

Smell loss is associated with severe and uncontrolled disease in children and adolescents with persistent allergic rhinitis

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Clinical Implications

- In pediatric patients with persistent allergic rhinitis, the loss of smell is a clinical marker to identify severe and uncontrolled disease. Routine assessment of the sense of smell in clinical practice may improve the management of allergic rhinitis in children and adolescents.

TO THE EDITOR:

Smell loss is often experienced by patients with allergic rhinitis (AR). However, few studies, most of them performed in adult population, have assessed olfaction in patients with AR.¹

We have previously reported that nasal obstructive disorders (NODs), such as nasal septal deformity and turbinate enlargement, cause resistance to medical treatment and worsen quality of life in patients with pediatric persistent AR (PER).^{2,3}

The aim of this study was to assess the impact of PER and NOD on the sense of smell of treated pediatric patients and its relationship with response to medical treatment, disease severity, and control.

This was a real-life, prospective, observational study performed in children and adolescents diagnosed with PER and classified according to the modified Allergic Rhinitis and its Impact on Asthma (m-ARIA) guidelines criteria⁴ (see the Methods section in this article's Online Repository at www.jaci-inpractice.org). All patients received treatment with daily intranasal corticosteroids (fluticasone or mometasone), and desloratadine or montelukast for 2 consecutive months.

Patients were stratified into children (6-11 years) and adolescents (12-17 years). Nasal examination was carried out with a 2.4-mm flexible nasal endoscope to assess NOD as described elsewhere.²

Subjective loss of smell and other nasal symptoms (nasal obstruction, rhinorrhea, itching, and sneezing) were assessed using a visual analogue scale (VAS) ranging from 0 (not at all bothersome) to 10 cm (extremely bothersome) for each individual symptom. Children were additionally guided by the FACES Pain Rating Scale located above the VAS line. The FACES Pain Rating Scale is a picture projection technique in which 6 emoticon-like faces are shown to a child. The first picture is a very happy smiling face and the last is sad and crying⁵ (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

The presence of self-reported olfactory loss was defined as a VAS score of loss of smell of 1 or more out of 10 cm.

A total VAS (mean of nasal obstruction, itching, sneezing, and rhinorrhea) score of 2 or less of 10 cm was used to define *well-controlled AR*. A total VAS score of 5 or more out of 10 cm was used as a cutoff criterion to define *medical treatment refractoriness* and classify patients into responders (≤ 5 cm) or nonresponders (> 5 cm).⁶

One hundred forty-two patients (99 adolescents; mean age, 13 ± 2.8 years; 32.3% females) were included. Clinical and demographic characteristics of patients were analyzed with descriptive statistics (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

More than 60% ($n = 87$) of patients referred smell dysfunction. Prevalence of self-reported olfactory loss (VAS score > 1 cm) increased with rhinitis severity and in patients with medical treatment refractoriness (Figure 1, A). Conversely, prevalence of smell loss was lower in patients with well-controlled AR (26% [$n = 6$]) than in patients with not-controlled PER (68% [$n = 81$]; $P = .0003$). No differences were observed in the frequency of smell loss between children (53.4% [$n = 23$]) and adolescents (64.6% [$n = 64$]), or between females (67.3% [$n = 31$]) and males (58.3% [$n = 56$]).

Smell loss VAS score was higher for nonresponder (3.5 ± 3.1 cm; $P < .001$) than for responder (0.9 ± 1.6 cm) patients. In addition, patients with severe rhinitis displayed higher smell loss VAS compared with patients with moderate rhinitis (Figure 1, B). Conversely, smell loss VAS score was lower for patients with well-controlled AR (3.0 ± 2.9 cm; $P = .0001$) than for patients with not-controlled AR (0.4 ± 0.9 cm).

Figure E2 in this article's Online Repository at www.jaci-inpractice.org shows a moderate correlation between the smell loss VAS score and the average values of total symptom score by VAS for all patients ($R^2 = 0.24$; $P < .001$).

Smell loss VAS score was higher for patients with severe turbinate enlargement than for patients with nonobstructive turbinates, or for patients with a combined obstructive septal deformity and turbinate enlargement. However, we found no differences in terms of smell loss VAS score between patients with or without obstructive septal deviation or adenoidal hyperplasia alone (see Table E2 in this article's Online Repository at www.jaci-inpractice.org), between females (3.2 ± 2.3 cm) and males (2.2 ± 1.6 cm), or between children (2.1 ± 1.5 cm) and adolescents (2.7 ± 2.0 cm).

Based on odds ratios of the logistic regression analysis (described in this article's Online Repository at www.jaci-inpractice.org), smell loss was associated with medical treatment refractoriness, the presence of severe rhinitis, and the presence of severe turbinate enlargement (Figure 2). Contrariwise, well-controlled AR was inversely associated with olfactory loss. However, we found no association between smell loss and the presence of obstructive septal deformity, obstructive adenoids, asthma, or conjunctivitis.

Receiving-operating characteristic analysis (described in this article's Online Repository at www.jaci-inpractice.org) of the presence of hyposmia (VAS score $> 1/10$ cm) yielded an area under the curve of 0.677 (61.54% sensitivity, 66% specificity), representing poor accuracy to predict lack of improvement after medical treatment. However, an area under the curve of 0.766

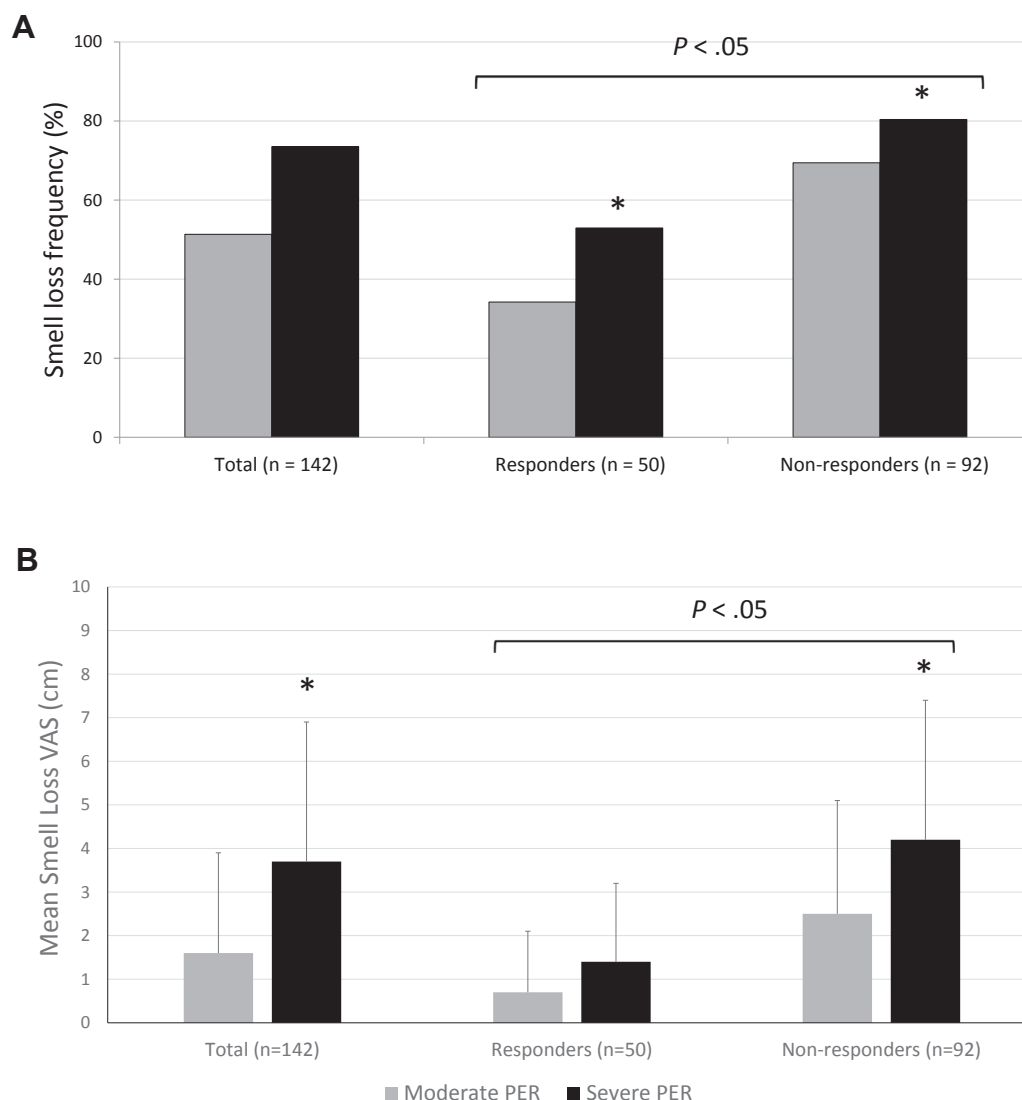


FIGURE 1. A, Frequency of smell loss in patients with moderate (gray columns) or severe (black columns) PER (m-ARIA classification) according to treatment response. **B,** Smell loss severity (VAS) in patients with moderate (gray columns) or severe (black columns) PER according to treatment response. * $P < .05$ severe compared with patients with moderate PER (ANOVA).

(68.4% sensitivity, 73.9% specificity) showed a fair accuracy to predict an uncontrolled disease.

To our knowledge, the present study is the first to investigate the relationship between olfactory dysfunction with medical treatment response, and disease severity and control in pediatric patients with AR, using the m-ARIA classification to evaluate rhinitis severity. Significantly, this is the first study to investigate the impact of endoscopic NODs on olfaction in the pediatric population.

AR has been previously associated with moderate olfactory loss in adults¹ and, very recently, in nontreated children.⁷ Smell loss seems to be related to a higher duration and severity of rhinitis, probably caused by a mixed etiology in which both nasal obstruction and mucosal inflammation may be responsible.¹

In the Nasal Obstructive Disorders in Pediatric Allergic Rhinitis (NODPAR) study² we have previously demonstrated

that NODs are associated with lack of improvement after medical treatment, worse nasal symptoms, and greater disease severity in pediatric patients with PER. The presence of NOD in an inflamed allergic nose with hyperplastic and swollen turbinate mucosa may diminish drug delivery into the nasal cavity. However, in the present study, septal deformity alone was not associated with smell loss, whereas obstructive turbinate enlargement alone or combined with obstructive septal deformity was associated with worse smell loss (VAS). These findings suggest that mucosal inflammation probably thickens the layer odorants need to cross over to bind olfactory receptors at neuroepithelium.

Montoro et al³ reported that m-ARIA classification could discriminate between moderate and severe AR untreated children. In the present study, we observed that treated pediatric patients with severe PER showed higher frequency and intensity of smell loss when compared with moderate patients, with this

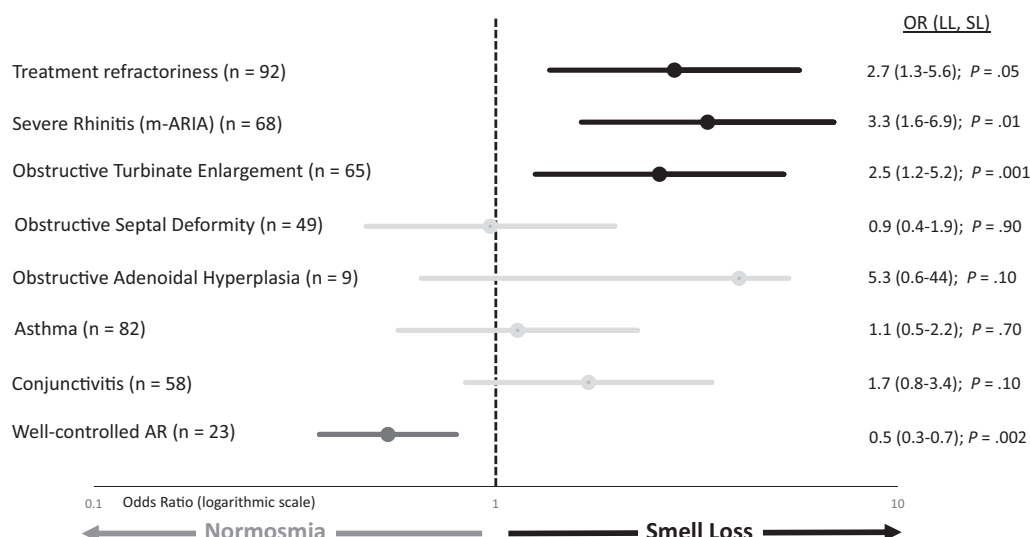


FIGURE 2. Logistic regression with risk factors for olfactory dysfunction (presence or absence) as independent variables and smell loss (VAS) as dependent variable. Black lines represent association, light gray lines no association, and dark gray lines inverse association with olfactory loss. LL, Lower limit; OR, odds ratio; SL, superior limit.

olfactory impairment being associated with lack of improvement after medical treatment.

The main limitation of this study was the absence of smell measurements other than the olfactory loss VAS score. Objective electrophysiological (electroencephalography and electro-olfactography) and imaging (functional magnetic resonance imaging) olfactory techniques require delivery of a known concentration of odorant that must be precisely controlled using an olfactometer, which therefore limits their use for clinical purposes.

Few odor-identification tests for clinical use have been specifically developed for children in different countries. Because no pediatric smell test has been yet validated in the Spanish population, we used the VAS to assess olfactory function in pediatric patients with PER showing a good correlation with m-ARIA severity classification and with total symptom score. In real-life adult studies, VAS has been widely used to assess AR symptoms for effectiveness of treatments. It has been shown that VAS for AR can be used in all age groups, including preschool children.⁸ Moreover, VAS has been compared with other quality-of-life outcome measures between adults (18-75 years), adolescents (12-17 years), and children (6-11 years) in a real-life setting, confirming the correlation between a VAS score for AR symptoms and the AR quality-of-life scores similarly in the 3 age groups.⁹ Our study showed a correlation between total symptom score by VAS and smell loss VAS scores. Hence, the VAS appears to be a simple tool with much of the same properties in adults, adolescents, and children. However, smell loss VAS score alone had a low sensitivity to predict medical treatment response.

In conclusion, smell loss is associated with greater disease severity and poor response to medical treatment in pediatric PER. Therefore, smell loss using VAS should be included in future pediatric AR management protocols, to be used in daily medical care to better tailor AR treatment regimens. However,

future studies with objective and/or validated smell tests in children may be helpful to confirm our results.

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Conflicts of interest: J. Bousquet reports personal fees and other fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach, and Kyomed outside the submitted work. J. Mullol reports personal fees and/or research grants from Sanofi-Genzyme-Regeneron, MEDA Pharma/Mylan, URIACH Group, ALK-Abelló A/S, Menarini Group, MSD, GlaxoSmithKline, Novartis, UCB Pharma, and Genentech outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

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METHODS

Study design, setting, and participants

This real-life study was performed from February 2014 to March 2016 at a tertiary care pediatric hospital. Children and adolescents ($n = 150$) diagnosed with PER according to ARIA guidelines criteria (nasal symptoms for more than 4 days a week and for more than 4 consecutive weeks)^{E1} being referred from the Allergy Department to the ENT Department were consecutively included. All patients received treatment with daily oral intranasal corticosteroids (fluticasone or mometasone) for at least 2 consecutive months at recommended doses. Subjects without asthma also received daily antihistamines (desloratadine) as the first choice in all types of AR for Spanish physicians and the most preferred by patients.^{E2} In addition, patients with asthma received daily leukotriene receptor antagonists (montelukast). Treatment adherence was corroborated by direct questions (forgetfulness of using intranasal corticosteroids fewer than 8 times in 2 months).

Demographic data (age and sex) and the presence of comorbidities including asthma and conjunctivitis were evaluated.

Skin prick tests were performed using allergen extracts from house dust mites (*Dermatophagoides pteronyssinus* and *farinae*), pollens (*Parietaria judaica*, grass, *Plantago*, *Artemisia*, *Salsola*, *Chenopodium*, Olive tree, Cupressaceae, Plane tree), animal dander (cat and dog), and *Alternaria alternata*.

AR severity

PER severity was assessed by the m-ARIA items (sleep, daily activities/sport/leisure, school performance, and troublesome symptoms)^{E3} to classify patients into different levels: mild (no items affected), moderate (1-3 items affected), and severe (all 4 items affected).

Nasal obstructive disorders

Nasal examination was carried out, as routinely performed in our department, with a 2.4-mm flexible nasal endoscope as described elsewhere.^{E4}

Septal deformity was scored (0-2) as follows: 0, no deformity; 1, non-obstructive with a partial nasal pathway obstruction; and 2, obstructive with the septum contacting the lateral nasal wall.

Turbinate size was classified into 4 grades (0-3) according to Friedman classification^{E5}: 0, normal; 1, mild enlargement; 2, moderate enlargement with no obvious obstruction; and 3, severe enlargement with complete occlusion of the nasal cavity.

Adenoid size was scored in 4 grades (1-4) according to Parikh's endoscopic classification^{E6}: grade 1, adenoids without contact with other anatomic structures; in grades 2, 3, and 4, adenoids are in contact with *torus tubarius*, vomer, or soft plate (at rest), respectively. Thus, grades 3 and 4 cause bilateral choanal obstruction.

Exclusion criteria were chronic rhinosinusitis according to European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) criterion^{E7} (8 patients excluded for this reason), upper respiratory tract infection in the last 2 weeks, known psychiatric or neurocognitive impairment, previous nasal surgery, or the presence of a serious concomitant illness.

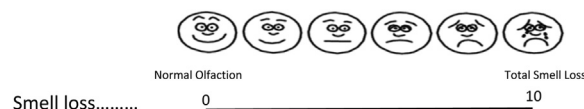


FIGURE E1. VAS (0-10 cm) and the FACES Pain Rating Scale above the VAS line used to guide children to score their subjective loss of smell.

Statistical analysis

The data management and statistical analysis were performed using Epiinfo for Windows (Epiinfo 7.1.5; Atlanta, Ga). A Bartlett test for inequality of population was first performed to see the homogeneity of variances. Differences among group means were studied by an ANOVA. The intergroup and intra-group analyses were performed with 2-tailed tests with significance at the $P < .05$ level, and data were presented as mean $\pm$ SD. Differences among group frequencies were studied by chi-square—corrected (Yates) test. Descriptive analysis was carried out for the demographic characteristics, and a comparative analysis between groups was performed using the chi-square test. To determine the relationship between olfaction and medical control or rhinitis severity, an unconditional logistic regression test was performed with the binary outcome of lack of improvement or severe rhinitis as the dependent variable, respectively, and the presence of loss of smell as the independent variable.

The correlation between smell loss by VAS and the total symptom score by VAS was assessed using a linear regression analysis for all patients (Figure E2).

To investigate how the presence of smell loss can predict lack of improvement after medical treatment and/or lack of control of AR, a receiver-operating characteristic curve analysis was performed using smell loss VAS score as the independent variable, determining its sensitivity and specificity levels with a 95% CI.

Finally, in an effort to determine what effect of smell loss on medical treatment refractoriness would be detectable given these results, an exploratory post hoc power analysis was conducted by means of the observed cohort size and proportion of self-reported hyposmia using Epidata software (EPIDATA 3.1; Galician Department of Public Health, Santiago de Compostela, A Coruña, Spain; and Pan American Health Organization, Washington, D.C.). Assuming our results of 87 patients in the nonresponders group with 75.8% prevalence of self-reported smell loss, a 40% prevalence of hyposmia in responder patients, and a 0.6 not diagnosed/diagnosed ratio, this analysis yielded 98.4% power to detect a statistically significant difference with a 95% CI. These results suggest adequate statistical power (within the limitations of a retrospective power analysis) to detect potential associations between AR control and loss of smell.

This protocol followed the STrengthening the Reporting of OBservational studies in Epidemiology.^{E8}

The Ethics Committee of our institution approved the study and signed informed consent was obtained from patient's legal guardians.

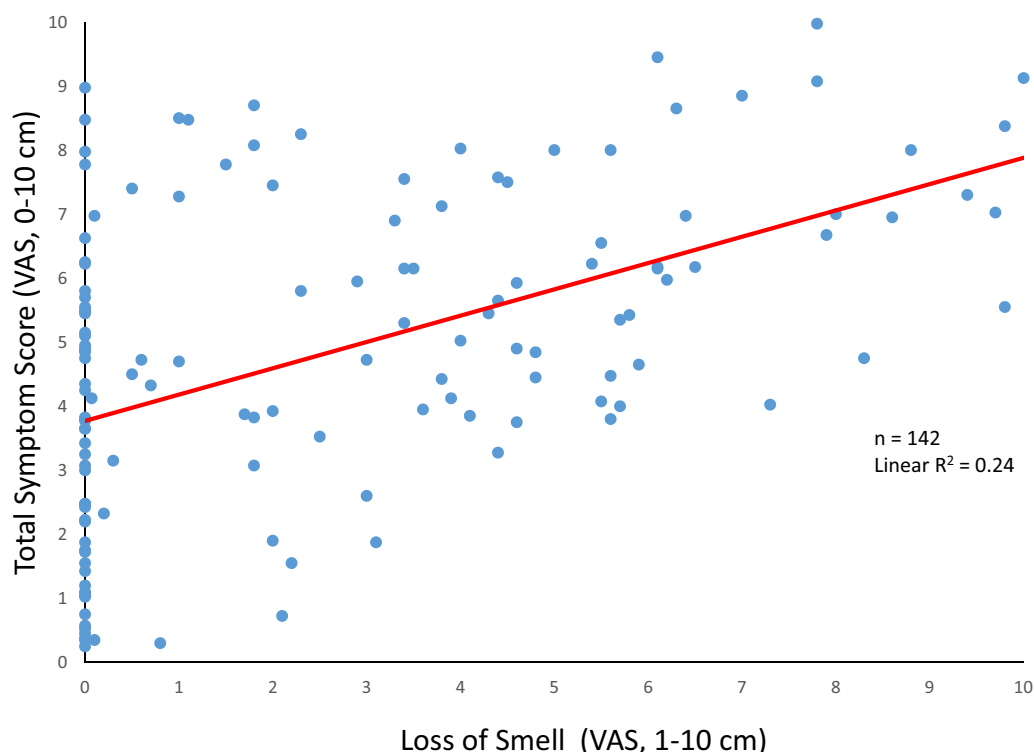


FIGURE E2. Linear regression analysis of correlation between recorded values of smell loss by the VAS and average values of total symptom score by VAS scores for all patients. VAS (0-10 cm); red line, tendency line.

TABLE E1. Demographic and clinical characteristics of pediatric patients with PER

Demographic and clinical characteristics	Total	Nonresponders		Responders		P*
		Children	Adolescents	Children	Adolescents	
Patients, n (%)	142 (100)	26 (28.2)	66 (71.7)	17 (34)	33 (66)	NS
Age (y), mean $\pm$ SD	13 $\pm$ 2.8	9.6 $\pm$ 2.7	14.6 $\pm$ 1.6	9.4 $\pm$ 1.7	14.3 $\pm$ 1.6	NS
PER severity (m-ARIA), n (%)						
Mild	0 (0)	0 (0)		0 (0)		<.001
Moderate	74 (52.1)	35 (38)		39 (78)		
Severe	68 (47.9)	57 (62)		11 (22)		
Asthma, n (%)	82 (57.7)	50 (54.3)		32 (64)		NS
Conjunctivitis, n (%)	58 (40.8)	42 (45.6)		16 (32)		NS
Well-controlled AR, n (%)	23 (16.2)	0 (0)		23 (100)		<.001
Medical treatment received, n (%)						
INCS + anti-H ₁	60 (42.3)	42 (45.6)		18 (36)		NS
INCS + LTRA	82 (57.7)	50 (54.3)		32 (64)		
Sensitization according to skin prick test, n (%)						
Monosensitization	46 (35.3)	57 (61.9)		38 (76)		NS
HDM	130 (91.5)	80 (86.9)		50 (100)		NS
Pollens	39 (30)	30 (34.9)		9 (20.4)		NS
Animal dander	25 (19.2)	18 (20.9)		7 (15.9)		NS
Alternaria	8 (6.1)	5 (5.81)		3 (6.8)		NS

Anti-H₁, Antihistamines; HDM, house dust mite; INCS, intranasal corticosteroid; LTRA, leukotriene receptor antagonist; NS, not significant.

*P values comparing nonresponder with responder groups by χ^2 -corrected (Yates) test.

TABLE E2. Smell loss according to NODs of pediatric patients with PER

Nasal endoscopic obstructive disorders	NOD (+)	NOD (–)	<i>P</i> *
	Smell loss (VAS, cm), mean ± SD	Smell loss (VAS, cm), mean ± SD	
Obstructive turbinate enlargement	3.6 ± 3.2	1.6 ± 2.3	<.001
Obstructive septal deformity	2.8 ± 3.2	2.4 ± 2.7	NS
Obstructive adenoidal hyperplasia	4.1 ± 2.8	2.4 ± 2.9	NS
Combined obstructive septal deformity and turbinate enlargement	3.8 ± 3.5	2.2 ± 2.6	<.05

NS, Not significant.

P* values comparing the presence (+) with the absence (–) of nasal obstructive endoscopic disorders by χ^2 -corrected (Yates) test.REFERENCES**

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