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RESEARCH NOTE

Olfactory dysfunction in people with cystic fibrosis with at least one copy of F508del

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Additional Supporting Information may be found in the online version of this article.

KEYWORDS
CFTR modulator therapy, computed tomography, cystic fibrosis, olfaction, olfactory cleft, quality of life, smell testing

INTRODUCTION

Olfactory dysfunction (OD) is a core component of chronic rhinosinusitis (CRS) and is common in people with cystic fibrosis (PwCF).[1,2] However, limited research has investigated factors associated with OD in PwCF.

Olfaction is commonly evaluated via psychophysical testing.[3] Additional methods to augment olfactory assessment include measures of olfactory-specific quality of life (QOL) and olfactory cleft opacification (OCO). OCO has been shown to correlate with olfactory function in individuals with non-CF-CRS. These measures have not been widely used in PwCF. This study sought to prospectively investigate factors associated with OD using psychophysical testing and to evaluate the utility of complementary measures of olfactory status in PwCF.

SUBJECTS AND METHODS

Population and study design

Adults with CRS and CF homozgyous for F508del or heterozgyous for F508del/minimal function mutations were prospectively enrolled from National Jewish Health (NJH) in an observational study from August 2019 to March 2020.[4,5] All subjects provided written informed consent for this Institutional Review Board–approved study. This analysis was conducted using baseline participant data from a study whose primary aim investigated the impact of elexacaftor/tezacaftor/ivacaftor (ETI) on CRS.[4] Data in this analysis was collected prior to initiation of ETI.

Olfactory assessments

The 40-item Smell Identification Test (SIT; Sensonics Inc.) was used to assess olfaction. Normative cutoff values were applied to SIT scores to dichotomize the cohort into normosmic (total SIT score >35–36) and dysosmic status (total SIT score <35–34).[6]

The Questionnaire of Olfactory Disorders-Negative Statements (QOD) is a validated, olfactory-specific QOL survey.

The olfactory cleft (OC) was segmented from sinus computed tomography (CT) scans obtained at enrollment. OCO was calculated using a threshold of −500 Houndsfeld units (HU) (Fig. S1).[5] Sinus CT opacification was assessed via a deep learning algorithm using the same HU threshold and via the Lund-Mackay score.[4,5]

Statistical analysis

Patient and disease factors were evaluated for potential associations with OD using univariable and multivariable logistic regression models. Multivariable models were fit using stepwise selection using a significance level for entry (SLE) of 0.2 and significance level for staying in the model (SLS) of 0.15. Pearson correlations were used to investigate potential associations across SIT score, QOD score, %OCO, 22-item Sino-Nasal Outcome Test (SNOT-22) score, and percent sinus opacification. Two-sided tests using $\alpha = 0.05$ were used. Analyses were completed using SAS (SAS Institute, Inc.).

RESULTS

Final study population

Overall, 30 participants' data were analyzed (Table 1). On average, the cohort was hyposmic with mean SIT score 30.6. Using normative thresholds, 19 individuals were dysosmic and 11 people were normosmic. Participants had elevated %OCO; however, most participants did not report abnormal values on the QOD.

TABLE 1 Characteristics of 30 individuals with cystic fibrosis and chronic rhinosinusitis

Characteristic	Mean (SD)	*n* (%)
Age (years)	34.0 (8.8)	
Sex, female		18 (60)
Race, white		30 (100)
Genotype: F508del/F508del		17 (57)
Genotype: F508del/minimal function		13 (43)
History of prior sinus surgery		24 (80)
History of nasal polyps		21 (70)
Body mass index (kg/m^2)	22.4 (3.9)	
CFTR modulator therapy[a,b]		18 (60)
Tezacaftor/Ivacaftor		10
Lumacaftor/Ivacaftor		7
Ivacaftor		1
Percent predicted forced expiratory volume in 1 second	65.6 (25.8)	
Cystic fibrosis-related diabetes		13 (43)
Pancreatic insufficiency		30 (100)
Sino-Nasal Outcome Test-22 total score	32.1 (16.1)	
Lund-Mackay total score	11.4 (3.8)	
Sinus CT opacification, deep learning analysis (%)	62.5 (21.7)	
40-Item Smell Identification Test total score	30.6 (6.7)	
Olfactory cleft opacification (%)	66.0 (9.4)	
Questionnaire of olfactory disorders total score	5.5 (6.7)	

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; CT, computed tomography; SD, standard deviation.

[a]Twelve participants were on modulators at the start of the study and 6 additional subjects were on modulator therapy previously.

[b]The mean duration of modulator use was 42.9 months.

Factors associated with olfactory dysfunction

In univariate analyses, F508 heterozygosity and CF-related diabetes (CFRD) were associated with lower odds of normal olfaction. Nasal polyp status and markers of CRS disease severity were not associated with differential odds of OD. A stepwise selection model based on predetermined SLS and SLE incorporated CFRD, genotype, percent predicted forced expiratory volume in 1 second (ppFEV$_1$), and SNOT-22 score and demonstrated that CFRD and F508

TABLE 2 Regression analysis of potential factors associated with olfactory dysfunction in people with cystic fibrosis

	Univariable models			Multivariable model		
Factor	**Odds ratio**	**95% Wald CI**	***p***	**Odds ratio**	**95% Wald CI**	***p***
Age	0.94	0.84–1.05	0.27			
Sex, female	0.38	0.08–1.75	0.22			
Nasal polyps	1.23	0.24–6.36	0.80			
SNOT-22 total score	0.98	0.94–1.03	0.54			
Lund-Mackay total score	0.98	0.80–1.19	0.84			
Sinus CT opacification	0.98	0.95–1.02	0.32			
Olfactory cleft opacification	0.99	0.91–1.08	0.83			
F508 heterozygosity	0.16	0.03–0.96	**0.04**	0.05	0.003–0.69	**0.02**
CFTR modulator use	5.00	0.85–29.56	0.08			
Prior sinus surgery	0.21	0.03–1.39	0.11			
Body mass index	0.88	0.68–1.12	0.29			
$ppFEV_1$	0.98	0.96–1.01	0.32	0.96	0.91–1.01	0.11
Cystic fibrosis–related diabetes	0.06	0.006–0.56	**0.01**	0.02	<0.001–0.41	**0.01**
Nasal steroid use	0.93	0.21–4.11	0.92			
Oral steroid use	0.85	0.07–10.61	0.90			
Environmental allergies	0.70	0.16–3.17	0.64			

The odds ratio represents the likelihood of normal olfaction on the 40-Question Smell Identification Test. SNOT-22 score was not retained in the final multivariate mode. P values < 0.05 are bolded.

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; CI, confidence interval; CT, computed tomography; ppFEV1, percent predicted forced expiratory volume in 1 second; SNOT-22, 22-question Sino-Nasal Outcome Test.

heterozygosity remained associated with differential (worse) odds of normal olfaction (Table 2).

Associations among olfactory outcome measures

SIT scores were correlated with QOD scores and trended toward correlation with %OCO. %OCO was correlated with total sinus opacification on CT. SIT scores were not correlated with SNOT-22 scores or total sinus opacification (Table S1).

DISCUSSION

This study was undertaken to investigate OD in individuals with CF/CRS, which is an understudied area. Findings from this prospective study add to the literature by identifying factors that are associated with worse olfactory status in PwCF with F508del, which aid with prognostication, and by evaluating the use of complementary olfactory measures. Although many PwCF are now eligibile for ETI, OD does not improve after 6 months of therapy, and not all PwCF are eligibile for ETI, including a higher percentage of individuals of racial and ethnic minorities.[5,7]

In this study, CFRD was associated with OD. CFRD, which occurs in ~30% of adults with CF, is a marker of overall CF disease severity and is associated with more frequent pulmonary exacerbations, decreased lung function, worse CRS severity, and shorter lifespan.[8,9] Our findings extend the import of CFRD as a negative prognostic factor to the olfactory domain and are consistent with prior non-olfactory studies. In our findings, F508del heterozygosity was associated with worse olfaction. This finding may result from the fact that PwCF who are homozygous for F508del were eligible for less effective modulator therapy prior to this study, and that long-term modulator therapy had a protective effect on olfaction.

Several factors that are traditionally associated with OD in individuals with non-CF-CRS were not associated with OD, including nasal polyp status and CRS severity.[10] These data suggest that olfactory impairment in PwCF may have different pathophysiologic components than OD in individuals with non-CF-CRS, and identifies a need for further study of olfaction in PwCF. Results from this study did not demonstrate an association between OD and body mass index. In this study, SIT scores correlated with QOD scores and approached significant correlation with OCO. These complementary measures provide a valuable means of assessing olfactory status in PwCF beyond psychophysical testing.

Study findings should be interpreted cautiously. Results may not extend to the approximately 10% of PwCF without F508del. The possibility of type 2 error exists in a study of modest size. No control group was available. Although

NJH is the country's largest CF center and includes PwCF from >30 states, individuals were enrolled from a single center.

CONFLICT OF INTERESTS

Daniel M. Beswick: Medtronic, prior consultant (ended 2020); Stephen M. Humphries: Boehringer Ingelheim, Parexel and Imidex, consultant not affiliated with this work; David A. Lynch: Parexel, Boehringer Ingelheim, Siemens, Veracyte, consultant, not related to this work; Jennifer L. Taylor-Cousar: received grants from Vertex Pharmaceuticals Incorporated, Gilead, N30, Celtaxsys, Proteostasis, and Bayer; has received fees from Vertex Pharmaceuticals Incorporated related to consultation on clinical research design, participation on advisory boards, and speaking engagements; has received speaking fees from Celtaxsys; and has served on advisory boards and/or provided consultation for Novartis, Genentech, Gilead, Protalix, Santhera, 4DMT, AbbVie, and Proteostasis; Connor D. Balkissoon, Matthew Strand, Jessa Miller, and Eszter K. Vlada: none.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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