News Release

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ATS Press Room: 504-670-6926 (May 15 to 20)

Poster session time: 8:15-10:45 a.m. May 17
Location: CC-Room 291-292 (Second Level), Morial Convention Center

Lung Disease May Be Genetic, Despite Lack of Family History

ATS 2010 NEW ORLEANS—Patients who encounter serious lung diseases in middle age, despite an absence of family history or other predisposing factors, may still have their genes to blame, according to a new study conducted by researchers at the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health.

The study also determined that the use of a simple screening test may help identify those genetic abnormalities and allow detection before the onset of disease.

"Earlier reports have indicated a correlation between certain nontuberculous mycobacterial respiratory infections and specific gene abnormalities," noted lead author Kenneth Olivier, M.D., M.P.H., NIAID staff clinician. "The results of this study confirm the correlation, and indicate the usefulness of simple testing in identifying these abnormalities, especially in an older population."

The results will be reported at the ATS 2010 International Conference in New Orleans.

The study of 32 patients focused on the movement of cilia, the tiny hair-like filaments that line the respiratory tract. In normal respiration, cilia help move dust and other fine particles out of the airway, keeping passages clear of harmful bacteria and other

pathogens. When cilia are altered as the result of genetic mutation, they may fail to function properly, allowing disease-causing bacteria to build up.

“Genetic abnormalities in this clearance mechanism may predispose some older individuals to the development of certain pulmonary diseases, even though those individuals do not appear to have any predisposing factors,” Dr. Olivier said.

Physicians can determine whether patients are at risk of the cilia not functioning correctly through a simple, noninvasive test that measures the levels of nitric oxide produced in the nose and sinuses. In patients who are predisposed to nontuberculous lung diseases, Dr. Olivier noted nitric oxide levels significantly lower than those of healthy individuals.

“Measurement of nasal nitric oxide production is easily performed, and can be an effective and noninvasive screen for identifying patients who may have abnormal ciliary function,” he said. However, the screening test may also be abnormal for some patients with cystic fibrosis or acute viral respiratory infections, he added.

In patients with no known risk factors for lung disease, identifying which individuals are most likely to develop illness has posed a dilemma for physicians. Dr. Olivier said the results of this study may help researchers determine additional genetic abnormalities that could cause lung disease to develop, and may even lead to effective treatments.

“These results may lead to better understanding of predisposing genetic factors that will allow identification of at-risk individuals before the typical middle-age disease onset,” he noted. “It may also allow development of preventive strategies or therapeutic interventions aimed at correcting airway clearance deficiencies.”

“The next step is to focus on the identification of mutations in genes associated with ciliary dysfunction, to search for as yet unidentified novel cilia genes, and to utilize evolving technologies to better characterize genetic risks in patients with these diseases,” he added.

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“Mucosal Defense Abnormalities in Idiopathic Bronchiectasis Associated with Nontuberculous Mycobacteria” (Session B24, Monday, May 17, 8:15- 10:45 a.m., CC-Room 291-292 (Second Level), Morial Convention Center; Abstract 2215)

**Please note that numbers in this release may differ slightly from those in the abstract. Many of these investigations are ongoing; the release represents the most up-to-date data available at press time.*

Mucosal Defense Abnormalities in Idiopathic Bronchiectasis Associated with Nontuberculous Mycobacteria

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Introduction: Significant overlap between idiopathic bronchiectasis with nontuberculous mycobacteria (NTM) and genetic disorders of mucociliary clearance such as primary ciliary dyskinesia (PCD) and cystic fibrosis (CF) is suggested by recent reports of a similarly high prevalence of NTM among older patients with PCD and CF and by the findings of CFTR abnormalities in up to half the idiopathic bronchiectasis patients with NTM. A systematic evaluation of ciliary dysfunction in this population has not been done.

Methods: Patients who met ATS criteria for pulmonary NTM disease were evaluated in a Genetic Diseases of Mucociliary Clearance Consortium protocol. Nasal nitric oxide (NO) production was assessed by direct sampling through a NO chemiluminescence analyzer as a screen for abnormal ciliary or CFTR function. Nasal scrape biopsies were evaluated for abnormalities in ciliary waveform via high speed videomicroscopy and ultrastructure via transmission electron microscopy. Transepithelial ion transport through CFTR (delta PD) was assessed via nasal potential difference (NPD) measurement.

Results: No patient had confirmed CF or PCD prior to presentation with NTM lung disease. Of 32 patients evaluated, 84% were women. Age of NTM disease diagnosis ranged from 23 to 72. Mean nNO for patients was 187±SD110 nL/min compared to healthy controls (n=25) 290±78 nL/min ($p<0.001$). Nasal NO was <100 nL/min (diagnostic range for PCD) in 9 (28%) patients. Four had confirmed PCD with compatible history and either missing dynein arms (1 outer; 1 outer & inner) with immotile cilia by videomicroscopy or the presence of 2 mutations in DNAH11 (n=2). The remain 5 had CFTR mutations (Q1352/WT, delta PD = -5.5; R668C/WT, delta PD = -6.7; S1235/WT, delta PD = -15.2; Q1352H/4006-4A>G, delta PD = -20.8). Variant CF was diagnosed in 3 patients with nNO >100 nL/min who had compatible clinical phenotype (including absence of the vas deferens in 2 males), borderline elevated sweat chloride, 2 CFTR mutations, and abnormal chloride secretion through CFTR (mean delta PD = -0.5±1). Patients with low nNO had significantly more upper airway disease (symptom + radiographic evidence of sinusitis or complicated otitis) (78%) than those with nNO > 100 nL/min (9%, $p<0.001$).

Conclusions: Mucosal defense abnormalities are present in adult presentations of pulmonary NTM disease. Measurement of nasal nitric oxide in idiopathic bronchiectasis can identify a population of patients with significant upper airway disease with probable cilia dysfunction in whom more extensive testing for PCD is indicated.