Evaluation of olfaction in patients with pemphigus vulgaris

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ABSTRACT

Background: *Pemphigus vulgaris (PV) is an autoimmune disease characterized by acantholysis. PV decreases quality of life and leads to morbidity and mortality. Although the association between PV and otolaryngeal disease has been studied, its effect on olfaction has not been investigated objectively and quantitatively.*

Methods: *Twenty-eight patients with PV and 28 healthy volunteers were included in the study. Lesions were identified* via *nasal endoscopic examination. Nasal symptoms (itching, obstruction, pain, bleeding, and crusting) were recorded. Volunteers were asked to evaluate their olfactory function* via *a visual analog scale. The Connecticut Chemosensory Clinical Research Center (CCCRC) olfactory test was performed (butanol threshold test and identification test), and the score was calculated as the mean ± SD.*

Results: *The mean age of the PV group (group 1: 10 male 18 female subjects) was 48.7 ± 8.9 years. The mean age of the control group (group 2: 17 male and 11 female subjects) was 48.0 ± 1.1 years. All nasal symptoms, except itching, were more severe in the PV group ($p < 0.05$). Nasal lesions were more common in the PV group ($p = 0.0001$). Evaluation of olfactory function revealed significantly lower scores in the PV group for both the butanol threshold test and the identification testing as well as the CCCRC total score ($p = 0.001$). PV patients with nasal lesions had significantly more nasal symptoms ($p < 0.05$). A negative correlation was found between the number of lesions and the olfactory scores in group 1 for the butanol threshold test, identification testing, and the CCCRC total scores, respectively ($p = 0.002$, $p = 0.010$, and $p = 0.001$, respectively).*

Conclusion: *PV causes olfactory dysfunction leading to eventual hyposmia that decreases quality of life. We suggest that olfactory testing be included in PV evaluation for the diagnosis and treatment of hyposmia, when necessary.*

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Pemphigus is an autoimmune disease characterized by intraepithelial vesicles and bullous formations in the mucosa and dermis. Immunoglobulin E antibodies bind to the desmoglein 3 protein of desmosomes. Desmosomes bind keratinocytes of the epidermis together, and their impairment results in vesicle and bullous formation.[1] The most common form is pemphigus vulgaris (PV), and female subjects are affected more commonly.[2] The regions most commonly involved are the oropharynx, larynx, nasal mucosa, and esophagus.[3–7] Although mucosal involvement is commonly seen in otolaryngological practice, the incidence is unknown. Nasal involvement manifests as obstruction, crusting, and epistaxis.[3]

Olfactory dysfunction is caused most commonly by head trauma and inflammatory infections originating from the paranasal mucosa.[8,9] Studies have shown that PV lesions can be either symptomatic or asymptomatic.[3–7]

A literature search of English language publications revealed no studies regarding olfactory dysfunction associated with PV. The aim of this study was to evaluate olfactory function in PV patients compared with a healthy control group.

MATERIALS AND METHODS

This study was performed in the Department of Dermatology from 2009 to 2013, where PV patients (group 1, $n = 28$) were diagnosed clinically and histopathologically by means of indirect immunofluorescence. This study was conducted with the approval of the Institutional Review Board (Bezmialem Vakif University, Ethics Committee). Informed consent was obtained from each volunteer (11 patients had mucocutaneous PV and 19 had mucosal PV). Twenty-eight healthy volunteers with similar demographic characteristics were recruited for the control group (group 2, $n = 28$).

All participants ($n = 56$) were examined in detail for conditions other than PV that may cause olfactory dysfunction: septum deviation, nasal polyposis, congenital olfactory dysfunction, history of a septum operation or head trauma, chronic rhinosinusitis, allergic rhinitis, and psychiatric and neurological disorders such as Parkinson's and Alzheimer's Disease. Any of these conditions were criteria for exclusion from the study. An incompatible mental status or current medications, other than corticosteroids for the PV group, were also criteria for exclusion. Demographic parameters of the volunteers (age, gender, and duration of symptoms) were recorded. Volunteers were questioned about nasal symptoms (itching, obstruction, crusting, epistaxis, and pain).

Nasal Endoscopy

Meticulous nasal endoscopic evaluation was performed on each patient. Patients received an oxymetazoline decongestant 5 minutes before assessment. A Karl Storz rigid endoscope 0° (4-mm diameter) was used for the procedure. Pathological nasal lesions were recorded by the same otorhinolaryngologist. The inferior turbinate and Little's area were examined *via* nasal endoscopy. The septum was scrutinized for any presence of a septal crest or deviation. The middle meatus was examined and the middle turbinate, uncinate, and ethmoid bulla were observed when possible. The superior turbinate was observed along with the superior meatus when possible. The olfactory cleft was also examined, although this was not possible in some patients because of discomfort. Typical endoscopic lesions at typical sites were photographed and are included in Figs. 1 and 2.

Visual Analog Scale

Self-assessment of olfactory function by means of a visual analog scale (VAS) was used to evaluate each subject. Olfaction was assessed with a 100-mm VAS (0, worst possible olfaction; 100, best possible olfaction) marked "worst possible olfaction" at the left end and "best possible olfaction" at the right end. The scale was unmarked except for the two verbal anchors at each end. The observer was asked to make a mark along the horizontal scale, and numeric scores were obtained by measuring the horizontal distance from the left end of the scale and rounded to the nearest millimeter. VAS scores were evalu-

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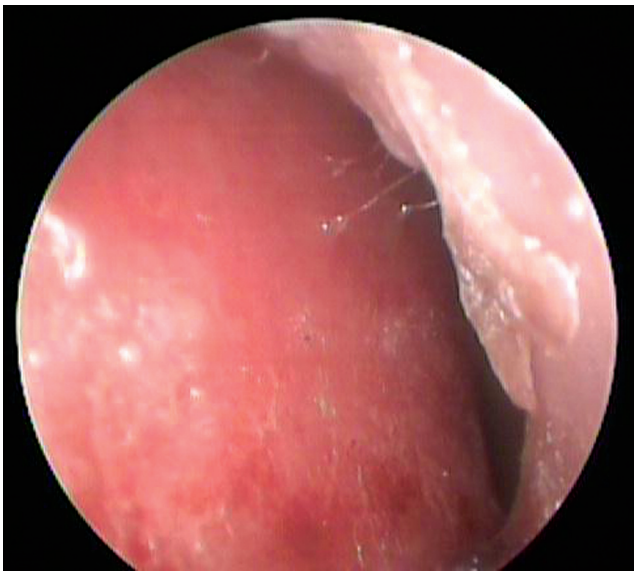

Figure 1. *Erosion in the nasal mucosa of a pemphigus vulgaris (PV) patient located mainly in Little's region.*

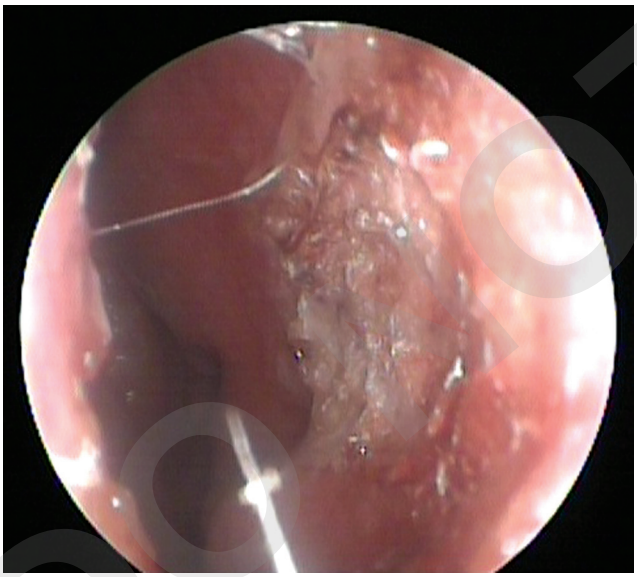

Figure 2. *Crusting in the nasal mucosa of a pemphigus vulgaris (PV) patient located mainly in Little's region.*

ated based on prior reports (0–29, very bad; 30–49, bad; 50–69, good; 70–89, very good; and 90–100, perfect).[10]

A well-established orthonasal olfaction test that was developed at the Connecticut Chemosensory Clinical Research Center (CCCRC) was used. The CCCRC test includes a butanol threshold test and an odor identification test that uses common odors. These tests were conducted as described previously.[11,12]

Butanol Threshold Test

For each trial, two glass bottles were presented to the subject. One contained water and the other, dilute butanol. The bottles appeared identical and were presented simultaneously. Subjects were instructed to occlude one nostril and place the tip of the first bottle immediately beneath the other nostril. The second bottle was then sampled in a similar manner, and the subject chose which bottle contained butanol. If the choice was incorrect, the next higher concentration of butanol was presented along with a bottle containing only water. After the subject had correctly identified the same butanol concentration five consecutive times, the score was recorded for that nostril. The other nostril was tested independently, and the scores for both nostrils were averaged. The strongest butanol concentration (bottle 0) was 4% butanol in deionized water. Each subsequent bottle (bottles 1–9) contained a 1:3 dilution in deionized water. Possible scores ranged from 0 to 9, but scores of ≥7 were scored as 7 per the CCCRC test protocol.

Identification Test

Common household odorants including peanut butter, soap, mothballs, Vicks (Kimetsan Chemicals, Ankara, Turkey), chocolate, coffee, cinnamon, and baby powder were contained within opaque jars. Subjects chose from a printed list containing the correct identifications with an equal number of distractor items. The forced choice items included the following: Vicks, burnt paper, wood shavings, coffee, baby powder, peanut butter, spearmint, cinnamon, soap, chocolate, mothballs, grape jam, ketchup, black pepper, and rubber. The ability to smell Vicks indicates intact trigeminal nerve function, and it was easily identified by all subjects so it was not included in the final score. Possible scores ranged from 0 to 7 (items correctly identified), and scores for both nostrils were averaged. Scores for the butanol threshold test and identification tests were subsequently averaged to for a composite score of orthonasal olfactory ability. As for the CCCRC test, scores were grouped into categories as detailed previously.[13]

Olfactory function was evaluated based on *n*-butanol threshold scores, identification scores, and the calculated CCCRC total score. These scores were compared between PV patients and healthy controls.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences Version 13.0 software for Windows (SPSS, Inc., Chicago, IL). All quantitative variables were estimated using measures of central location (*i.e.*, mean and median) and measures of dispersion (*i.e.*, SD). Data normality was evaluated using the Kolmogorov-Smirnov test of normality.

Student's unpaired *t*-test was used for evaluation of parameters with a normal distribution. Variance equality was calculated with the Levene test. The Pearson χ^2-test was used for comparison of nasal symptoms (itching, obstruction, pain, epistaxis, and crusting), nasal lesions, and gender. Pearson's and Spearman's tests were used for correlation analysis. A value of $p < 0.05$ was taken to indicate statistical significance.

RESULTS

The PV group (group 1) consisted of 10 male and 18 female subjects; the mean age was 48.7 ± 8.9 years. The control group (group 2) consisted of 17 male and 11 female subjects; the mean age was 48.0 ± 1.1 years. The demographics of the two groups (age and gender) were similar ($p = 0.707$ and $p = 0.061$, respectively).

All nasal symptoms, with the exception of itching ($p = 0.064$), were significantly more pronounced in the PV group ($p < 0.05$). The nasal symptoms experienced by group 1 and group 2 are detailed in Table 1. Nasal lesions were seen more commonly in the PV group ($p = 0.0001$). In group 1, 14/28 subjects had mucosal erosions (Fig. 1), and 5/28 subjects presented with crusting (Fig. 2). Lesions were located most commonly in the anterior ⅓ of the nose, particularly Little's area and the inferior turbinate.

Evaluation of olfactory function revealed significantly lower scores in the PV group for both the butanol threshold test, identification testing, and CCCRC total scores ($p = 0.001$; Table 2). Detailed scores and correlation analyses are shown in Table 2.

Table 3 shows mean CCCRC scores, VAS scores, and correlation analyses for both groups. The CCCRC scores of both groups were

Table 1 **Nasal lesions and nasal symptoms**

	Itching	Obstruction	Epistaxis	Crusting	Pain	Lesion
Group 1 (pemphigus group)	10 (35.7%)	12 (42.8%)	14 (50%)	15 (53.5%)	9 (32.1%)	19 (67.8%)
Group 2 (control group)	4 (14.2%)	3 (10.7%)	0 (0%)	3 (10.7%)	0 (0%)	0 (0%)
Pearson χ^2 (p)	0.064#	0.007*	0.0001*	0.0001*	0.0001*	0.0001*

**Pearson χ^2−test was used for samples ($p < 0.05$). Significance level obtained.*
#Insignificant level obtained.

Table 2 **Statistical comparison between *n*-butanol, identification, and mean CCCRC olfactory scores**

	Butanol Threshold Test (mean ± SD)	Identification Test (mean ± SD)	Mean CCCRC Score (mean ± SD)	Pearson Correlation Test		
				Butanol vs Identification	Butanol vs CCCRC mean	Identification vs CCCRC mean
Group 1 (pemphigus)	4.7 ± 1.1	4.8 ± 1.0	4.7 ± 0.8	$r = 0.122$ $p = 0.538$#	$r = 0.768$ $p = 0.0001$*	$r = 0.711$ $p = 0.0001$*
Group 2 (control)	6.3 ± 0.9	6.0 ± 1.0	6.2 ± 0.9	$r = 0.873$ $p = 0.0001$*	$r = 0.963$ $p = 0.0001$*	$r = 0.972$ $p = 0.0001$*
Student's unpaired t-test	$F = 1.605$ $p = 0.001$*	$F = 0.004$ $p = 0.001$*	$F = 0.153$ $p = 0.001$*	F: Test statistic (Student's unpaired t-test) r: Test statistic (Pearson's correlation test)		

**Significance level obtained.*
Insignificant level obtained.
CCCRC = Connecticut Chemosensory Clinical Research Center.

Table 3 **Mean CCCRC and VAS scores**

		Group 1 *n* (%)	Group 2 *n* (%)
CCCRC orthonasal test			
Normosmia	6.0–7.0	3 (10.7%)	20 (71.4%)
Mild hyposmia	5.0–5.75	9 (32.1%)	5 (17.8%)
Moderate hyposmia	4.0–4.75	11 (39.2%)	2 (7.1%)
Severe hyposmia	2.0–3.75	4 (14.2%)	1 (3.5%)
Anosmia	0.0–1.75	0 (0%)	0 (0%)
VAS			
Very poor	0–29	0 (0%)	0 (0%)
Poor	30–49	9 (32.1%)	1 (3.5%)
Good	50–69	9 (32.1%)	8 (28.5%)
Very good	70–89	9 (32.1%)	15 (53.5%)
Excellent	90–100	1 (3.5%)	4 (14.2%)
Pearson's correlation	r	$r = 0.54$	$r = 0.627$
Test (CCCRC versus VAS)	p	$p = 0.003$	$p = 0.001$

CCCRC = Connecticut Chemosensory Clinical Research Center; VAS = visual analog scale.

significantly correlated with VAS scores ($p = 0.003$ and $p = 0.001$, respectively; Table 3). Patients in group 1 (PV) with nasal lesions had significantly more nasal symptoms ($p < 0.05$). Negative correlations between the number of lesions and the olfactory scores in group 1 for the butanol threshold test, identification testing, and CCCRC total scores were identified ($p = 0.002$, $p = 0.010$, and $p = 0.001$, respectively). The olfactory scores and the disease duration were not correlated ($p = 0.077$).

DISCUSSION

The assessment of olfactory function in daily practice is subjective, qualitative, and lacks standardization. For the clinician, quantitative olfactory assessment can substantiate a diagnosis and guide treatment of many disorders.[14–16]

PV is an autoimmune disease that is characterized histopathologically by acantholysis. PV decreases quality of life and leads to morbidity and mortality. Clinical findings mainly include bullous formations and erosions.[17] The olfactory scores for PV patients were significantly lower than the control group ($p < 0.05$). Although the association between PV and otolaryngeal mucosal diseases has been investigated, its effect on olfactory function has not been measured objectively and quantitatively[3–7,18] (Table 3).

In the present study, evaluation of olfactory function showed significantly lower scores for the PV group in the butanol threshold test, identification testing, and CCCRC total scores ($p = 0.001$; Table 2).

Patient medication history was recorded. The exclusion criteria included taking a medication that could potentially cause olfactory dysfunction. Several patients in the PV group were taking 1 mg/kg of corticosteroids while in the acute disease phase. The use of corticosteroids, either systemically or topically, is a common therapy in patients with anosmia or hyposmia. Therefore, use of this medication was not a basis for exclusion.

Otolaryngeal manifestations of PV are associated with higher morbidity in patients.[4] All nasal symptoms, except itching, were significantly more pronounced in the PV group ($p < 0.05$). Studies indicate that the prevalence of nasal symptoms in PV patients ranges from 13.5 to 81.6%. Nasal symptoms were present in 60.7% of PV patients, in concordance with the literature. Olfactory dysfunction was self-assessed *via* VAS score, and 32.1% of subjects in group 1 reported olfactory dysfunction. This rate was significantly higher than the control group ($p < 0.05$). The VAS scores were correlated with CCCRC scores (Table 3). A study reported a 20% prevalence of dysosmia–hyposmia in PV patients.[4] The prevalence of olfactory dysfunction in the current study was greater, which might be caused by use of the VAS methodology for olfactory dysfunction assessment. Our study used a self-assessment for olfactory function on a 0–100 scale; a 20% score was achieved by evaluating olfactory function on a yes/no basis.

Table 4 **Studies about PV**

	Symptoms					Lesions			Correlation	Age (mean)	PV Type
	n	yr	*n*	%	Symptoms	*n*	%	Lesions			
Hale and Bystryn	53	2001	12	23	Stuffiness, crusting, bleeding, and blood-tinged mucus	3	75	NA	NA	NA	NA
Espana *et al*.	16	2007	6	38	Stuffiness (25%), bleeding (38%), and blood-tinged mucus (19%)	10	62	Crusting Erosions	$p < 0.05$	NA	62.5% MPV 37.5% MCPV
Su *et al*.	37	2010	5	14	Stuffiness, bleeding, and blood-tinged mucus	8	21,6	Crusting Erosions	NA	52,1	16.2% MPV 83.8% MCPV
Kavala *et al*.	38	2011	31	82	Stuffiness (64.5%), blood-tinged mucus (58.1%), crusting (80.6%), and bleeding (16%)	29	76,3	Crusting Erosions	$p < 0.01$	53.1	13.2% MPV 86.8% MCPV
Robati *et al*.	41	2012	—	—	—	15	36,6	Erosions	NA	44.5	NA
Fernandez *et al*.	40	2012	19	48	Blood-tinged mucus (47.5), stuffiness (27.5%), and dysosmia–hyposmia(20%)	28	70	Erosions Crusting	NA	57	45% MPV 55% MCPV
Our series	28	2013	17	61	Stuffiness (42.8%), itching (35.7%), bleeding (50%), pain (32.1%), crusting (53.5%), and dysosmia–hyposmia (32.1%)	19	67,8	Erosions Crusting	$p < 0.05$	48.3	67.8% MPV 32.2% MCPV

PV = pemphigus vulgaris; MPV = mucosal pemphigus vulgaris ; MCPV = mucocutaneous pemphigus vulgaris.

Nasal mucosal lesions associated with PV ranged in prevalence from 21.6 to 76.3%, and nasal symptoms in our study occurred in 67.8% of patients. The location and nature of nasal lesions are similar to those reported previously. Erosive lesions were more common in Little's area covered with pseudostratified squamous epithelium (Figs. 1 and 2).[4] The nasal area responsible for olfactory function was also covered with pseudostratified squamous epithelium, which may be associated with the olfactory dysfunction documented in this study.

There was a correlation between nasal lesions and nasal symptoms in the PV group. Espana *et al*.[6] and Kavalla *et al*.[18] reported a strong correlation between nasal lesions and nasal symptoms (Table 4). Although Robati *et al*.[5] reported that nasal lesions were associated with the acute disease phase, Espana *et al*. stated otherwise.[6] In the PV group, 17 (60.7%) were in the active stage of the disease. Olfactory dysfunction can occur as the result of acute inflammatory responses[8,9] as well as chronic irritation.[19]

Although the presence of nasal lesions and olfactory dysfunction were correlated, no relationship between disease duration and olfactory dysfunction severity was found. Olfactory dysfunction can occur at any disease stage, as reported by Espana *et al*.[6] who said that the patient does not necessarily have to be in the acute phase of the disease for nasal lesions to be present. PV is commonly treated with high doses of oral corticosteroids, intravenous methylprednisolone, and/or immunosuppressive therapy (especially azathioprine).[5] After diagnosis, the olfactory function can be evaluated, and nasal corticosteroid treatment can be initiated in cases of hyposmia. This may prevent irreversible olfactory dysfunction and reverse impairment. Nasal lesions associated with PV can be treated medically.[5]

Limitations of the study include the lack of histopathological evaluation of the nasal mucosa and the olfactory bulbus and the use of no additional imaging modalities. Additional prospective studies are required.

The association of olfactory dysfunction with PV disease was shown quantitatively and objectively: 32.1% had mild hyposmia, 39.2% had moderate hyposmia, and 14.2% had severe hyposmia. Otolaryngeal PV manifestations require a multidisciplinary approach. Previous studies have underlined the importance of otolaryngeal assessment and endoscopic evaluation of patients after diagnosis and treatment.[4–7,18,20–22] We believe that olfactory evaluation as well as endoscopic examination is important for assessment and treatment of this disease to increase the quality of life of patients.

CONCLUSION

PV causes deterioration of olfactory function, leading to hyposmia and a decreased quality of life. Olfactory testing should be included in the diagnostic examination of PV so nasal lesions can be treated when necessary. This is, to our knowledge, the first objective and quantitative study to show that olfactory dysfunction is associated with PV.

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