Original Article

Cystic Fibrosis: The Sense of Smell

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Antonella M. Di Lullo, MD, PhD[1,2], Paola Iacotucci, MD[3], Marika Comegna, PhD[2,4], Felice Amato, PhD[2,4], Pasquale Dolce, PhD[5], Giuseppe Castaldo, MD, PhD[2,4], Elena Cantone, MD, PhD[1], Vincenzo Carnovale, MD[3], and Maurizio Iengo, MD[1]

Abstract

Background: Cystic fibrosis (CF) is a multisystem disease that involves the upper airways with chronic rhinosinusitis (CRS) causing nasal congestion, rhinorrhea, mouth breathing, facial pain, and olfactory dysfunction. Twelve percent to 71% of CF patients report smelling alterations with an impact on nutrition and quality of life.

Objectives: The goal was to study olfaction performance in CF patients with CRS that worsens quality of life.

Methods: A total of 121 subjects were enrolled in this study. Seventy-one had CF and underwent ear, nose, and throat evaluation with nasal endoscopy, sinonasal outcome test 22 (SNOT-22), visual analog scale (VAS), and "Sniffin' Sticks." Fifty subjects were age-matched with healthy controls.

Results: All 71 CF patients were affected by CRS; 59 of 71 (83.1%) had CRS without nasal polyps and 12 of 71 (16.9%) had CRS with early nasal polyps. None of the 50 controls had CRS. Total SNOTT-22 mean values in the 71 CF patients were 38.10 ± 21.08 points. If considering only the 59 CF patients without nasal polyps, the SNOTT-22 mean value was 36.76 ± 21.52 points. Moreover, based on the VAS scores, the degree of nasal symptoms was classified as mild for facial pain, smell alteration, nasal discharge, and sneezing and resulted in moderate symptoms for nasal blockage and headache. Among the CF patients, 55 of 71 (76.5%) declared to be normosmic, while the smelling ability assessed by "Sniffin' Sticks" showed that only 4 of 71 (5.63%) were normosmic, 58 (81.69%) were hyposmic, and 9 (12.68%) were anosmic. In the controls, 41 (82%) were normosmic, 9 (18%) were hyposmic, and none were reported to be anosmic ($P < .001$).

Conclusions: We confirm that most CF patients have a relevant olfactory impairment, although only a low percentage declares such alteration. A careful evaluation with simple and rapid tests helps to select the patients who may benefit from specific therapies.

Keywords

cystic fibrosis, smell, chronic rhinosinusitis, hyposmia, anosmia, normosmia, nasal polyps, quality of life, SNOTT-22, VAS

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease affecting mainly the lower airway (LAW), the upper airway (UAW), and the digestive system.[1–3] The incidence in Italy is estimated to be 1 of 4238 newborns.[4] CF is caused by more than 2000 mutations of the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*).[5–7] This gene encodes a protein that transports chloride and sodium across the apical membranes of epithelial cells.[8,9]

The involvement of the UAW in CF patients includes chronic rhinosinusitis (CRS) with or without nasal polyposis. The principal symptoms of CRS are nasal

[1]Division of Otolaryngology—Head and Nek Surgery, Department of Neuroscience, Reproductive and Odontostomatologic Sciences, University of Naples Federico II, Naples, Italy
[2]CEINGE—Advanced Biotechnology, Naples, Italy
[3]Adult Cystic Fibrosis Center, Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy
[4]Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, Naples, Italy
[5]Department of Public Health, University of Naples Federico II, Naples, Italy

Antonella M. Di Lullo and Paola Iacotucci contributed equally to this study and should be considered first authors.

Corresponding Author:
Antonella M. Di Lullo, Department of Neuroscience, Reproductive and Odontostomatologic Sciences—ENT Unit, University of Naples "Federico II", Pansini Street No. 5, 80131 Naples, Italy.
Email: antonella.dilullo@libero.it

congestion, rhinorrhea, mouth breathing, facial pain, and olfactory dysfunction (anosmia/hyposmia).[10,11] Smelling deficiencies are reported in 12% to 71% of CF patients with a relevant impact on nutrition and overall health.[11] Sinonasal symptoms relevantly impair quality of life (QoL),[2] but only 50% to 63% of CF patients report their sinonasal symptoms,[2] because the early onset of CRS in childhood causes a lack of awareness of a symptom-free state, and sinus symptoms are masked by the severity of other medical issues.[12] Thus, sinonasal symptoms and olfactory alterations are frequently underestimated by CF patients.

To define the occurrence and the type of olfactory alterations, we evaluated the olfactory impairment by "Sniffin' Sticks" (SS) and their impact on the QoL through the sinonasal outcome test 22 (SNOT-22) and visual analog scale (VAS) score in (1) CF patients and (2) age-matched healthy controls.

Materials and Methods

Ethical Considerations

This study complied with the rules set forth by the Ethics Committee at the Medicine School, University of Naples Federico II, Naples, Italy. Informed consent was obtained from all subjects.

Patients

A total of 121 subjects were enrolled in this study at the Ear, Nose, and Throat (ENT) Clinic—University of Naples Federico II, Naples, Italy. Seventy-one subjects (mean age: 30.07 ± 9.34 years; 35 males and 36 females) had a diagnosis of CF according to the current guidelines[8] with different *CFTR genotypes* (Table 1). We excluded subjects with acute upper respiratory tract infection, nasal polyps obstructing nasal cavities and consequently olfactory cleft, facial/head trauma, neurodegenerative diseases such as Alzheimer's or Parkinson's disease, like hepatic or renal disorders, endocrine pathology such as diabetes mellitus,[13] and those that underwent sinonasal surgery previously.

The 71 CF patients included in the study had CRS with ($n = 12$) or without polyps ($n = 59$).[10] All computed tomography (CT) scans of our CF patients reflected the clinical status of CRS without obstruction of the olfactory cleft.

Fifty subjects were age-matched with healthy controls (mean age 28.4 ± 5.7; 14 males and 36 females) (Table 2), but not for sex. However, sex did not affect the prevalence of olfactory dysfunction.[14]

Mean age and sex distribution were compared between control and the case groups. As expected, the 2 groups were homogeneous with respect to age ($P = .23$), but sex distribution was significantly different between the 2 groups ($P = .03$) (Table 2).

Table 1. CFTR Genotypes in 71 Patients With CF.

	N	%
Cystic fibrosis patients	71	
Genotype		
F508del/F508del	24	33.8
F508del/non F508del	21	29.6
Non F508del/non F508del	26	36.6

Nasal Endoscopy

All subjects underwent the ENT examination by nasal endoscopy to assess the endoscopic appearance of the nose standardized by Lund and Kennedy that evaluates the clinical status of the nasal cavities (ie, the presence of nasal polyps, edema, discharge, scarring, and crusting).[15] The ENT examination was performed by a 2.7-mm 30° rigid endoscope (Storz, Tuttlingen, Germany).

QoL: SNOT-22 and VAS

The 22-item SNOT-22 is a validated questionnaire reporting a self-patient measure of all major symptoms included in CRS with or without nasal polyps.[10] It contains 22 items with 6 possible answers ranging from 0 (no problems) to 5 points (points) (maximal problems) obtaining a total score between 0 and 110. Higher scores indicate an increased rhinosinusitis-related burden.[2] All 71 CF patients completed the SNOT-22.[16]

Many of the SNOT-22 questions can be grouped into 4 main subscores[16]:

- Nasal symptoms (NS);
- Ear and facial symptoms (EFS);
- Quality of life-related (QoL) symptoms; and
- Psychological symptoms (PS).[16]

Moreover, all CF patients filled out also a self-reported VAS questionnaire to evaluate the severity of the sinonasal symptoms. It consists of a continuous scale of a 10-cm horizontal line anchored by 2 verbal descriptors (0, not troublesome; 10 cm, most troublesome imaginable). Based on the VAS scores, the degree of the disease's severity was classified into 3 categories: mild (VAS score = 0–3), moderate (VAS score = 4–7), and severe (VAS score = 8–10). A VAS > 5 indicated poor QoL.[10]

Olfactory Performance With "SS"

Smell function was assessed in 71 CF patients and in 50 age-matched healthy controls by the same examiner.

Table 2. Demographic Characteristics of the 2 Groups of Patients.

	Cystic Fibrosis Group	Control Group	*P*
No. of participants	71	50	
Age	30.07 (±9.34)	28.4 (±5.7)	.23
Sex			.03
Male	35 (49%)	14 (28%)	
Female	36 (51%)	36 (72%)	

Data are reported as number of patients (%) or mean (± standard deviations). *P* values were obtained using Student's *t* test for unpaired samples, to compare age between the 2 groups, and χ^2 test to compare sex distribution.

It was measured using the "SS" (Burghart Medical Technology, Wedel, Germany) which is a test of nasal chemosensory performance based on a pen-like odor dispensing device.[11] All cases were nonsmokers. They did not consume food or beverages other than water within 6 hours before "SS." The test includes 3 subtests on olfactory function including butanol odor thresholds, odor discrimination, and odor identification. The odorants were approximately presented 2 cm in front of both nostrils for 2 seconds. The sum of the 3 subtests determined the TDI score with a maximum of 48 points that categorized the olfactory sensitivity of each subject.[17] A score of more than 30.5 points indicated normosmia, a score between 16.5 and 30.5 points indicated hyposmia, and a score of fewer than 16.5 points indicated functional anosmia.

Statistical Analyses

A *t* test for unpaired samples was used to test differences between CF patients and the control group in terms of TDI scores and the corresponding 3 subscores. The distribution of the latter variables was represented by using box plots. χ^2 test was used to compare olfactory performance between the 2 groups. All analyses were performed using R, version 3.2.5.[18] A P value $< .05$ was considered significant.

Results

Nasal Endoscopy

All subjects underwent nasal endoscopy. All 71 CF patients were affected by CRS. From the total pool of 71 patients, 59 (83.1%) patients had CRS without nasal polyps, 12 (16.9%) had CRS with early nasal polyps (confined to the middle meatus), while none of the 50 healthy subjects had CRS or nasal polyps. Moreover, all individuals enrolled in this study had a normal healthy olfactory cleft without mechanical obstruction confirmed by CT scans of our patients. Patients with CF presented an endoscopic nasal score between 2 and 13, mean 5.65 ± 2.87, characterized by the presence of purulent discharge and diffuse edema of nasal mucosa in most of the cases. The age-matched controls presented an endoscopic nasal score of 0 characterized by the absence of any endoscopic signs of CRS.

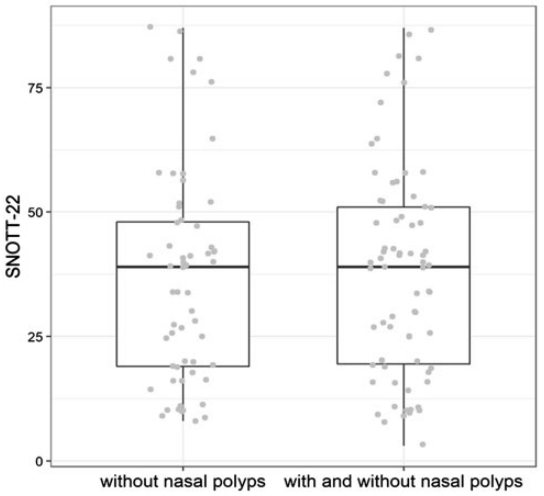

Figure 1. SNOT-22 total score distribution in the 71 patients with CF affected by CRS with and without nasal polyps and in the 59 patients with CF affected by CRS without nasal polyps. SNOT-22, sinonasal outcome test 22.

QoL: SNOT-22 and VAS Scores

Total SNOT-22 values in our 71 CF patients ranged from 0 to 110 points. The mean value was 38.10 ± 21.08 points and decreased to 36.76 ± 21.52 points considering only the 59 CF patients with CRS without nasal polyps (the difference was not statistically significant). Figure 1 illustrates the distribution of the SNOT-22 score for all of the 71 CF patients and for the 59 CF patients without nasal polyps. Mean values of the SNOT-22 subscores were 17.15 ± 8.35 points (NS), 4.25 ± 4.38 points (EFS), 12.24 ± 8.42 points (QoL), and 4.72 ± 3.93 points (PS) (subscore distributions are represented in Figure 2).

In addition, the mean of the VAS score in the 71 CF patients was 4.20 ± 2.63 points for nasal blockage (VAS_nb), 4.0 7 ± 3.11 points for headache (VAS_h), 1.93 ± 2.80 points for facial pain (VAS_fp), 2.17 ± 3.26 points for smell alteration (VAS_sa), 2.94 ± 2.79 points for nasal discharge (VAS_nd), and 2.63 ± 2.34 points for sneezing (VAS_s). Moreover, based on the average severity of the VAS scores, the degree of the disease severity was classified as mild for facial pain, smell alteration, nasal discharge, and sneezing and was moderate for nasal blockage and headache. None of the NS was considered severe.[10]

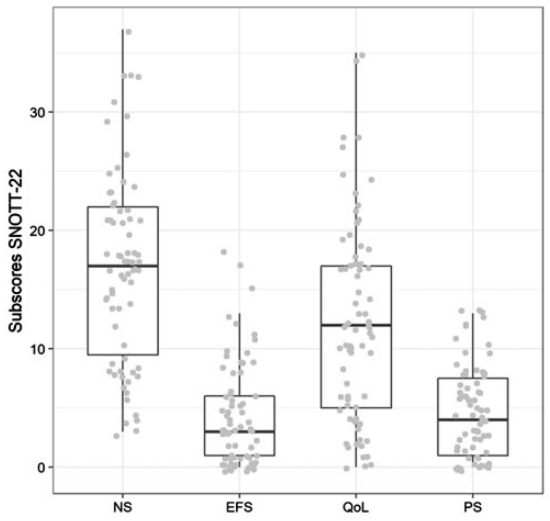

Figure 2. Subscores distribution of SNOT-22 for NS, EFS, QoL, and PS in the 71 patients with CF. EFS, ear and facial symptoms; NS, nasal symptoms; PS, psychological symptoms; QoL, quality of life; SNOT-22, sinonasal outcome test 22.

Olfactory Performance

Of the 71 CF patients, 55 (77.46%) declared normosmia, while hyposmia was declared by 15 (21.13%), and anosmia by 1 (1.41%). The corresponding distribution in the 50 healthy controls was significantly different ($P = .018$), with 48 (96%) cases that declared to be normosmic, only 2 (4%) cases declared hyposmia, and 0 had anosmia (see Table 3).

If we excluded 12 (17%) CF patients with early nasal polyps (hyperplastic mucosa not obstructing nasal cavities), we obtained a cohort of 59 patients with CF-affected by CRS without nasal polyposis. In this group, 50 (85%) patients declared normosmia, 9 (15%) hyposmia, and 0 anosmias (see Table 4). This distribution did not significantly differ from the distribution obtained in 50 healthy controls ($P = .104$).

The smelling ability in CF patients and in controls assessed by "SS" is shown in Table 3. Among 71 CF patients, 4 (5.63%) were normosmic, 58 (81.69%) were hyposmic, and 9 (12.68%) anosmic. On the contrary, from the 50 healthy controls, 41(82%) cases were normosmic, 9 (18%) hyposmic, and 0 anosmic. These 2 distributions were significantly different ($P < .001$). If we exclude the 12 CF patients with early nasal polyps, of the remaining 59 CF patients, 4 (6.78%) were normosmic, 52 (88.14%) were hyposmic, and 3 (5.08%) anosmic (see Table 4). This distribution was still significantly different as compared to the distribution of the 50 healthy controls ($P < .001$).

Finally, olfactory results are illustrated according to different smelling characteristics: odor threshold, discrimination, and identification of CF patients and healthy controls. The TDI score (the sum of results for odor threshold, discrimination, and identification) is shown in Figures 3 and 4. Results of olfactory performance significantly differed between CF patients and controls ($P < .0001$) (see Table 3). In CF patients, the olfactory threshold was significantly lower than in controls in fact, the 71 CF patients identified n-butanol at 2.97 ± 2.89 and 3.25 ± 2.96 dilution steps (mean), respectively, whereas healthy controls identified n-butanol at 7.29 ± 1.61 dilution steps ($P < .0001$). The TDI score was significantly lower in CF patients (with and without early nasal polyps) than in controls (mean score 23.28 ± 6.02, 24.61 ± 4.95 vs 33.31 ± 2.45 points, $P < .0001$). At the same time, odor identification and discrimination ability did not significantly differ between CF patients and controls.

Table 3. Anamnestic Data of Smell Performance in 71 Patients With CF Compared to 50 Healthy Controls.

	Cystic Fibrosis Group With and Without Nasal Polyps	Control Group	*P*
Anamnestic			.018
Normosmia	55 (77.46)	48 (96)	
Hyposmia	15 (21.13)	2 (4)	
Anosmia	1 (1.41)	0 (0)	
Smell performance			<.001
Normosmia	4 (5.63)	41 (82)	
Hyposmia	58 (81.69)	9 (18)	
Anosmia	9 (12.68)	0 (0)	

Data are reported as number of patients and (%).

Table 4. Anamnestic Data of Smell Performance in 59 Patients With CF Compared to 50 Healthy Controls.

	Cystic Fibrosis Group Without Nasal Polyps	Control Group	*P*
Anamnestic			.104
Normosmia	50 (85)	48 (96)	
Hyposmia	9 (15)	2 (4)	
Anosmia	0 (0)	0 (0)	
Smell performance			<.001
Normosmia	4 (6.78)	41 (82)	
Hyposmia	52 (88.14)	9 (18)	
Anosmia	3 (5.08)	0 (0)	

Data are reported as number of patients and (%).

Discussion

This study is the first that prospectively evaluated nasal endoscopy and the QoL (SNOT-22 and VAS score)

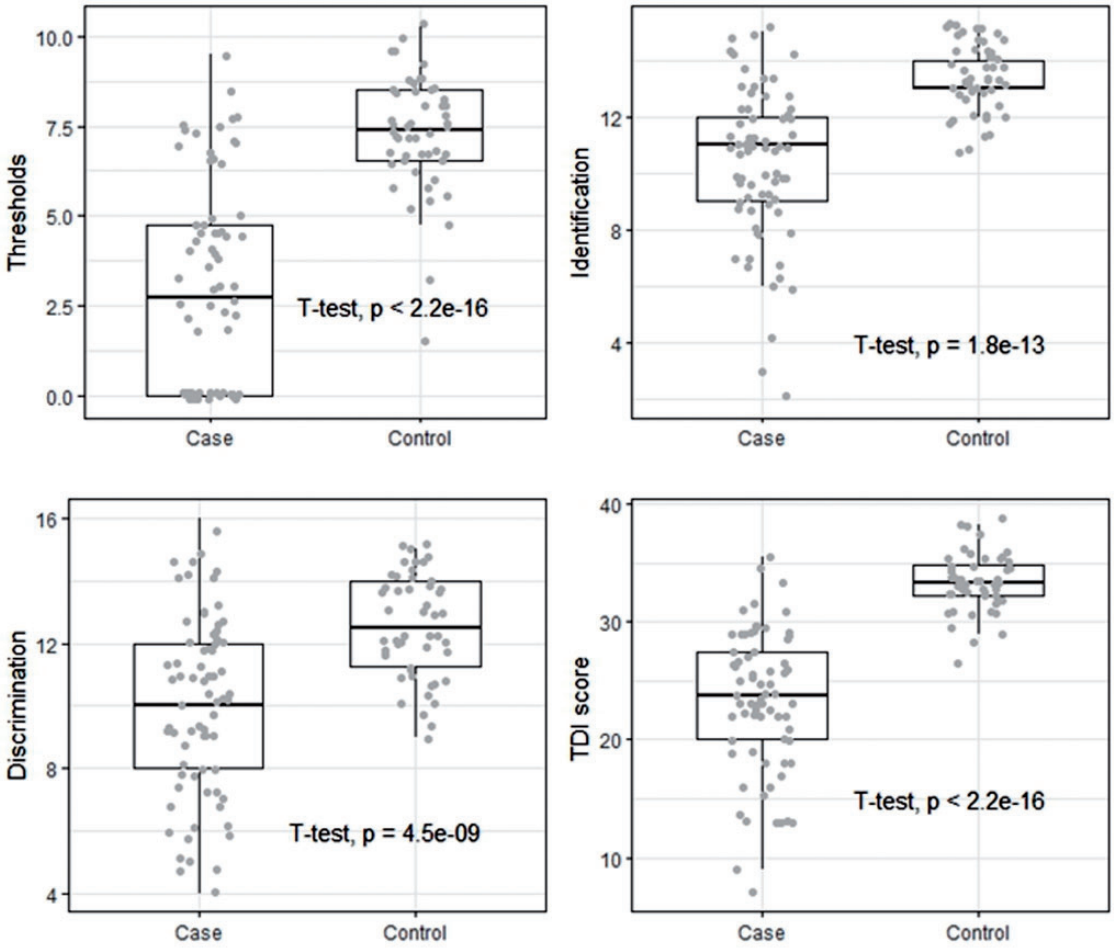

Figure 3. Olfaction subscores (odor threshold, discrimination and identification) in all 71 patients with CF and in 50 healthy controls and TDI score.

associated with olfactory performance in a cohort of 71 CF patients. In our series, patients with CF had an endoscopic nasal score[15] of 5.65 ± 2.87, according to the score data between 2.3 and 2.8 obtained in a sample of only 7 CF subjects.[19] In fact, all 71 CF patients from our study had CRS characterized by purulent discharge and diffuse edema of the nasal mucosa.

Our CF patients had a medium value of the SNOT-22 (ie, 38.10 ± 21.08 points) which decreased to 36.76 ± 21.52 points in patients without nasal polyps. Such data agree with those previously described by Willis et al.[20] that found a mean value of 33.9 ± 16.8 points in 17 patients with CF and CRS and a value of 39.1 ± 19.9 points in 10 patients with CRS, not due to CF. Thus, despite the presence of CRS, patients with CF had a low value of SNOT-22 as compared to other groups of patients with CRS,[16] and these data confirm that CF patients do not feel the severity of sinus alterations because of the early onset of CRS in childhood and because sinus symptoms are masked by the severity of other medical issues.[12] However, the values of the SNOT-22 subscores of 17.15 ± 8.35 points for NS and 12.24 ± 8.42 points for QoL indicated that patients perceived a general condition of worsening according to the English literature,[2] while the subscore of 4.72 ± 3.93 points for PS indicated that our patients were in a condition of psychological well-being, possibly thanks to the continuous psychological support offered by the regional center for CF. These data are further confirmed by the VAS score that invariably classified patient symptoms as mild for the smell alterations, nasal discharge, and sneezing.

However, although most CF patients reported a condition of well-being at the sinonasal level and about 80% of them declared normosmia, the "SS" olfaction test revealed hyposmia in 81.69% of our cases, while in the control group the olfaction test confirmed the data reported by the subjects. With regard to the smelling subscores (ie, odor threshold, discrimination, and identification), the main difference was the olfactory

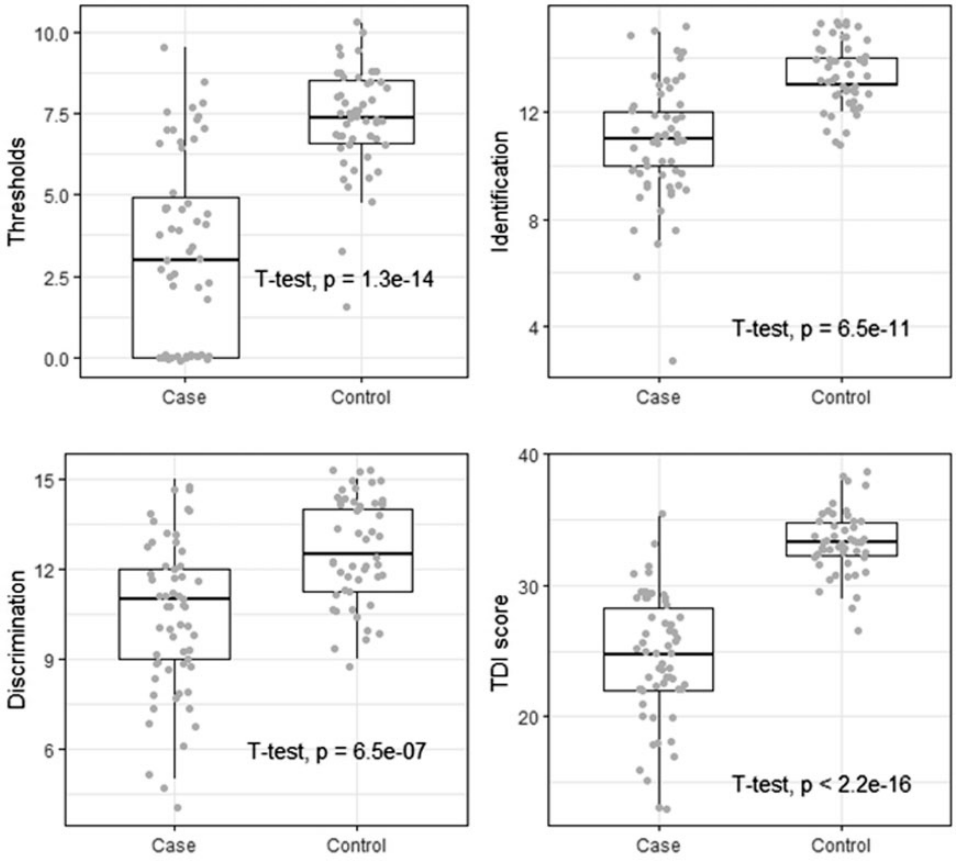

Figure 4. Olfaction subscores (odor threshold, discrimination and identification) in 59 CF patients without nasal polyps and healthy controls and TDI score.

threshold that was significantly lower in patients than in controls, while odor identification and discrimination ability did not significantly differ. Indeed, the olfactory threshold mainly evaluates the peripheral causes of olfactory impairment, while the suprathreshold tests of discrimination and identification mainly assess central or cognitive causes of olfactory loss.[14] Thus, the smelling impairment recorded in our patients with CF seems to be mainly due to peripheral alterations. This may depend on the young mean age of our patients (ie, 30 years old) since patients with CRS gradually develop central or processing alterations.[14]

In CF patients, the low olfactory threshold values were mainly attributable to the CRS with or without polyps. CRS is an inflammatory condition affecting the sinonasal mucosa[21] that can be associated with hyposmia and anosmia. The olfactory dysfunction due to CRS is likely caused by a combination of factors such as mechanical obstruction of odorant transmission to the olfactory cleft (mucosal edema, discharge, or polyps with possibility of olfactory cleft opacification on CT),[22] eosinophilia,[23] binding dysfunction due to inflammation within the neuroepithelium,[24] neuroepithelium, and olfactory bulb remodeling.[25] In addition, some drugs (such as macrolides, aminoglycosides, and tetracyclines) can affect the sense of smell involving either peripheral neuroepithelial or central damage.[14,26] These anatomical-physiological and therapeutic aspects related to CRS and smell in our CF and control population suggest that olfactory dysfunction due to CRS in CF patients is mainly determined by peripheral damage.

In any case, the olfactory impairment can affect the QoL and may cause food and weight disturbances[14] that may add to the well-known causes of malnutrition typical of patients with CF (ie, pancreatic insufficiency and altered biliary salt secretion). Also, olfactory impairment has a negative correlation with body mass index, clinically supporting the concept that olfaction enhances appetite and food enjoyment.[14]

Nowadays, effective medical therapy for CRS and subsequent olfactory dysfunction is still considered a challenge. Medications by nasal lavage with an isotonic solution and hyaluronic acid, in addition to surfactant combined to steroids (by both topical and systemic corticosteroids), remain the mainstay of treatment in CRS

associated with olfactory dysfunction due to anti-inflammatory effects, to improve mucociliary clearance and to modify olfactory gene expression.

In conclusion, the ENT evaluation associated with olfactory tests could represent a new clinical tool to improve the management of CF patients that underestimate smell disorders.

Conclusion

CF invariably involves the UAW causing CRS with chronic thick purulent discharge associated with diffuse edema of the nasal mucosa. Surprisingly, our CF patients have low values of SNOT-22 and VAS score for the assessment of sinonasal symptoms and QoL because our patients underestimate their sinonasal symptoms, especially smell dysfunction, due to the lack of awareness of a symptom-free state caused by the early onset of CRS in childhood or the masking of their sinus symptoms by the severity of other medical issues. In fact, our patients were hyposmic with a major impairment of odor threshold on the "SS" test.

The CF olfactory impairment can predominantly result from conductive factors due to olfactory periphery dysfunction (CRS and impaired mucociliary clearance owing to thickened mucus) associated with sensorineural and even central components in established disease.

In conclusion, our data confirm that smell disorders in CF patients affected by CRS are mainly caused by peripheral problems. To ensure optimal management of CF patients, we suggest integrating ENT examination by nasal endoscopy with symptomatic evaluation (SNOT-22, VAS score) and "SS." The latter is a cheap and noninvasive tool to improve the management and follow-up of CF patients evaluating benefits to health, thus deserving to be further investigated.

Declaration of Conflicting Interests

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ORCID iD

Antonella M. Di Lullo https://orcid.org/0000-0002-4482-6782

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