Study.

	Healthy Controls	PER patients		
		All	without SRH	with SRH
Patients, n (%)	60	49	16 (33%)	33 (67%)
Age, years (mean $\pm$ SEM)	35 $\pm$ 1	31.9 $\pm$ 1.4	33.7 $\pm$ 2	31.1 $\pm$ 1.6
Female (%)	50	42.9	37.5	45.5
M/F ratio	1:1	1.3:1	1.6:1	1.2:1
PER severity				
- Mild, n (%)	NA	17 (34.7%)	12 (75%)	5 (15.2%)*
- Moderate/severe, n (%)		32 (65.3%)	4 (25%)	28 (84.8%)*

Unpaired Student *t* test: **P* < .05, compared to patients without SRH.
F = female; M = male; NA = not applicable; PER = persistent allergic rhinitis; SEM = standard error of the mean; SRH = self-reported hyposmia.

global rhinitis score (60 ± 28.1 vs. 21.5 ± 20.7 ; *P* < .001), nasal congestion (61.3 ± 15.8 vs. 42.1 ± 15.8 ; *P* < .001), and perceived loss of smell (43.4 ± 25.8 vs. 14.2 ± 25.7 ; *P* < .001) score were significantly lower than in mild PER (Fig. 1). There was a significant correlation between the self-reported global rhinitis score and nasal congestion (*R*: 0.55; *P* < .001), and the perceived loss of smell (*R*: 0.62; *P* < .001). In addition, correlation was also found between nasal congestion and the perceived loss of smell (*R*: 0.4; *P* < .001).

Olfactory function: For the first CN odors, patients with PER had worse scores in smell detection ($95.8\% \pm 1.9\%$ vs. $99.5\% \pm 0.2\%$; *P* < .05), identification ($41.7\% \pm 2.9\%$ vs. $61.4\% \pm 3\%$; *P* < .001), and forced choice ($56.8\% \pm 2.9\%$ vs. $77.4\% \pm 1.6\%$; *P* < .001) than healthy controls. For the fifth CN, patients with PER also had poorer scores for smell detection ($78.6\% \pm 3.3\%$ vs. $98.7\% \pm 0.7\%$; *P* < .001), identification ($29.6\% \pm 3.4\%$ vs. $64.2\% \pm 3.6\%$; *P* < .001), and forced choice ($36.2\% \pm 3.2\%$ vs. $46.2\% \pm 3.4\%$; *P* < .05) than healthy controls (Table II, Fig. 2).

Patients with moderate/severe rhinitis ($98\% \pm 1.5\%$; *P* < .05) and with SRH ($94.3\% \pm 2.9\%$; *P* < .05) had poorer smell detection (first CN) than healthy controls ($99.5\% \pm 0.2\%$). All PER patients, especially, those with moderate/severe PER and SRH, showed poorer scores in smell identification, but not in forced choice. There was a correlation between the VAS score and forced choice by BAST-24 (*R*: 0.3; *P* < .05) in the loss of smell. No correlation was found between nasal congestion and the smell characteristics by BAST-24.

Nasal function: Using acoustic rhinometry, no differences were found between mild and moderate/severe PER patients with SRH in nasal volume 0–6 (13.5 ± 0.6 cm³ vs. 11.5 ± 1.3 cm³) and MCA (1.1 ± 0.3 cm² vs. 0.94 ± 0.2 cm²). In PNIF, mild PER (142.5 ± 32.5 l/min; *P* < .05) had better scores than moderate/severe (86.1 ± 7.9 l/min) patients. No correlation was observed between nasal congestion, loss of smell, and GRS scores, on the one hand, and the patency measurements by PNIF and acoustic rhinometry, on the other.

Nasal NO: In PER patients with SRH, no significant differences were observed between mild ($1,155 \pm 236$ ppb) and moderate/severe ($1,542 \pm 190$ ppb)

patients. However, the levels of nNO correlated with the loss of smell (*R*: 0.4; *P* < .05).

DISCUSSION

Our study is the first to describe the presence and characteristics of olfactory dysfunction in patients affected by PER. Many studies have previously reported smell disorders in patients with SAR^{10–16} but few have addressed smell disorders and PAR.^{15,16} The major findings of the present study were: 1) there is a high prevalence of smell dysfunction in PER; 2) a high prevalence of olfactory dysfunction is found in the detection, identification, and forced choice in PER patients, compared to healthy controls; 3) the loss of smell detection and identification is particularly present in moderate/severe PER and in SRH patients. In conclusion, these results strongly support the notion that PER has a moderate impact on the sensation of loss of smell.

Allergic rhinitis has been associated with loss of smell,^{6,8,14} although less so than in the cases of chronic rhinosinusitis and nasal polyps.⁶ Chronic rhinosinusitis, nasal polyps,²² and viral infections could be underlying cases of allergy-related hyposmia. Previous studies have

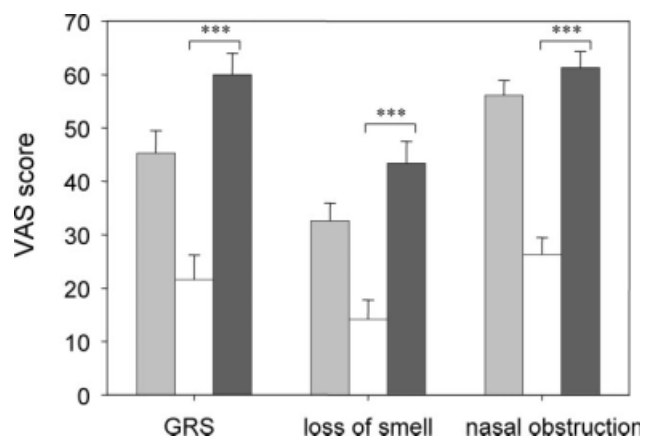


Fig. 1. VAS score on global rhinitis score (GRS), loss of smell, and nasal obstruction depending on PER severity of patients (grey: total PER; white: mild PER; black: moderate/severe PER). ****P* < .001, compared to mild PER.

TABLE II.
Olfactometry Outcomes in PER Patients and Healthy Controls Depending on PER Severity and Self-Reported Hyposmia (SRH).

	Healthy Controls N = 60	Severity of PER		Self-reported hyposmia	
		Mild N = 17	Mod./Severe N = 32	Without N = 16	With N = 33
First cranial nerve odors (mean ± SEM)					
Smell detection, (%)	99.5 ± 0.2	98 ± 1.5	94.6 ± 2.8*	98.7 ± 0.8	94.3 ± 2.9*
Smell identification, (%)	61.4 ± 3.1	44.7 ± 5.4*	40.2 ± 3.4‡	48.1 ± 4.5*	38.6 ± 3.6‡
Smell forced choice, (%)	77.4 ± 1.6	56.8 ± 3.6‡	56.9 ± 4.1‡	53.1 ± 2.7‡	58.6 ± 4.2‡
Fifth cranial nerve odors (mean ± SEM)					
Smell detection, (%)	98.7 ± 0.7	76.5 ± 5.9†	79.7 ± 4.1‡	82.8 ± 5.9†	76.5 ± 4‡
Smell identification, (%)	64.2 ± 3.6	33.8 ± 6.4‡	27.3 ± 3.9‡	29.7 ± 6.5‡	29.5 ± 4‡
Smell forced choice, (%)	46.2 ± 3.4	33.8 ± 4.2	37.5 ± 4.2	35.9 ± 5.5	36.4 ± 4

Unpaired Student *t* test: **P* < .05, [†]*P* < .01, [‡]*P* < .001, compared to healthy controls.
PER = persistent allergic rhinitis; SEM = standard error of the mean.

reported that about 50% of patients with allergic rhinitis have experienced a loss or reduction in smell once or more often.⁸ In addition, the duration and severity of this olfactory loss are associated with the presence of severe sinonasal disease in patients with allergic rhinitis.⁷

Viral upper respiratory tract infection (URTI) is one of the most common causes of smell disorders.^{23,24} When the viral infection is resolved, most patients' loss of smell resolves itself as well, but some may retain olfactory dysfunction as their single nasal symptom, sometimes for months or forever. High levels of viral particles have been detected in turbinate epithelial cells of patients with a post-viral olfactory dysfunction.²⁵ More than 30% of patients experienced improvement in olfaction after URTI-induced loss of smell, compared to 10% in trauma-induced olfactory loss.²⁶ In addition, patients with allergic rhinitis might also have an increased risk of smell disorders as a result of allergic rhinitis, promoting the development of recurrent upper respiratory tract infections.^{27,28} In particular, patients whose olfactory problems began with upper respiratory tract infections reported a distortion of odors.⁷

The pathogenesis of olfactory dysfunction in AR is not fully understood. In studies where olfactory function was measured in AR patients, the prevalence of hyposmia ranged from 23% to 88%.^{8,29,30} Two potential causes may be involved: obstruction and inflammation. Blockages in the transportation of odor particles to the olfactory epithelium on account of nasal congestion partly explain the loss of smell in AR. Some studies have outlined that the degree of nasal obstruction is not directly related to the loss of smell in AR patients.^{11,12} Another study maintains that decongestion of AR patients' nasal mucosa with epinephrine drops did not normalize the olfactory function.³¹ These studies suggest a potential role for inflammatory changes in nasal mucosa.³² Patients with AR showed a close correlation between the loss of smell and inflammatory markers such as the eosinophilic cationic protein (ECP)¹³ and the blood eosinophil concentration.⁹ In fact, intranasal ste-

roid treatments are efficient in improving the smell disorder in AR patients.¹⁰

Patients with SAR develop a moderate hyposmia during natural allergen exposure but this is not the case out of the season.¹³ The pathophysiological conditions responsible for hyposmia in SAR need less than 3 weeks to become clinically objectified. Moll et al.¹⁶ have directly compared the olfactory function in patients with seasonal and perennial allergies. Patients allergic to house dust mites (HDM) performed significantly worse than preseasonal allergic patients in olfactory threshold, identification, and discrimination tests using a modified CCCRC. However, during the pollen season the loss of smell increased in SAR patients to a higher degree than in PAR patients. Differences in the chronology, the duration of the inflammatory changes and the type of allergen exposure may lead to different mechanisms of olfactory dysfunction.¹⁶ Late-phase allergic reactions

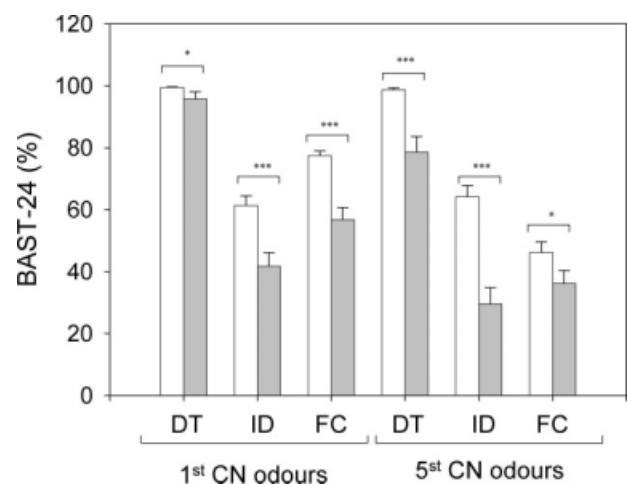


Fig. 2. Olfactory function measurements by using BAST-24, for smell detection (DT), identification (ID), and forced choice (FC) for both the first and fifth cranial nerves (CN) on PER patients (grey bars) and healthy controls (white bars). Unpaired Student *t* test: **P* < .05, ****P* < .001, compared to healthy controls.

involving eosinophil granulocytes and other cellular and humoral changes in the nasal mucosa are more pronounced in patients with perennial allergies than in patients with seasonal allergies.³³ Thus, PER patients may have a more prolonged mucosal inflammation compared with IAR patients. This chronic inflammation may reduce the flow of information from the olfactory receptor cells to the brain, thereby provoking impairment in olfactory identification.

In our study, although the changes in nasal congestion and olfaction were moderate, they were difficult to demonstrate, even using PNIF and acoustic rhinometry for nasal congestion. Using BAST-24, forced choice was more sensitive than detection and identification, and this correlated with the olfactory dysfunction. In AR patients, the nasal symptom score is more sensitive than measurements for each symptom. When applying the VAS score to evaluate the severity of PER, we have found similar results. This finding suggests that VAS can be used to assess the severity of AR.³⁴

This study has demonstrated that there is a relationship between olfactory dysfunction, nasal obstruction, and nasal inflammatory changes (nNO). In patients with SRH, the existence of nasal congestion preceded the olfactory dysfunction by 3 years. These results suggest that olfactory disorders in PER patients may have a mixed etiology in which the main factors responsible are nasal obstruction and inflammation.

In summary, no studies have investigated in depth the impact of PER on the sense of smell or differentiated the olfactory function in terms of subjective hyposmia or severity, using ARIA criteria. This is the first study to show a moderate impact of PER on the sense of smell or a relationship between the severity of PER, SRH, and the loss of smell. It is also the first to suggest a mixed etiology (obstruction/inflammation) as an explanation for smell disorders. Thus, a simple question to patients about their sense of smell may be a reasonable guide in defining the severity of PER.

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