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Cystic Fibrosis in a Hispanic Adolescent

Jenny H. Lin, MD, **Joseph M. Collaco, MD**, and **Shruti M. Paranjape, MD***
Eudowood Division of Pediatric Respiratory Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland

Summary

We describe the presentation of a Hispanic adolescent with chronic respiratory symptoms and poor growth that led to a diagnosis of cystic fibrosis (CF) based on an indeterminate sweat chloride result and DNA sequence analysis that revealed a single new frameshift mutation, Nt3878insATCAG, which results in a premature stop codon in exon 20 of the *CFTR* gene. This case, highlighted by the identification of a deleterious, disease-causing mutation, illustrates the importance of maintaining both a high clinical suspicion for CF and low threshold for obtaining genetic testing in a non-Caucasian Hispanic adolescent with a characteristic clinical presentation.

Keywords

cystic fibrosis; frameshift mutation; Hispanic

INTRODUCTION

As the most common life-shortening autosomal recessive disease among Caucasians, much has been elucidated about cystic fibrosis (CF) since the initial description by Dorothy Andersen in 1938 and subsequent discovery of disease-causing mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene in 1989. To date, 1930 mutations have been identified.[1] Although the incidence of CF is highest in non-Hispanic Caucasians (1:3,200), the incidence in other races and ethnicities is becoming increasingly recognized. For example, CF has an incidence of 1: 9,200 in Hispanics and 1:15,000 in African-Americans.[2] In this case report, we describe a novel frameshift mutation, Nt3878insATCAG, which results in a deleterious, disease-causing, premature stop codon and was identified in a Hispanic adolescent who presented with poor weight gain and chronic respiratory symptoms.

Case Report

A 14-year-old boy presented for evaluation of a 4-year history of chronic cough and was found to have indeterminate sweat chloride elevation. He was a full-term infant born to non-Caucasian Hispanic parents before CF newborn screening was mandated in his state of birth.

*Correspondence to: Shruti M. Paranjape, MD, Eudowood Division of Pediatric Respiratory Sciences, DM Rubenstein Child Health Building, 200 North Wolfe Street, Baltimore, MD 21287. sparanj1@jhmi.edu.

Conflict of interest: None.

Always described as a “small” child, he was never evaluated for poor growth. Throughout his infancy and childhood, he was reported to be generally healthy without chronic respiratory symptoms. Beginning at age 10 years, he developed a productive cough that persisted despite conventional asthma therapies. He later presented for emergent evaluation of fever and cough; a chest radiograph revealed peribronchial cuffing and bronchiectasis. Sweat chloride measurements obtained at a North American Cystic Fibrosis Foundation (CFF) accredited tertiary care center were 60 and 65 mmol/L. Repeat sweat chloride testing at another CFF accredited center was 53 mmol/L. On physical examination, his height was 153.2 cm (4th percentile), weight 40.8 kg (5th percentile), and body mass index (BMI) 17.38 (16th percentile). He had mildly erythematous nasal mucosa without polyposis, moderate pectus excavatum, coarse breath sounds on auscultation, and digital clubbing. Initial pulmonary function tests (PFTs) were consistent with a moderate restrictive defect (FVC 64% predicted, FEV_1 61% predicted, FEV_1/FVC 0.82). Plethysmography revealed an elevated RV (199% predicted) and RV/TLC ratio (221% predicted), and normal TLC (81% predicted).

A clinical diagnosis of CF was based on his presentation of productive chronic cough, growth failure, and digital clubbing in the setting of an indeterminately elevated sweat chloride. He was treated with a course of trimethoprim-sulfamethoxazole, vitamin D_3, albuterol, and standard airway clearance therapy. He improved briefly with near-complete resolution of cough, but was admitted to the hospital several weeks later for treatment of pulmonary exacerbation with intravenous antibiotics. Flexible fiberoptic bronchoscopy revealed copious mucus throughout the lower airways with isolation of methicillin-sensitive *Staphylococcus aureus* on bronchoalveolar lavage fluid cultures.

Additional diagnostic evaluation yielded normal stool pancreatic elastase (>500 mcg/g) and a normal CFTR analysis (32 mutation panel) by OLA and PCR amplification. Full *CFTR* DNA sequencing revealed a novel frameshift mutation with a premature stop codon in exon 20, Nt3878insATCAG, which was present in heterozygosity and predicted to be deleterious and disease-causing. Since initial presentation, hospitalization, and subsequent CF diagnosis, the patient has demonstrated improvements in nutritional status (BMI 27th percentile) and spirometry (FEV_1 2.09 L; 70% predicted), with *S. aureus* as the only organism isolated on routine throat cultures.

DISCUSSION

We report a new frameshift mutation, Nt3878ins-ATCAG, resulting in a deleterious, disease-causing, premature stop codon in exon 20 identified by *CFTR* DNA sequencing, which detects up to 99% of known and new mutations.[3] Premature stop codons (class I) are pathogenic and result in a truncated, nonfunctional CFTR protein.[2] Without a properly functioning CFTR protein, regulation of Na^+ absorption and Cl^- secretion is disrupted and leads to impaired mucociliary clearance and the development of characteristic clinical symptoms.

Over the past decade, the percentage of Hispanic patients with CF in the United States has increased from 5.5% to 7.3%.[4] Hispanic CF patients are diagnosed at an earlier age,

suggesting increased disease severity. They acquire *Pseudomonas aeruginosa* at an earlier age, have lower percent predicted FEV_1 and increased frequency of liver disease. Coupled with worse clinical outcomes and lower socioeconomic status, these factors contribute to an annual risk of mortality that is 85% higher than non-Hispanics.[5] Through the limited number of studies examining the mutation spectrum in the Hispanic population in the US,[6–11] there appears to be a pattern of increased frequency of specific mutations (i.e., 3876delA) and stop mutations, suggesting that an ethnicity-specific mutation panel defined by techniques that identify alterations in *CFTR* coding regions and transcription[12] would facilitate diagnosis in pancreatic insufficient and sufficient patients.

Although predominantly a disease affecting Caucasians, CF is being diagnosed with increasing frequency in diverse races and ethnicities. Given the increased morbidity and mortality in Hispanics, early intervention and treatment is crucial. Classification of disease-causing mutations in this population, which may not be detected by newborn screening,[13] can also identify patients who would benefit from current mutation-specific therapies. Though CF remains a clinical diagnosis, this patient's presentation may be more accurately classified as a CFTR-related disorder because strict diagnostic laboratory criteria were not met. Alternatively, the patient may have a second unidentified mild mutation. Nevertheless, maintaining a low diagnostic threshold for CF in patients presenting with a compatible clinical picture, regardless of race or ethnicity, is important. When there is any clinical suspicion, a sweat test should be performed, and when abnormal or indeterminate, should be followed by further genetic testing to expedite diagnosis and early intervention.

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