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CF Patient's Pneumothoraxes Unique Genes

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Cystic fibrosis (CF) has multiple clinical manifestations of which the most prevalent are pancreatic insufficiency with malnutrition and progressive chronic obstructive bronchitis, accounting for 85% of CF patient deaths.[1] CF is an autosomal recessive monogenic disorder involving more than 1000 mutations within the cystic fibrosis transmembrane conductance regulator (CFTR) or CF gene with incidence 1 in 2500 live births in Caucasian populations and carrier frequency of 1 in 25 in the United States.[1-4] Advancement in understanding the CFTR gene, availability of CF genetic diagnostic protocols, and involvement of a multispecialty health care team at outset of CF diagnosis have improved CF patient median life expectancy to 40 years or more.[1,2,5,6] Increased survival has led to more frequent diagnoses of complications such as CF-related diabetes mellitus (CFRD), with prevalence increasing with age: 9% at age 5 to 9 years, 26% at age 10 to 20 years, and about 50% by 30 years of age.[7,8] Blood sugar (BG) control plays a major role in CF patient survival, establishing a place for pediatric endocrinologists within a CF health care team.[9] CF multiorgan involvement with chronic pulmonary infection, malabsorption with exocrine pancreatic insufficiency, and CFRD pose enormous challenges for CF health care teams. We present our 5-year experience with a male CF patient who developed recurrent pneumothoraxes between 14 and 15 years of age leading to an explanation involving recognition of an additional rare genetic diagnosis along with his CF gene documented diagnosis.

Our patient was born by near term C-section with low body weight 4 lb 2½ oz. His nursery course was normal except for bilateral congenital hip dysplasia/dislocation successfully treated with bracing over 9 months. He developed flu-like illness at 3 months of age with persistent cough and failure to thrive, leading to positive sweat test and genetic diagnosis with North America common CF associated delta-F508 homozygote mutation within his CFTR gene on chromosome 7 with clinical pulmonary and malabsorption components. He had surgical repair of an inguinal hernia at 6 months and hospitalization at 5 years of age for uncomplicated pneumonia. His CF care was relatively uncomplicated until 10 years of age.

At 10 years of age he noted 2-month course of progressive polyuria, polydipsia, about 10 lb weight loss to 40th percentile for age, height steady at 20th percentile for age, and lethargy leading to diagnosis CFRD. He had ketonuria and glucosuria with BG 287 mg/dL, sodium 132 mmol/L, and chloride 92 mmol/L with venous pH 7.44. His 2- to 3-month interval average BG-related hemoglobin A1c 12.7%, c-peptide 0.8 ng/mL, low amylase and lipase levels, and negative polyclonal islet directed antibodies were consistent with insulin requiring CFRD. He responded well to subcutaneous insulin and American Diabetes Association recommended diabetes mellitus nutrition adjusted for CF management with overnight high caloric glycemic control liquid tube feedings maintaining hemoglobin A1c less than 7% soon after CFRD diagnosis and transferred to insulin pump therapy at 12 years of age. He maintained CFRD control with hemoglobin A1c 8% or less over the entire 5-year observation reported here. However, he was noted to have benign joint hypermobility with easily correctable episodes of spontaneous shoulder dislocation.

At 14 years of age he developed respiratory distress after correction of a right shoulder dislocation with X-ray documentation of large left pneumothorax. This responded well to tube thoracotomy but reoccurred 1 month later. About 2 months later the left pneumothorax reoccurred with a small right-sided pneumothorax (Figure 1). Initial treatment was with mechanical pleurodesis, after which talc pleurodesis was performed without pneumothorax reoccurrence. Physical exam was remarkable for mild joint hypermobility (Beighton hypermobility score 5) and tissue laxity but no history of

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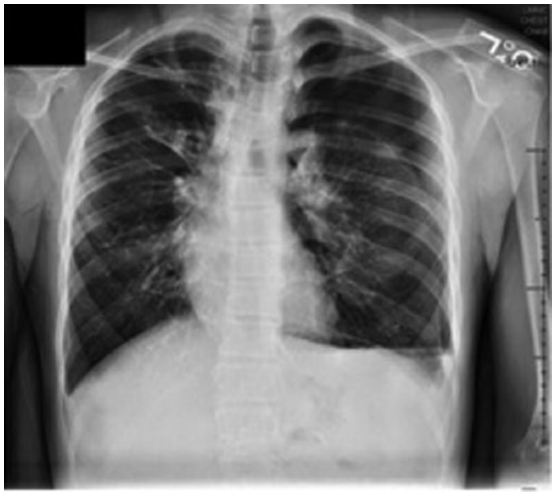

Figure 1. Bilateral pneumothoraxes: Left pneumothorax greater than right.

ectopia lentis.[10] His echocardiogram was reported within normal limits. His family pedigree reviewed over 4 generations added no relevant details other than father's finger-thumb hypermobility and less hypermobility in mother. Genetic consult was obtained.

Our patient's clinical presentation best fit a connective tissue disorder in addition to his CF. His physical exam brought out several features of note: prominent hypermobility of hand-finger joints, thin skin with easily visible veins over hands and feet, easy bruising of feet. He did not meet criteria for Marfan or Loeys-Dietz syndromes or homocystinuria. Ehlers-Danlos type IV (EDIV) vascular type with less prominent hypermobility but life-threatening risk of vascular and various organ rupture was most likely. Sequencing of our patient's Type III procollagen (COL3A1) gene on chromosome 2 documented a heterozygous c.2977G>C(Gly993Arg) mutation in exon 42, confirming EDIV. Our patient was advised to add to his Medic Alert device risks for vascular and organ rupture to avoid invasive arterial studies if at all possible. Our patient appeared unique within medical literature for occurrence of CF and EDIV within one individual.

CF is the most common lethal autosomal recessive disorder in the Northern European population, affecting 1 in every 2500 persons in the United States with a carrier frequency of 1 in 25.[1,2] Since discovery of the CFTR gene in 1989, almost 2000 genetic mutations within CFTR gene are identified to date.[3,5,6] The CFTR protein is made up of 1480 amino acids with its main function that of a c-AMP regulated chloride channel located on apical membrane of epithelial cells expressed in a variety of tissues including lungs, pancreas, and gastrointestinal tract.[4] CFTR gene mutations are categorized into 6 classes based on their effect on the CFTR protein, including impaired biosynthesis, folding and maturation, trafficking and conductance of ions across the membrane, and these classes account for about 80% of all CF-associated mutations.[2] The delta-F508 mutation accounts for about 60% of CF alleles worldwide with about 80% allelic frequency in the United States.[2] With early recognition and intervention of a well-defined health care team, CF patient median survival has increased beyond 36.5 years along with prevalence of CFRD about 26% at age 10 to 20 years.[8] Despite CF being considered a single gene disorder, there is significant variability in phenotypic expression, even among different organ systems of the same individual.[11]

Multiple factors contribute to CF phenotypic expression: CF modifier genes (protective and enhancing), genetic background, epigenetics, and environmental factors such as diet, lifestyle, infection, chemical exposures, and drug use. A strong correlation is noted between more "severe" genotypes (Class I no functional CFTR to low severity Class VI low levels CFTR mutations) and occurrence of exocrine pancreas insufficiency, considered by some to be a prerequisite to CFRD.[11] Some investigators correlate delta-F508 with development of CFRD, and antibodies associated with diabetes mellitus type 1 are not confirmed to be associated with CFRD any more than in the general population.[8] Heterozygous CF mutations in the general population are not considered risk factors for diabetes mellitus.[12]

About 3.4% of CF patients experience a pneumothorax during their lifetime and about 20% occur by 20 years of age.[13] Recurrent pneumothoraxes are estimated to occur in 50% to 90% of these patients.[13] Early-onset pneumothoraxes in the setting of mild lung disease and easy joint dislocation and hypermobility led to discovery of an additional rare genetic disorder in our patient.

EDIV is a rare autosomal dominant mutation in the COL3A1 gene on chromosome 2.[14] Hypermobility of large joints and hyperextensibility of skin noted in more common Ehlers-Danlos types I through VI are reported to be less notable or absent in EDIV, often leading to its diagnosis only after catastrophic complication or postmortem exam. Patients with EDIV are at risk for pneumothorax, arterial and bowel rupture, though the timing and course of occurrence of complications are not well documented. As an isolated diagnosis reviewed by Pepin et al,[14] EDIV complications are rare in childhood though 25% have their first complication by 20 years of age. The median survival of reviewed subjects with isolated EDIV is 48 years.[14,15]

Our patient and his caretakers adapted relatively well to his complex diagnoses and limited prognosis. His plan of care benefited from his genetic documentation of 2 rare mutations within 2 disconnected genes occurring within one individual. Our patient received emotional support to calm his anxiety from family and psychology service as

part of his health care team. Knowledge of his genetic diagnoses assisted his caretakers' early recognition and response when our patient experienced a bowel rupture resulting in colostomy care near the end of our 5-year interval observation. His pulmonology care emphasized airway clearance with attention to intrapleural pressure changes and early treatment of his lung infections. Pediatric Gastroenterology assisted gastric acid reduction and colostomy care. Pediatric Endocrine continued consults at 3- to 4-month intervals either inpatient or outpatient to review CFRD control with adequate nutrition and adjust insulin pump therapy with at least 4 times daily BG or continuous glucose sensor to maintain BG 80 to 180 mg/dL and hemoglobin A1c below 7%.[16]

Our patient and his clinical course demonstrate the importance of considering more than one genetic disorder in an individual patient experiencing an unusual course for the initially identified rare genetic mutation. Recognition of 2 distinct genetic disorders in our patient assisted his health care team, family, and patient to design and accept an effective patient plan of care to optimize appropriate responses to anticipated cataclysmic events and realistic prognosis.

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Author Contributions

Jillian McKee: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
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George Moll: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Authors' Note

Dr McKee conceptualized and made an unpublished oral presentation of this case report at the Southern Pediatric Endocrine Society Meeting; November 1-2, 2014. Dr Moll sponsored and assisted Dr McKee's oral presentation.

Declaration of Conflicting Interests

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