Cystic Fibrosis—A Genetic Dilemma

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Cystic fibrosis is a common genetic disease that usually presents in early childhood as a devastating disease affecting pulmonary function and at times gastrointestinal functioning and nutritional status. Variant forms of this disease have been described, which may have a delayed age of onset or a milder clinical course. Numerous genetic mutations have been described in cystic fibrosis. There are several mutations that are known to be associated with late onset disease or mild clinical disease. Research continues into these genetic mutations and various modifiers that may help to more accurately predict the final phenotypic presentation.

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CASE PRESENTATION

The proposed insured is a 35-year-old software designer who is applying for a $5000 per month disability income policy. There will be a 90-day elimination period with benefits payable to age 65. He is a non-smoker. On the application he admitted to a hydrocele repair after an episode of epididymitis 2 years prior to the application. The family history showed his parents and 3 siblings to be alive and well. Finally, he admitted to being rated in the past for disability insurance because of his “weight.”

The paramed examination showed his height to be 5’11”, weight 225 lbs, and his blood pressure was 118/74. A blood chemistry profile was entirely normal, and the urine specimen confirmed that he was a non-smoker.

An attending physician’s statement (APS) was obtained. A review of these records showed that there was a history of a remote vasectomy, with a vasovasotomy being performed 1 year prior to his application. A follow-up semen analysis to check on the success of the procedure showed no sperm to be present. There was also a history of a fall from a horse many years ago, with the development of intermittent chronic low-back pain. An MRI of his lumbar spine in 2000 showed evidence of degenerative disc disease but no foraminal stenosis or spinal stenosis.

Lastly, 3 months prior to the application, he consulted his doctor for an episode of acute bronchitis. He was treated with antibiotics.
Several laboratory tests were obtained during this visit, although it was unclear why they were done. These tests included a genetic test for cystic fibrosis, which revealed compound heterozygosity for the common ΔF508 and R117H mutations. He also had tests for hepatitis B and C and HIV, which were negative, and tests were also done for HTLV I and II, which were also negative. As noted, it was completely unclear why these genetic tests and serologies were performed at the time of this episode of bronchitis.

DISCUSSION

On the surface, this young individual appeared to be in relatively good health. He did have mild chronic low-back pain, which may require the use of a lumbar spine exclusion waiver. There appeared to be no chronic history of any pulmonary problems and the family history was also negative for pulmonary disease and cystic fibrosis. Why then were these genetic tests for cystic fibrosis done and what do the results mean?

Cystic fibrosis (CF) is a genetic disease with the major manifestations being obstructive airway disease, recurrent pulmonary infections, and pancreatic exocrine insufficiency. Other manifestations include obstructive azoospermia secondary to congenital absence of the vas deferens, recurrent sinusitis, intestinal obstruction in newborns, and a tendency towards hyponatremic dehydration. CF is an autosomal recessive disease, with a prevalence of the carrier state estimated to be 4%–5%. It is caused by a mutation in the CFTR gene on chromosome 7, which controls the production and function of a protein referred to as the cystic fibrosis transmembrane conductance regulator. Mutations in this gene result in the production of a shortened or defective protein, with subsequent impairment of transmembrane chloride ion conductance and abnormalities of water transport in cells. Mucus secretions in the lung, pancreas and gastrointestinal tract become more viscous; and in the lung, there is impairment of mucociliary transport. This predisposes to colonization in the lungs by various bacteria, which then leads to chronic infection. Patients are often colonized with unusual organisms such as staphylococcus and pseudomonas. There may be increased bronchial reactivity, airflow obstruction, cystic dilatation of air spaces, and development of bronchiectasis. In the Caucasian population, it is estimated that 1 in 2500 live births is affected with CF.

Over 1000 mutations of the CFTR gene have been discovered, although 90% of all cases are associated with the 70 most common mutations. Almost all the mutations cause an elevated chloride concentration in the sweat, which is the basis for the sweat chloride test used in the diagnosis of CF. Usually the disease manifests itself in early childhood, but approximately 3% of patients have a variant form of the disease in which symptoms can begin in adolescence or early adulthood. In years past, the disease was often fatal within a short period of time, but currently children are surviving an average of 30 years from the time of diagnosis.

Chronic airway obstruction is present in virtually all adult CF patients, usually following a progressive course. Any young adult with unexplained bronchiectasis or evidence of infection with staphylococcus or pseudomonas should be suspected of having CF. It should also be considered in cases of refractory asthma, failure to thrive, chronic malabsorption and hyponatremic dehydration. The diagnosis can be confirmed by an abnormally elevated sweat chloride. Genetic analysis of the CFTR gene is also commercially available for carrier identification, prenatal diagnosis and to help resolve clinically ambiguous cases, particularly in minimally–affected adults. A NIH expert panel has suggested that genetic testing be offered to adults with a positive family history of CF, to partners of people with CF, to couples currently planning a pregnancy, but not to the general population or all newborns.

In the laboratory studies provided in the APS, the genetic test for CF revealed compound heterozygosity for the ΔF508 and the R117H mutations, but was negative for the
polymorphic 5T allele in intron 10. There was a subsequent narrative regarding the significance of these results. The ΔF508 allele does not produce a functional CFTR, while the R117H mutation decreases but does not completely eliminate the activity of the protein. The lab slip noted that this genotype is “often associated with atypical or milder presentations of CF.” The lab slip also noted that since the specimen was negative for the 5T allele, “the R117H mutation was not expected to lead to a typical CF clinical phenotype.”

The ΔF508 mutation is the most common morbid allele in CF, accounting for over 70% of all CFTR mutations. Homozygosity for ΔF508 is highly correlated with the classic severe form of CF. As noted, a number of other mutations of the gene have been identified, resulting in defects in the production or function of CFTR. These changes of the CFTR allele have been grouped into 5 functional classes, each acting at a different level in the functioning of the CFTR producing the phenotypic variation among persons with CF. Several of these defects are associated with only mild lung disease, and occasionally even a normal sweat chloride concentration. Between 1%–2% of persons with clinical CF have normal sweat chloride values.

The treatment for cystic fibrosis includes antibiotics for infections and the use of respiratory therapies to mobilize secretions. In children, percussion and postural drainage are done, and a pneumatic bronchial drainage vest has also been developed. Lung transplant is being performed in CF patients who have end-stage respiratory function. In theory, CF should be amenable to gene therapy. Strategies aimed at correcting the genetic defect in the respiratory epithelia have been tried, to date with only limited and short-term success. Further studies and research continue.

How does all of this fit in with our proposed insured and his application for disability insurance? Except for the episode of acute bronchitis 3 months prior to the application, there is no history of recurrent pulmonary infections or any pulmonary symptoms. There is no history to suggest pancreatic insufficiency. It is possible that the records provided to us are incomplete. Perhaps the azoospermia noted after his vasovasostomy could be consistent with CF (as opposed to inadequate surgical correction of his vasectomy). There is also no narrative in the APS regarding why the other blood tests were done. It could be that all of this was part of prenatal planning by the proposed insured. Most importantly, what do his positive genetic tests mean regarding his future pulmonary status? Is he at risk of developing progressive pulmonary problems at some time in the future, which could easily result in a disability claim?

Proper evaluation of this case depends on a correct interpretation of his genetic tests. As can be noted from the following discussion, this is not always easy. The reason for this is that the relationship between phenotypic disease expression and the mutational genotype is not completely straightforward. An excellent review of the effect of genotype on phenotype and mortality in cystic fibrosis can be found in the article by McKone et al published in Lancet in May 2003. The authors use the database of the US Cystic Fibrosis Foundation national registry, which includes genetic and clinical data that was developed between 1991 and 1999 on over 17,000 patients with cystic fibrosis. They analyzed the mortality rates for the 11 most common genotypes over a 9-year span of time, comparing various compound heterozygous ΔF508 mutations with those homozygous for ΔF508.

Even though homozygous ΔF508 is the cause of classic severe cystic fibrosis, earlier matched-sibling studies had shown that there is considerable variation in the phenotype among family members with the same mutations, suggesting that modifying genes play a major role in disease expression. The standardized mortality rate ranged from 21.8 in individuals homozygous for ΔF508 down to a mortality rate of 4.7 for individuals with the ΔF508/R117H mutation.

The Cystic Fibrosis Foundation is currently funding a large collaborative multi-year pro-
ject to examine how modifying genes affect pulmonary disease and CF-associated liver disease phenotypes (Also see Nabholtz et al. J Insur Med. 2004;36:47–53.). This information is crucial in understanding why genotype/phenotype correlations in CF are not necessarily reproducible when considering only the CFTR mutation alone. Overall, McKone et al demonstrated that there were significant differences in mortality depending on what heterozygous genotype was present.

The ΔF508/R117H compound mutation was one of those studied by McKone et al. The authors noted that the age at diagnosis for this genotype averaged 13.7 years of age, compared to the classic homozygous ΔF508 onset at age 2.5 years. The sweat chloride concentration was also less, while body weight and forced vital capacity were both greater. The incidence of pancreatic insufficiency was less, and colonization with pseudomonas was also significantly decreased.

However, our proposed insured has no evidence to suggest any manifestation of cystic fibrosis. The reason for this may come from a closer inspection of his genetic testing, which revealed that his R117H mutation was not associated in cis (that is, on the same chromosome) with the 5T polymorphism. There are likely to be one or more modifiers of many known mutations, which may have a profound effect on the expression of any phenotype.

The R117H mutation (substitution of the normal arginine residue at codon 117 by histidine) itself is an otherwise fairly benign missense mutation. However, when it is linked to the 5T allele modifier, it correlates with increased pathogenicity. When the R117 mutation is linked instead to the 7T or 9T variant, then there is empirically less chance of any clinical disease being expressed. Even though our proposed insured had the R117 mutation, the 5T allele was absent, suggesting little risk for the phenotypic expression of active disease. He does not have clinical cystic fibrosis.

The situation might be further clarified by a review of the pedigree in the family; but in this case, this information is not available to us. Another favorable implication would be if this proposed insured had been demonstrated to be fertile prior to his vasectomy, as this would also suggest a benign CF phenotype (males with CF are almost invariably infertile). It is unknown whether or not he has any children. The fact that he is a life-long non-smoker is also favorable.

As has been demonstrated in other inherited disorders such as hemochromatosis, familial hyperlipidemia and Hirschsprung’s disease, there are almost certainly other unlinked modifier genes whose own variations may affect his risk of developing clinical disease. Candidate genes include alpha-1-antitrypsin, beta-2-adrenergic receptors, mannose-binding lectin gene and others. With the constraints of our existing technology and understanding of the complexities of this condition, it is not possible to be absolutely certain that clinical CF could not develop in the future.

Overall, it is our assumption that the likelihood of increased morbidity in the future is quite low. Acceptance of this individual as a standard pulmonary risk does not seem unreasonable. This case was of interest because of the complexity of interpreting the genetic tests in this individual. While genomic medicine has made great strides, there are still many areas of confusion where it is not always clear what a specific genetic mutation will mean regarding the development of actual clinical disease.

REFERENCES