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Case report

Chronic cough with normal sweat chloride: Phenotypic descriptions of two rare cystic fibrosis genotypes

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ABSTRACT

While our understanding of cystic fibrosis genetics has expanded in recent decades, the genetics and clinical manifestations of the disease remains highly heterogeneous. Diagnosis of CF in non-classical mutations remains a clinical challenge. We describe the clinical presentation of two patients with chronic cough found to have normal sweat chlorides. We discuss the subsequent evaluation that lead to the diagnosis of two rare CF mutations. We briefly discuss the use of the expanded 106-panel of CF mutations (homozygous 3849 + 10 kb C > T), and the role of whole CFTR gene sequencing (heterozygous c.2752-26 A > G/5T).

1. Introduction

Cystic fibrosis (CF) is a multisystem life-threatening genetic disorder of Caucasian populations with an estimated incidence of 1 in 2500 live births. While CF survival has improved in recent decades, life expectancy of CF patients remains just 40.7 years [1]. Early detection has been shown to improve outcomes, allowing clinicians to better manage cystic fibrosis prior to development of irreversible respiratory complications as well as to optimize nutrition, particularly during childhood and adolescence [2]. In recent years, the detection of cystic fibrosis has improved substantially with the widespread introduction of infant CF screening coupled with improved understanding of CF genetics.

Despite improvements in our understanding of CF genetics, diagnosis of CF in nonclassical mutations remains a clinical challenge. Adult patients may be more likely to present with nonclassical mutations not detected on conventional CF screens [3,4], often with a phenotype distinct from classical CF. We describe the genetics and phenotype of two cases of rare CF mutations, one diagnosed through an expanded 106-panel of CF mutations and one through whole CFTR gene sequencing.

2. Case presentation

2.1. Case 1: homozygous 3849 + 10KbC > T mutation in a 19-year-old male

A 19-year-old Caucasian male was evaluated for chronic cough, recurrent bronchitis, recurrent sinus infections and pneumonias since age 9. He denied gastrointestinal symptoms and had no exposures. He has a past surgical history of bilateral inguinal repair. He had normal pulmonary function testing (PFT) and negative cystic fibrosis work up including normal sweat chloride test in the past. His ethnic background was Ashkenazi. Family history was significant for paternal first cousin with CF. He had recently recovered from an acute exacerbation of bronchiectasis requiring anti-infectives for Mycobacterium abscessus and Aspergillus. He appeared malnourished (BMI 16.5 kg/m^2) but had an otherwise normal physical examination. He does not have congenital absence of vas deference.

Laboratory studies showed a normal CBC and sweat chloride (<30 mmol/L) [5]. Exhaled oral nitric oxide was normal and nasal nitric oxide level excluded ciliary dyskinesia [6]. He had severe extensive bilateral central cylindrical bronchiectasis on CT, micronodularity, and patchy air space consolidations. Sinus CT showed pansinusitis. Comprehensive immunodeficiency evaluation was unrevealing. The 23-panel ACMG panel for CF mutations was negative. His overall clinical presentation remained suspicious for CF. A 106-mutation multiplex PCR assay (Sequenom MassArray, University of Arizona Genetics Core) revealed two copies of

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3849 + 10 kb C > T mutation in CFTR intron 19. He responded to aggressive airway clearance maintenance therapy with nebulized albuterol and 7% hypertonic saline. His respiratory symptoms had resolved and he was able to gain weight. At last follow up, his weight is now in normal range and he is able to cycle over 10 miles daily.

2.2. Case 2: trans c.2752-26 A > G and intron 8 polyT 5T/7T mutation in a 21-year-old male

A 21-year-old Caucasian male was evaluated for chronic cough, nasal congestion and postnasal drip present for 3-years. His ethnic background was Ashkenazi and he had no family history of CF. He was well nourished (BMI 23.5 kg/m^2) and had a normal physical examination. There was some improvement in chronic cough after treatment for rhinitis and excessive posterior rhinorrhea. Pulmonary function testing was within normal limits: FEV1: 4.70 L (105% predicted), FVC: 5.20 L (100% predicted), FEF25-75: 90.6%. He also had normal sweat chloride levels (<30 mmol/L), chest X-ray and CT of the sinuses. CT of the chest showed mild bronchial wall thickening only, and no evidence of bronchiectasis. He developed chronic diarrhea prompting gastrointestinal evaluation. Celiac testing, upper endoscopy, small bowel biopsy and GI functional imaging were all normal. Stool examination for ova and parasites were negative. A 72-h fat collection study confirmed steatorrhea (13 g of fat/24 h). Fecal elastase was normal at 498.6 μg elastase/gram stool. A 106-multiplex PCR assay (Sequenom MassArray, University of Arizona Genetics Core) was negative for cystic fibrosis. Due to continued clinical suspicion for cystic fibrosis, full CFTR gene sequencing analysis was performed. He had two mutations usually considered benign: a c.2752-26 A > G mutation on intron 14a and an intron 8 polyT allele 5T/7T of the CFTR gene. Parental gene analysis revealed that the mutations were in *trans* position. His diarrhea responded to pancreatic enzyme supplementation.

3. Discussion

While our understanding of cystic fibrosis genetics has expanded in recent decades, the genetics and clinical manifestations of the disease remains highly heterogeneous. Most patients not identified at infancy undergo screening after development of characteristic pulmonary or gastrointestinal symptoms. Most current centers first screen patients with sweat chloride testing followed by genetic screening for the American College of Medical Genetics (ACMG) panel of the 23 most common CF-causing mutations. This panel will detect 90% of mutations in Caucasian populations, 97% of mutations in Ashkenazi Jews but just 69% of mutations in Hispanic populations [7]. Consequently different regions modify their testing panels to suit local population demographics.

This report describes the presentation and the stepwise genetic workup of two exceedingly rare CF mutations. Both cases meet diagnostic criteria for CF by having clinical CF-like symptoms and two abnormal CF genes in *trans* position [8,9]. Both had normal sweat chlorides (<30 mmol/l). The first patient was homozygous for 3849 + 10KbC > T splicing mutation. The heterozygous 3849 + 10 kb C > T mutation generally has a mild clinical phenotype [10]. It occurs most commonly with the**Δ**508 deletion [11–13]. To our knowledge, this is just the seventh case report of homozygous 3849 + 10 kb C > T mutation [14–17]. The patient

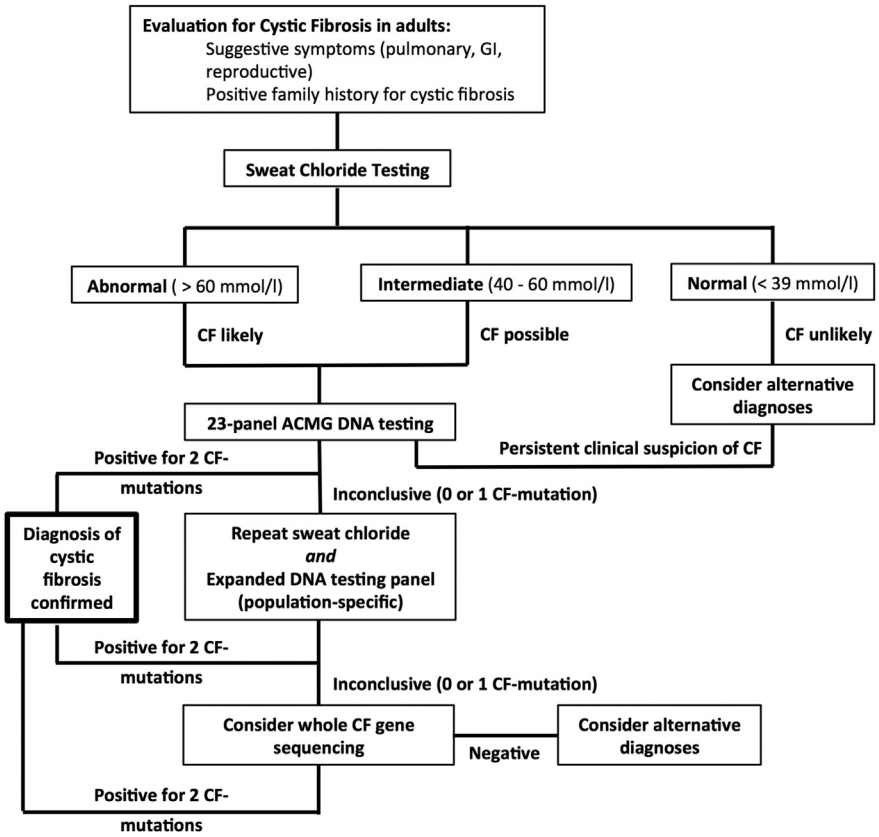

Fig. 1. Algorithm for the diagnosis of suspected cystic fibrosis in adults presenting with symptoms suggestive of cystic fibrosis. CF: cystic fibrosis, ACMG: American College of Medical Genetics, DNA: deoxyribonucleic acid.

homozygous for 3849 + 10 kb C > T did not have any notable gastrointestinal symptoms or nutritional deficiencies, but was malnourished with an initial BMI of 16.6. This is probably due to recurrent acute illness, and BMI increased to 18.6 with nutritional counseling. The patient also had significant sinus disease at a young age, and ultimately had severe areas of bronchiectasis and colonization with resistant organisms (*Mycobacterium Avium Complex, Burkoldheria Cepacia, Aspergillus sp.* and *Pseudomonas Aeruginosa*). Even though our patient had severe airway damage at the time of evaluation, his spirometry was normal.

The patient with *trans* c.2752-26 A > G splicing defect and 5T allele had persistent cough and sinus symptoms for many years, with relatively minimal structural lung disease. This is the first reported case of cystic fibrosis with heterozygous c.2752-26 A > G/5T mutation and second case of the c.2752-26 A > G mutation causing clinical disease. The original description of c.2752-26 A > G splicing defect was in a toddler with failure to thrive [18]. Although the second CF allele in the child was not tested, sweat tests were borderline and there was no pulmonary disease or pancreatic insufficiency at time of diagnosis. This case in particular highlights the importance of stepwise genetic testing, starting with the 23-mutation panel, followed by the 106 multiplex PCR panel and, finally, full CF gene sequencing.

In recent years, improvements in diagnostic testing have allowed identification of milder phenotypes, often with only partially reduced CFTR function [19]. Algorithms published have based diagnostic workup on sweat chloride levels [8]. Sweat chloride can be normal in individuals with CF [20]. These patients with normal sweat chloride levels may not have mutations commonly tested in the 23-mutation ACMG panel. Consequently, this may lead to misdiagnosis or delayed diagnosis, the possibility of developing disease complications before eventual diagnosis, and lack of time-appropriate genetic counseling. The 106-gene multiplex PCR may be an intermediary step before full gene sequencing especially in young adults with history suspicious for CF. Full CFTR genetic sequencing is best reserved as the final genetic test for the presence of a mutation in all 27 exons of the CFTR gene. Occasionally, it can be helpful to genotype a patients' parents to determine whether mutations are in *cis* (same chromosome) or in *trans* position. An algorithm for the stepwise diagnosis of CF in adult patients presenting with symptoms suggestive of possible CF is outlined in Fig. 1.

4. Conclusion

Mutations in 3849 + 10KbC > T and c.2752-26 A > G are rare, and associated with a milder phenotype of cystic fibrosis. 3849 + 10KbC > T mutation was only detected with an expanded 106-mutation analysis, while detection of c.2752-26 A > G required whole CFTR gene sequencing. Our report highlights the importance of further genetic testing in patients where clinical suspicion of CF remains despite initially normal CF testing.

Conflict of interest

None.

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