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Olfactory Dysfunction in Primary Ciliary Dyskinesia

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Abstract

Objective. Individuals with primary ciliary dyskinesia (PCD) frequently report olfactory dysfunction, yet this deficit is poorly documented. The purpose of this study was to characterize the presence and degree of olfactory dysfunction in PCD compared to controls and determine whether certain PCD genes are associated with worse olfaction.

Study Design. A prospective cohort study.

Setting. Tertiary referral center.

Methods. We administered the University of Pennsylvania Smell Identification Test (UPSIT) to individuals with PCD. Participants were divided into 3 age groups (15-29 years, 30-44 years, and 45+ years) and compared to age- and sex-matched normal controls (n = 2170).

Results. Twenty-nine individuals with PCD (8 males and 21 females) met the criteria (median age: 38 years; interquartile range: 22-47). Only 27.6% of patients with PCD had UPSIT scores within the normosmia range. The UPSIT median scores of each PCD age group were significantly lower than the median scores of the controls ($P < .0001$ for each age group). UPSIT scores generally worsened with age: mean 33 (mild hyposmia) for 15 to 29 years, 26.8 (moderate hyposmia) for 30 to 44 years, and 20.9 (severe hyposmia) for 45+ years. The most common genes coded were absent inner dynein arm/microtubule disorientation (IDA/MTD) defect (11/24, 45.8%), followed by absent outer dynein arm defect (8/24, 33.3%). The *CCDC39* gene (IDA/MTD) was associated with worse olfactory dysfunction.

Conclusion. Individuals with PCD have a substantially higher prevalence and degree of olfactory dysfunction compared to age-matched controls. Our study is the first to report greater olfactory dysfunction with age in PCD patients, highlighting an important area for research.

Keywords

chronic rhinosinusitis, motility disorder, primary ciliary dyskinesia

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First described in 1933, primary ciliary dyskinesia (PCD) is characterized by bronchiectasis, sinusitis, and otologic disease, with approximately half of patients having an organ laterality defect.[1,2] PCD is a rare genetic disorder of mucociliary clearance (estimated prevalence of 1 in 10,000 to 1 in 20,000)[3,4] that is predominantly autosomal recessive, although other modes of inheritance have also been described.

The cytoskeletal structure (axoneme) of motile cilia consists of 9 outer doublets of microtubules encircling a central pair of microtubules: the classically described "9 + 2" ciliary ultrastructural configuration.[5] Mutations implicated in PCD can occur in genes related to the structure or function of motile cilia, genes involved in ciliary beat coordination, or genes involved in ciliogenesis.[5] Genetic heterogeneity is common in PCD, and over 50 PCD-causing genes have been identified.

Chronic rhinosinusitis (CRS) is observed in the vast majority of adult patients with PCD.[6–8] Over half of pre-school-aged children with PCD have pansinusitis by pre-school,[9] with an increase in prevalence to over 80% during the school-age years.[7,10] Sinonasal polyps have

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been reported in PCD patients with CRS[11]; however, most studies suggest infrequent occurrence in this population.[12,13] From clinical observation, olfactory dysfunction is common in PCD; however, few studies have highlighted the prevalence or degree of clinical impairment.[14,15]

Olfaction is critical in detecting potentially harmful substances such as gas, smoke, or spoiled food while modulating social and emotional behavior.[16] Prior research has demonstrated greater safety concerns, decreased quality of life, and increased disability in activities of daily living in individuals with olfactory dysfunction.[16,17] Olfaction occurs in the olfactory cleft of the nasal cavity, and mucociliary clearance has a critical role in maintaining the health of the sinonasal mucosa. Given the importance of the sense of smell and the minimal research evaluating olfactory dysfunction in individuals with PCD, the objective of this study was to characterize the presence and degree of olfactory dysfunction in patients with PCD compared to controls.

Methods

We performed an institutional review board (IRB)-approved (IRB# 98-1015, The University of North Carolina at Chapel Hill) prospective cohort study of patients with PCD presenting to the Clinical and Translational Research Center, Adult Pulmonology Clinic, or the Children's Hospital Specialty Clinic at the University of North Carolina at Chapel Hill, a nationally recognized Primary Ciliary Dyskinesia Foundation (PCDF) center in 2015. All patients were screened by expert clinicians and met diagnostic criteria for PCD based on clinical phenotype and additional lab tests (nasal nitric oxide [nNO] measurements, ciliary ultrastructure, and/or genetics).[7] Patients without the aforementioned diagnostic criteria and those who had a clinical phenotype of cystic fibrosis were excluded from the study. Electron microscopy (EM) was employed to identify ciliary ultrastructural defects. However, while it has been considered the "gold standard" for diagnosis in the past, at least 30% of PCD patients have normal ultrastructure on EM; thus, nNO measurements and genetic testing were simultaneously used.[8] The following PCD defects on EM and their associated genes were tested for:

- Outer dynein arm (ODA) defect: *DNAH5, DNAI1, DNAI2, DNAL1, NME8, CCDC114, CCDC151, ARMC4*
- ODA + inner dynein arm (IDA) defect: *DNAAF1, DNAAF2, DNAAF3, LRRC6, C21orf59, DNAAF5* (HEATR2), *ZMYND10, DNAAF5* (DYX1C1), *SPAG1, CCDC103*
- IDA defect + microtubule disorganization (MTD) defect: *CCDC39, CCDC40*
- Radial spoke/central pair defect: *RSPH1, RSPH3, RSPH4A, RSPH9, HYDIN*
- Normal EM: *DNAH11, CFAP57*
- EM not available: *DNAH1, DNAH8*

Informed consent was obtained, and the University of Pennsylvania Smell Identification Test (UPSIT)[18] was administered to adolescents and adults (N = 29). UPSIT is a validated, 40-odorant forced-choice odor identification test with scores ranging from 0 to 40. It was chosen due to its ease of administration, high reliability (test–retest Pearson's $r = 0.94$), and ability to classify the extent of olfactory function ranging from mild hyposmia to anosmia.[18–20] The degree of olfactory dysfunction on UPSIT accounts for sex-based differences in olfaction with slight variation in score ranges based on sex and age.[21] These UPSIT score ranges include the following: normosmia—males 34 to 40, females 35 to 40; mild hyposmia—males 30 to 33, females 31 to 34; moderate hyposmia—males 26 to 29, females 26 to 30; severe hyposmia—19 to 25 for both; total anosmia—6 to 18 for both; and probable malingering—0 to 5 for both.[21]

Our "control" group was derived from the UPSIT male and female olfactory dysfunction normograms that include 25th, 50th, and 75th percentile UPSIT scores for over 4000 individuals between the ages of 4 and 99 years.[21] The "control" group consisted of sex- and age-matched groups derived from these normograms. Since the normograms were more reliable for determining olfactory dysfunction for ages 15 and older,[21] we included 29 individuals with PCD over the age of 15 years for the comparison analysis.

UPSIT scores were divided into 3 age-based groups—15 to 29 years, 30 to 44 years, and 45+ years—and compared to age- and sex-matched normative olfaction data. Because the normograms provided UPSIT scores by percentile over 5-year age bins, we computed weighted medians over three 5-year ranges for comparison to the PCD cohort, adjusting for the total number of subjects in the normogram for each of the included age ranges. For example, the median UPSIT score was calculated based on the weighted average of the median UPSIT scores for 15 to 19, 20 to 24, and 25 to 29-year-old male and female controls when comparing the 15 to 29-year-old PCD cohort.

Statistical analysis was performed utilizing STATA™ 15 software (Stata Corporation). Data were extrapolated from the normograms for the control group as described. Due to significant differences in sample size and non-normal UPSIT distributions in the 2 analyzed groups, nonparametric Wilcoxon rank-sum tests were used to compare the differences in UPSIT scores between the 2 groups within each age range. UPSIT scores and age in the PCD cohort were also correlated using Spearman's rank correlation coefficient. Spearman's rank correlation was chosen because the data did not meet the assumptions of linearity or have a normal distribution. Sex-stratified

correlation coefficients were not calculated between UPSIT and age in the PCD cohort due to low fidelity resulting from the small total number of male subjects in the study. A P value of <.05 was considered statistically significant. Due to high variability in the PCD genes and EM findings, descriptive statistics were performed to assess the correlation with the extent of hyposmia.

Results

Twenty-nine individuals with PCD completed UPSITs, including 8 males and 21 females, with a median age of 38 years (interquartile range: 22-47 years). Twenty patients (68.9%) had previously undergone functional endoscopic sinus surgery. Additional demographic and baseline characteristics are described in **Table 1**.

The PCD UPSIT score distribution is shown in **Figure 1**. About 27.6% of patients (8 individuals) with PCD had no olfactory dysfunction (**Table 1**). PCD median scores were significantly lower (worse) compared to controls ($P < .0001$ for each age group; **Table 2**). Additionally, even 75th percentile PCD UPSIT scores were below the 25th percentile of normative data for each range (**Table 2**). UPSIT scores generally decreased (worsened) with increasing age: median 33 (mild hyposmia) for 15 to 29 years, 27 (moderate hyposmia) for 20 to 44 years, and 17.5 (severe hyposmia) for 45+ years in the PCD group. Although the control group UPSIT scores also decreased as participant age increased, they were relatively stable (**Table 2** and **Figure 2**). The Spearman's rank correlation coefficient for age and UPSIT score was −0.47 ($P = .010$).

Table 1. PCD Patient Characteristics

PCD patient characteristics	N (%)
Sex	
Male	8 (27.6%)
Female	21 (72.4%)
Age	
15-29 y	12 (41.4%)
30-44 y	9 (31.0%)
45+ y	8 (27.6%)
Race	
Caucasian	29 (100%)
Ethnicity	
Hispanic	1 (3.4%)
Non-Hispanic	28 (96.6%)
History of prior FESS	20 (68.9%)
History of polyps*	8 (27.6%)
Overall classification of olfactory dysfunction**	
Normosmia	8 (27.6%)
Mild hyposmia	9 (31.0%)
Moderate hyposmia	4 (13.8%)
Severe hyposmia	2 (6.9%)
Anosmia	6 (20.7%)
Malingering	0 (0%)

Abbreviations: FESS, functional endoscopic sinus surgery; PCD, primary ciliary dyskinesia.
*Patient-reported history of polyps.
**Based on UPSIT score ranges.

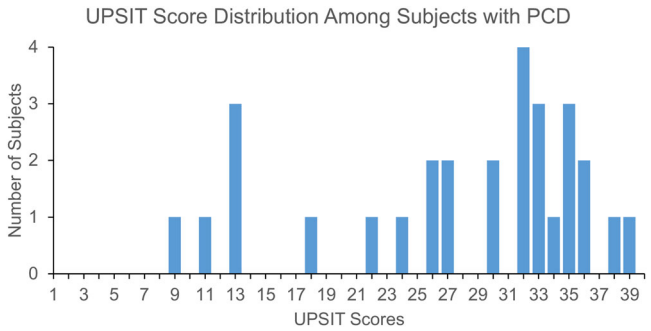

Figure 1. UPSIT score distribution among subjects with PCD. PCD, primary ciliary dyskinesia; UPSIT, University of Pennsylvania Smell Identification Test.

The genetic and ultrastructural defects in this population were heterogeneous. The combination of inner dynein arm/microtubule disorientation (IDA/MTD) abnormalities corresponding to *CCDC39* and *CCDC40* mutations were most common (11/24, 45.8%). The mean UPSIT score for the CCDC39 group (22.2 ± 11.7) was lower (worse) than that for the *CCDC40* group (31.2 ± 3.4) without a significant age- or sex-related difference in the 2 groups (**Table 3**). Overall, patients with ODA mutations had higher UPSIT scores compared to patients with IDA/MTD and ODA/IDA mutations (**Table 3**). The historically most common ODA mutations noted in PCD accounted for 8/24 patients with PCD. One patient had an abnormality of the central apparatus on EM. Finally, 3/24 patients had normal EM findings in the setting of known genetic mutations. A history of sinus surgery (as a surrogate for greater severity of CRS) had no correlation with any particular gene (**Table 3**). Patient-specific data are listed in Supplemental Table S1, available online.

Discussion

Our findings suggest that individuals with PCD have a much higher prevalence and degree of olfactory dysfunction compared to age-matched controls. This difference in olfaction is particularly more profound in older age groups. Although we demonstrate a weak negative correlation ($\rho = -0.47$) between age and UPSIT scores, we had relatively few patients in the 45+ age category (N = 8). Therefore, a sample size with a large older population with PCD may demonstrate a stronger correlation.

One other group has studied olfaction in individuals with PCD. Pifferi et al[15] analyzed olfactory dysfunction in a mixed group of children and adults with PCD using the Sniffin' Sticks Extended Test with CRS patients as the primary comparison group. They demonstrated greater prevalence of anosmia and hyposmia in the PCD group

Table 2. PCD Versus Control Group 25th Percentile, Median, and 75th Percentile UPSIT Scores

	25th percentile UPSIT score		Median (50th percentile) UPSIT score		75th percentile UPSIT score		
	PCD	Control	PCD	Control	PCD	Control	*P* value*
Age range							
15-29 y	30.5	35	33	36.8	30.5	38	<.0001
30-44 y	21	34.8	27	36.7	32.5	37.9	<.0001
45+ y	11.5	32.4	17.5	35.2	32.8	37	<.0001

Abbreviations: PCD, primary ciliary dyskinesia; UPSIT, University of Pennsylvania Smell Identification Test.
**P* values compare the median scores between the 2 groups using a Wilcoxon rank-sum test.

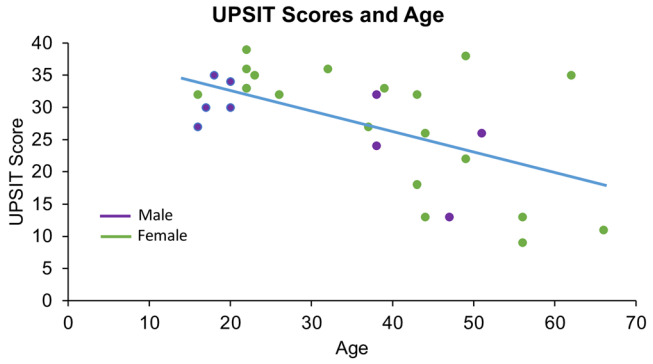

Figure 2. UPSIT scores and age among the PCD cohort. The Spearman's rank correlation coefficient was –0.47 (*P* = .010). UPSIT, University of Pennsylvania Smell Identification Test.

compared to CRS (29% anosmia and 45% hyposmia in PCD compared to 24% hyposmia and no anosmia in CRS).[15] However, they did not report CRS-related characteristics of the CRS cohort except for Lund-Mackay scores, which were comparable between the 2 groups.[15] Notably, the study observed a similar prevalence of olfactory dysfunction to CRS in a subset of PCD patients with the DNAH11 mutation, highlighting that mutations in different genes may differentially affect olfaction.[15] A 2018 editorial by Rimmer discussed preliminary findings of their study demonstrating a 74% prevalence of anosmia and hyposmia compared to 24% in non-PCD sinusitis.[14] Although comparisons of olfactory dysfunction in PCD and CRS are useful, a comparison to healthy controls best contextualizes olfaction in PCD, particularly given the scarce clinical literature.

Prior studies have not elucidated an association between certain PCD genes and worse olfaction. In this study, the *CCDC39* gene group (N = 6) had a much lower or worse UPSIT score compared to the *CCDC40* gene group, which has the same ultrastructural defect, as well as compared to all other genes studied. It is unclear why this would be the case, and further studies should assess the degree of CRS and olfactory dysfunction based on the genetic defect in a larger cohort. Overall, ODA defects are the first identified and thought to be the most common ultrastructural defects in PCD.[22] In this study, genes associated with the IDA/MTD ultrastructural defect group were the most common, followed by genes associated with ODA defects alone (**Table 3**). New genes implicated in PCD have been discovered in recent years, while some remain unknown and are active subjects of scientific investigation. Three individuals in this study who had dynein defects on EM tested negative for the known genes.

Olfactory dysfunction in CRS patients can occur because of a sensorineural or conductive loss. In patients with severe sinonasal edema or nasal polyposis, odorants can be physically blocked from delivery to the olfactory cleft.[23,24] Additionally, after years of recurrent infections and inflammation, it is thought that olfactory dysfunction can progress to a sensorineural loss whereby damage to olfactory epithelium and/or olfactory sensory neurons results in olfactory dysfunction.[23,24] It remains unknown if the olfactory impairment in PCD patients is simply because of chronic inflammation and mucosal disease or if a subset of PCD genes are also expressed in the olfactory epithelium and may alter olfactory function in a unique manner. Longitudinal olfaction data and larger studies that can be stratified by gene mutations are needed to better define the mechanisms underlying olfactory dysfunction in patients with PCD. This information will help optimize treatment and counsel patients.

This study had several limitations. First, we extrapolated our control data from normograms instead of using community controls. Although extrapolation is associated with some level of estimation or predictive error, it allowed us to have a much larger control group to better define olfactory dysfunction stratified by sex and age. We combined our male and female PCD data due to the low number of males in the PCD cohort (N = 8). We acknowledge the significance of sex-based analysis, particularly given slight differences in olfaction between males and females, and hope to expand our cohort to be able to analyze and account for this variation in the future. Control group UPSIT scores were weighted based on both age and sex for comparison to the combined male and female PCD cohort to account for sex-based differences. The *CCDC39* gene group that had greater hyposmia was small (only 6 participants); therefore, a

Table 3. UPSIT Scores by PCD Genes/Electron Microscopy Findings and History of FESS

Electron microscopy (gene correlate)	N	% Female	Mean age (St. Dev)	Mean UPSIT (St. Dev)	% sinus surgery
IDA/MTD mutations	11	64%	39 (9.8)	26.3 (9.8)	64%
CCDC39	6	67%	39.7 (19.1)	22.2 (11.7)	67%
CCDC40	5	60%	38.2 (18.8)	31.2 (3.4)	60%
ODA/IDA mutations	4	100%	43.75 (0.5)	22.3 (8.4)	75%
DNAAF3	2	100%	43.5 (0.7)	29 (4.2)	50%
DNAAF4 (DYX1C1)	1	100%	44	13	100%
Unsolved ODA/IDA	1	100%	44	18	100%
ODA mutations	8	75%	31.1 (12.4)	32.5 (5.6)	62.5%
DNAH5	5	80%	33 (15.6)	31.6 (7.2)	60%
DNAI1	1	0%	21	34	0%
Unsolved ODA	2	100%	31.5 (12.0)	34 (1.4)	100%
ODA mutation with normal ultrastructure	2	50%	20 (2.8)	34 (1.4)	0%
DNAH11	2	50%	20 (2.8)	34 (1.4)	0%
Normal/near-normal	4	75%	41.2 (18.0)	24.5 (10.3)	100%
RSPH4	1	100%	37	27	100%
CFAP57	1	0%	39	24	100%
Unsolved	2	100%	44.5 (30.4)	23.5 (17.7)	100%

There were 5 patients who did not test positive for the known genes above but otherwise met the phenotype of PCD. Of these, 3 patients had defects noted on electron microscopy. One patient had 4 siblings with diagnosed PCD, so further testing was not initiated. One patient had low nasal nitric oxide levels but tested negative for all known PCD genes with negative electron microscopy.

Abbreviations: CA, central apparatus; EM, electron microscopy; IDA, inner dynein arm; MTD, microtubule disorganization; ODA, outer dynein arm.

larger sample size is needed to confirm this finding. Additionally, the data included Caucasian patients only; however, the data set was closely representative of the predominantly Caucasian race distribution of PCD in the literature. Because this study was conducted predominantly in a pulmonary clinic environment, some CRS-related details including Lund-McKay and Lund-Kennedy scores were not captured to highlight the degree of CRS severity on imaging and endoscopy, respectively. However, this study demonstrates the presence of olfactory dysfunction and CRS in a typical PCD follow-up clinic. Finally, the available data in this study are cross-sectional, and future longitudinal studies that also include CRS severity measures are needed to more closely analyze the relationship between age and UPSIT score in PCD patients.

Individuals with PCD have a substantially higher prevalence and degree of olfactory dysfunction compared to age-matched controls. Our study is the first to suggest an accelerated deterioration in olfaction with age among PCD patients, highlighting an important area for further study in a larger PCD cohort. Future studies should also assess the degree of olfactory dysfunction by PCD gene mutation to better define treatment targets.

Author Contributions

Zainab Farzal, concept, data analysis, draft of manuscript, final approval; **Kelli M. Sullivan**, design, data acquisition, review/approval of manuscript; **Maimoona A. Zariwala**, design, acquisition and interpretation, review/approval of manuscript; **Brian D. Thorp**, interpretation, review/approval of manuscript; **Brent A. Senior**, interpretation, review/approval of manuscript; **Charles S. Ebert Jr**, interpretation, review/approval of manuscript; **Stephanie Davis**: design, data acquisition/interpretation, review/approval of manuscript; **Margaret W. Leigh**, design, concept, data analysis/interpretation, design, data acquisition, review/approval of manuscript; **Michael R. Knowles**, design, concept, data analysis/interpretation, design, data acquisition, review/approval of manuscript; **Adam J. Kimple**, design, concept, data analysis/interpretation, design, data acquisition, review/approval of manuscript.

Disclosures

Competing interests: None.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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