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Acquired Cystic Fibrosis Transmembrane Conductance Regulator Dysfunction and Radiographic Bronchiectasis in Current and Former Smokers: A Cross-Sectional Study

To the Editor:

Cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction is the major pathophysiologic defect leading to bronchiectasis in cystic fibrosis (CF) (1). Recently published data indicated that cigarette smoking causes acquired CFTR dysfunction, manifested by increased sweat chloride (2), altered sweat rate (3), and reduced CFTR activity in the upper (4) and lower respiratory tracts (5) measured by nasal and lower airway potential difference, respectively, in subjects with chronic obstructive pulmonary disease (COPD) and smokers without fixed airflow obstruction. The defect continues despite smoking cessation, which may be related to smoking intensity (2). COPD-associated bronchiectasis is a common COPD endotype, affecting between 25% and 69% of patients. It is identified by computed tomography (CT) and is associated with greater sputum production, poorer lung function, more frequent exacerbations, greater bacterial colonization, and worse outcomes compared with COPD patients without bronchiectasis (6, 7). We hypothesized that acquired CFTR dysfunction in smokers would be associated with CT-identified bronchiectasis in patients with COPD, defining a particular subphenotype and an indicator of the clinical impact of CFTR dysfunction in individuals without CF.

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Methods

This single-center study of current and former smokers without a known history of CF was conducted between January 1 and December 31, 2015, in participants previously enrolled in COPDGene (Genetic Epidemiology of COPD), a study intended to define subphenotypes of the disease (8). We collected demographic data, body mass index, smoking status (current vs. former), smoking history in pack-years, and self-reported chronic bronchitis. Spirometry was performed according to American Thoracic Society/European Respiratory Society standards (9), and severity of airflow limitation was grouped according to Global Initiative for Chronic Obstructive Lung Disease recommendations (10). Inspiratory and expiratory volumetric computed tomographic scans were acquired using multidetector CT scanners and image reconstruction algorithms as previously reported (8). The presence or absence of bronchiectasis was scored visually by a radiologist blinded to clinical characteristics as previously reported and validated by a second blinded scorer (11). Bronchiectasis was defined by the presence of bronchial dilation (bronchial diameter greater than the diameter of the accompanying pulmonary vessel). Intraobserver agreement for visual bronchiectasis was good (Cohen's $\kappa = 0.746$). Sweat chloride was measured by quantitative pilocarpine iontophoresis using the Macroduct collection system (Wescor) (2). CFTR genetics were analyzed by complete *CFTR* sequencing if the sweat chloride level was abnormal ($\geq$40 mmol/L) (12). Never smokers and subjects who had withdrawn from COPDGene were ineligible. Fisher's exact test and a nonparametric test (Wilcoxon rank-sum test) were used to assess the bivariate relationships between groups. The results were reported as median (interquartile range) for continuous variables. Statistical analyses were performed using SAS 9.4 software (SAS Institute

Inc.). This study was approved by the University of Alabama at Birmingham Institutional Review Board (F111209002), and all subjects provided written informed consent.

Results

Ninety-eight subjects were screened; 11 were excluded owing to the lifetime absence of smoking ($n = 6$) or because of missing radiologic data ($n = 5$). The baseline characteristics of the 87 subjects included in the study are presented in Table 1. About one-half (49%) of the cohort were current smokers with a median (interquartile range) 40 (30–57)–pack-year history. Post-bronchodilator forced expiratory volume in 1 second (FEV_1) percent predicted was 67.5 (53–88), and FEV_1/forced vital capacity ratio was 0.69 (0.5–0.78). Twelve (24%) of the patients had chronic bronchitis based on self-report; none used roflumilast, which can activate CFTR (13, 14).

Twelve subjects (14%) had bronchiectasis visualized by CT. Among those with bronchiectasis, 33% had COPD defined by spirometry. Sweat chloride was measured in all subjects. The median (interquartile range) was 30 (13–43) mmol/L. Sweat chloride was greater in subjects with bronchiectasis than in individuals without bronchiectasis (44 [24.5–53] vs. 24 [12–40] mmol/L; $P = 0.03$) (Figure 1). Elevated sweat chloride was associated with a 4.4-fold increased prevalence of visual bronchiectasis (prevalence ratio, 4.4; 95% confidence interval, 1.5, 13.5; $P = 0.008$). Among those with visual bronchiectasis, 8 (67%) of 12 patients had elevated sweat chloride (≥40 mmol/L) (15), whereas 19 (25%) of 75 of those without bronchiectasis exceeded this threshold ($P = 0.004$). Elevated sweat chloride was also more common in subjects with mosaic attenuation visualized by CT (43 [40–49] vs. 22.5 [12–40] mmol/L; $P = 0.03$).

Subjects with elevated sweat chloride underwent full-gene *CFTR* sequencing ($n = 25$). No individuals carried two CF-causing variants on separate chromosomes. Four carried a variant that required further consideration, although none had visual bronchiectasis. One subject carried the common CF-causing variant *p.Phe508del* (*c.1521_1523delCTT*), which was not unexpected, given the carrier frequency. A second subject had two variants (*p.Arg74Trp* [*c.220C>T*] and *p.Asp1270Asn* [*c.3808G>A*]), which are likely to be in *cis* and which have been associated with CFTR-related disorders (16). The remaining two variants identified (*p.Glu528* [*c.1584G>A*] and *p.Ser1235Arg* (*c.3705T>G*]) are rare and unlikely to be deleterious (17). *CFTR* variants of unknown significance ($n = 5$) were not more prevalent

Table 1. Baseline characteristics

Variables	Total (*N = 87*)	Presence of Bronchiectasis (*n = 12*)	Absence of Bronchiectasis (*n = 75*)	*P* Value*
Age, yr	64 (57–71)	68.5 (61–74)	68.5 (57–70)	0.20
Sex				1.00
Male	50 (57%)	7 (58%)	43 (57%)	
Female	37 (43%)	5 (42%)	32 (43%)	
Race				1.00
Non-Hispanic white	54 (62%)	8 (67%)	46 (61%)	
African American	33 (38%)	4 (33%)	29 (39%)	
Body mass index, kg/m^2	28.1 (24–32.6)	27.4 (21.2–31.4)	28.7 (24–33.2)	0.28
Smoking status				0.76
Current smoker	43 (49%)	5 (42%)	38 (51%)	
Former smoker	44 (52%)	7 (58%)	37 (49%)	
Smoking intensity, pack-years	39.8 (29.5–57)	43.8 (35–76.5)	39.7 (28.5–52.6)	0.29
COPD severity				0.45
GOLD 1	2 (2.3%)	1 (8.33%)	1 (1.33%)	
GOLD 2	23 (26.4%)	2 (16.67%)	21 (28%)	
GOLD 3	13 (14.9%)	1 (8.33%)	12 (16%)	
GOLD 4	6 (6.9%)	0	6 (8%)	
No COPD	43 (49.5%)	8 (66.67%)	35 (46.67%)	
Symptoms of chronic bronchitis	21 (24%)	2 (17%)	19 (26%)	0.72
Spirometry				
FEV_1, % predicted	67.5 (53–88)	86 (56.5–97.5)	66.5 (52–87)	0.14
FEV_1/FVC	0.69 (0.5–0.78)	0.72 (0.58–0.77)	0.65 (0.48–0.78)	0.61
Sweat chloride level, mmol/L	30 (13–43)	44 (24.5–53)	24 (12–40)	0.03
Sweat chloride ≥40 mmol/L	27 (31%)	8 (67%)	19 (25%)	0.007
Chest CT findings				
Bronchial wall thickening	23 (26%)	5 (42%)	18 (24%)	0.29
Percent emphysema	6.56 (1.9–17.1)	4.29 (1.4–10.1)	6.96 (2.1–18.3)	0.30
Pi10	3.68 (3.6–3.8)	3.69 (3.6–3.8)	3.68 (3.6–3.8)	0.47
Mosaicism	9 (10.3%)	1 (8.3%)	8 (10.7%)	1.00

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CT = computed tomography; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; Pi10 = square root of wall area of an airway of 10-mm internal perimeter.

Data are expressed as median (interquartile range) or frequency (percent).

*Estimated using Wilcoxon rank-sum test and Fisher's exact test for continuous and categorical variables, respectively.

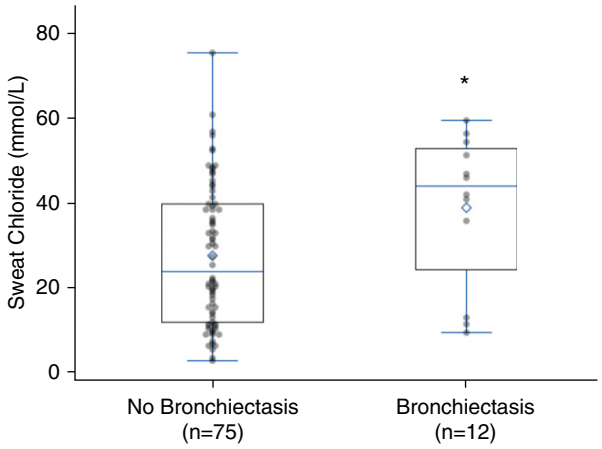

Figure 1. Comparison of sweat chloride levels in subjects with or without visual bronchiectasis on computed tomographic scans. Sweat chloride was significantly higher in those with visual bronchiectasis on computed tomographic scans. The horizontal line corresponds to the median, and the diamond represents the mean sweat chloride value. *$P = 0.03$ by Wilcoxon rank-sum test.

in patients with visual bronchiectasis. We also assessed for the presence of variants in the epithelial sodium channel genes (*SCNN1A*, *SCNN1B*, *SCNN1D*, and *SCNN1G*) and *CA12*, which are known or suspected to associate with bronchiectasis. Overall, seven patients had one or more variants in the epithelial sodium channel; these were not more prevalent in patients with visual bronchiectasis. The lack of detectable genetic contribution is consistent with experimental modeling (18), although heterozygosity may serve as a susceptibility risk factor and should be evaluated in well-powered studies.

Discussion

CFTR dysfunction identified by elevated sweat chloride is associated with CT bronchiectasis among current and former smokers. To our knowledge, this is the first study to evaluate this relationship, and it suggests a possible underlying pathophysiologic mechanism that contributes to the development of bronchiectasis in COPD (and in smokers without recognized COPD). The degree of sweat chloride abnormality reflects a 20–30% decrement in CFTR function based on genotype–phenotype correlations, levels comparable to those of individuals with CF who have CFTR-related disorders that manifest with bronchiectasis later in life (19). Of note, this association was independent of chronic bronchitis symptoms by self-report.

In addition to bronchiectasis, mosaic attenuation visualized by high-resolution CT is a sign of airway disease by inducing gas trapping and heterogeneity of the parenchyma. The association of mosaic attenuation with elevated sweat chloride further supports the concept that CFTR abnormality may contribute to airway disease. Of note, air trapping was rapidly reversible in *G551D CFTR* patients with CF with administration of the CFTR potentiator ivacaftor (20).

Our study has important implications for the understanding of the relationship between acquired CFTR dysfunction and CT bronchiectasis. Smoke-induced acquired CFTR dysfunction should be considered when evaluating the etiology of bronchiectasis, especially when patients have elevated sweat chloride but normal *CFTR* genetic analysis. Recent studies suggested that CFTR potentiators can reverse acquired CFTR abnormalities *in vitro* (2, 4, 21, 22) and that ivacaftor may restore CFTR function and improve symptoms in patients with COPD with chronic bronchitis (22). Thus, these results have potential therapeutic implications, given that CFTR potentiators used for treatment of CF may also restore CFTR activity in patients with COPD (22).

Limitations of the present study to consider include the observational design; the relatively small number of individuals with bronchiectasis; and that alternative etiologies of bronchiectasis, such as infection, immunodeficiency, and chronic aspiration (23), were not available for evaluation. Although our study did not reveal an association of bronchiectasis with lung function or chronic bronchitis (2, 4, 21, 22), the present analysis was underpowered for this analysis. The potential for CFTR dysfunction to contribute to worsened airway disease in patients with smoking-related lung disease and to identify a specific subphenotype warrants further investigation.

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Obstructive Sleep Apnea with Chronic Obstructive Pulmonary Disease among Medicare Beneficiaries

To the Editor:

The term "overlap syndrome" was introduced to describe the coexistence of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) in a single individual (1), and it is associated with a severe clinical course. An OSA-related nocturnal desaturation is more profound in the presence of COPD, and daytime hypoxemia due to COPD is worse in the presence of OSA (2). Patients with overlap syndrome are far more likely to develop pulmonary hypertension and right heart failure than patients with either condition alone (3, 4). As a result, patients with overlap syndrome have significantly worse quality of life, greater risk of morbidity and mortality, and a substantially higher medical care use and cost than those with either diagnosis independently (5–7). We conducted a claims-based study of Medicare beneficiaries to examine the diagnosed prevalence and trend of overlap syndrome, as well as its patient characteristics.

Methods

Data Source. This study used enrollment and claims data over 2004-2013 from a 5% national sample of Medicare beneficiaries. Data used in this study were gathered from multiple files: *1*) Medicare Denominator File, *2*) Medicare Provider Analysis and Review File, *3*) Outpatient Standard Analytic File, *4*) 100% Physician/Supplier Data File, and *5*) Durable Medical Equipment File (8).

Study Cohort. All patients with COPD were identified as previously reported (9). Exclusion criteria were age 65 years or younger, residence in a nursing facility or enrollment in a health maintenance organization plan, or lack of completed enrollment in Medicare parts A and B for 12 months or longer or until death in

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