Cystic Fibrosis (CF) is the most common, life-shortening genetic disease in Caucasians. It affects the transport of salt and water across cells and affects different organs, but lung disease is responsible for the majority of symptoms, burden of care, and lost years of life. The gene that causes the disease has now been identified and sequenced.

Whom does it affect?

Epidemiology, prevalence, economic burden, vulnerable populations

Cystic fibrosis affects at least 30,000 people in the United States; between 900 and 1,000 new cases are diagnosed every year (1). One in 29 people of Caucasian ancestry is an unaffected carrier of the CF gene mutation. In the United States, cystic fibrosis occurs at a rate of 1 in 3,400 births. While it occurs in persons of all racial and ethnic backgrounds, it is most common in Caucasians of Northern European ancestry. Historically, half of affected individuals were diagnosed by five months of age, though the average age at diagnosis was five years, and some individuals were not diagnosed until adulthood.
In 2010, however, all states began requiring that newborns undergo screening for cystic fibrosis. This should be helpful because early diagnosis and treatment reduce symptoms, improve health, and reduce costs associated with disease complications.

When CF was first described, most affected children died in infancy or early childhood. With improvements in nutritional therapy, antibiotics, and chest physiotherapy, life was extended into the second decade, and with continued attention to improving care, median survival has increased to 37.4 years, according to the most recent Cystic Fibrosis Foundation registry data. Today, about half of all patients are adults, and although the quality of life is lower than that of the general population, it has been steadily improving.

The cost of treating cystic fibrosis is very high. Most affected individuals must take pancreatic enzymes to digest food effectively, and some require insulin for diabetes mellitus. Many drugs that prevent and treat pulmonary complications are expensive. The average cost of care for a person with CF living in the United States in 2006 was just over $48,000, more than 20 times higher than that for someone without CF (2). Medications account for the single highest expenditure, followed by hospitalization. Each year, one in three patients with CF is hospitalized, mostly for treatment of “pulmonary exacerbations” caused by an infection requiring intravenous antibiotics. Time lost from work and school is

Median predicted survival age for those born with cystic fibrosis

CASE STUDY

A male child was born in 1980. He did not gain weight normally and had frequent, loose, foul-smelling bowel movements. At four months of age, he developed a cough that produced phlegm. A sweat test showed elevated chloride levels, which are diagnostic of cystic fibrosis. He was referred to a CF center and was treated with pancreatic enzymes, chest physiotherapy (to clear excessive secretions in the chest), and antibiotics. He was in fairly good health for a number of years, although he struggled to gain weight and had several hospital stays for breathing problems. At age 10, he became infected with the bacterium Pseudomonas aeruginosa. His pulmonary function worsened, and he required hospital stays lasting up to two weeks once or twice a year. At age 14, he began taking a new drug, dornase alfa, and showed improvement. Three years later, he began taking nebulized tobramycin, and showed further improvement. When he turned 18, he transitioned to an adult CF program. He continued to have frequent pulmonary exacerbations requiring repeated courses of intravenous antibiotics. He developed complications from the antibiotics, including kidney damage and hearing loss. At age 24, he received a lung transplant. He now maintains normal lung function but takes several medications to prevent infection and lung rejection. He works part time and takes classes at a community college.

Comment

This case is representative of an early presentation of an infant with cystic fibrosis with malabsorption and failure to thrive symptoms. Going forward, most patients will be diagnosed by newborn screening, which is now mandatory in all states. He developed bronchiectasis at an early age and became infected with the bacterium Pseudomonas aeruginosa, the most important infection for CF patients. He had severe pulmonary disease as marked by frequent pulmonary exacerbations, rapid loss of lung function, and need for a lung transplant.

common in CF. If indirect costs such as these are factored in, the overall expense is significantly higher. In addition to the cost, the treatment burden for CF patients is also significant. On average, CF patients spend nearly two hours a day performing therapies in order to maintain their health. For young children, this imposes a substantial burden on the family.
What we are learning about this disease

Pathophysiology, causes: genetic, environment, microbes

Cystic fibrosis was referred to in medieval folklore, which mentions infants with salty skin who were considered “bewitched” because they routinely died an early death. Salty skin is now recognized as a sign of CF. It was not until 1936, however, that Dr. Guido Fanconi named this condition “cystic fibrosis with bronchiectasis.” In 1949, Dr. Charles Upton Lowe established that CF was a genetic disorder, and in 1953, Dr. Paul A. di Sant’Agnese reported that children with CF secrete excessive salt in their sweat after observing dehydration in these children during a New York City heat wave. This finding is the basis of the “sweat test,” used to diagnose cystic fibrosis (3).

Much of research until the 1990s was aimed at learning more about the physiology of the surface layer of cells and why salt transport in tissues was defective. After discovering how to unravel the genetic code, the focus and tempo of research switched. In 1989, a collaborative effort using new molecular techniques led to the discovery of the genetic abnormality that causes CF and the sequencing of this gene. Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene. A recessive genetic disorder, it is inherited when two carrier parents (who have one normal gene and one gene with a mutation) each contributes the abnormal CFTR gene to their child. Thus, the likelihood that two carrier parents will have an affected child is 1:4 for each pregnancy. Carriers do not usually have symptoms of CF, but carrier status can be detected through genetic testing.

The abnormality in the CFTR gene causes a defective CFTR protein to be produced, resulting in abnormal transport of salt (sodium and chloride) and water across cells that line the respiratory, digestive, and genital tracts. This results in a reduction of water in the fluid lining the airways. Diminished water causes the respiratory secretions to become thicker and clog small airways. The stagnant sputum becomes infected as bacteria that are inhaled or brought into the lungs through the mouth become lodged there. Persistent stagnation allows persistent infection and chronic inflammation to develop. Inflammatory cells trapped in the sputum add to its tenacity. *Pseudomonas aeruginosa* and other bacteria from the environment thrive in the mucus that is retained in the airways of the CF lung. The bronchi dilate and their walls weaken, setting up a condition called bronchiectasis that results in further airflow obstruction. The vicious cycle of airway
obstruction, inflammation, and persistent infection leads to a progressive decline in lung function and eventually causes respiratory failure and death.

Clogged mucus secretions in the digestive tract can lead to malnutrition and vitamin deficiencies. The genital tract abnormality can lead to infertility in men and women. Other complications include CF-related diabetes, liver cirrhosis, bowel obstruction, chronic sinusitis, and osteoporosis. There is a high prevalence of depression and anxiety in CF patients.

Environmental exposures worsen CF lung disease. Children who are exposed to tobacco smoke have lower lung function and more pulmonary exacerbations than those who live in smoke-free environments. High levels of air pollution are associated with an increased rate of adverse pulmonary events.

How is it prevented, treated, and managed?

Prevention, treatment, staying healthy, prognosis

Cystic fibrosis carrier testing is recommended for Caucasian women who are considering pregnancy or who are pregnant. This can allow a couple who is at risk of having a child with CF to use reproductive technologies to avoid having a baby with CF, or to prepare for the birth of an infant with CF. Diagnosing CF before a child is born, or by newborn screening, allows earlier referral to a CF center and initiation of treatment with pancreatic enzymes before symptoms of abnormal absorption or poor growth occur.

In the United States, most people with CF are treated at specialized CF centers accredited by the Cystic Fibrosis Foundation. Multidisciplinary teams of physicians, nurses, respiratory therapists, dietitians, and social workers care for both adult and pediatric patients.

Individuals with CF who have better nutrition have higher lung function and longer life expectancy. Nutritional management with pancreatic enzymes and a high-calorie, liberal-fat diet is recommended from the time of diagnosis. Some people with CF benefit from supplemental feedings given overnight by a tube placed into the stomach. Specialized vitamin preparations are prescribed in order to reduce the risk of deficiency of certain fat-soluble vitamins.

Although most infants and young children have only intermittent symptoms of cough and wheezing, recent research shows that there are structural and functional abnormalities of the lung as early as the first few months of life. Most CF treatments for lung disease have been tested primarily in patients aged five
and older. These treatments include physical methods to clear thick secretions from the chest, the use of hand-held devices that cause an oscillation in the airways during expiration, and vests that provide external oscillations to the chest wall. Maintenance medications include those that thin sticky airway secretions, such as dornase alfa and hypertonic saline, bronchodilators such as albuterol, inhaled antibiotics such as tobramycin, and anti-inflammatory drugs such as ibuprofen and azithromycin. Practice guidelines assist physicians and patients in choosing appropriate therapies (4).

Frequent monitoring of nutrition and pulmonary function and screening for complications of CF are essential components of care. Current recommendations include quarterly visits to an accredited CF center, frequent pulmonary function testing and respiratory cultures, and annual screening tests for complications, including liver disease and diabetes. Prompt treatment of lung infections and worsening symptoms is extremely important.

Are we making a difference?

Research past, present, and future

Better understanding of the disease and application of this understanding are responsible for the steadily improving life expectancy in persons with CF. Prevention and treatment of respiratory infections may reduce the vicious cycle of bronchiectasis. Prevention of chronic Pseudomonas aeruginosa infection is now a goal of therapy for infants and young children. This strategy consists of frequent monitoring with sputum cultures and treatment with appropriate antibiotics whenever P. aeruginosa is found. Vaccines intended to prevent P. aeruginosa infection and new antibiotics to treat it are being developed.

Many new drugs that may help people affected with CF are being studied. Investigational drugs that help improve salt transport across cells include denufosol, which activates a non-CFTR chloride channel to increase the volume of airway surface liquid. Other potential treatments for infections are also being studied.

Among the most exciting advances in drug therapies for CF are new drugs that have been designed to correct the basic defect in the CFTR protein. The development and early clinical studies of these drugs have been complex, as different gene mutations cause different problems in protein production; therefore, these drugs are specific to defined gene mutations. Some of these drugs
have been shown to improve CFTR function as measured by improved sweat chloride levels and nasal potential differences, a way of directly measuring salt transport across the nasal membranes.

Survival has more than doubled over the last 40 years in conjunction with a greater understanding of the basic pathophysiology in CF. Because a single aberrant gene and its protein product are now known, research can concentrate on measures to correct this defect. If this research leads to another doubling of the lifespan in the next 40 years, life expectancy would approach normal. Application of these findings, however, would only be a part of the effort. Continued attention and research on the management of the patients will be needed to optimize not only length of life, but quality of life, for people living with cystic fibrosis.

**What we need to cure or eliminate cystic fibrosis**

The implementation of newborn screening for CF in every state will facilitate earlier diagnosis and initiation of therapies to preserve good nutrition and lung function. This may translate into better lung function over the long term and improved survival.
Though therapies that improve lung function and reduce infection exist and are a mainstay of therapy, more therapies with alternative mechanisms of action are needed. Therapies designed to improve chloride secretion in the airways or increase hydration of airway mucus may improve bronchial hygiene and preserve lung function. This could translate into improved survival.

While gene therapy has not yet lived up to its initial promise, research is ongoing to develop a safe, efficient method for delivering a normal CFTR gene to the airways of CF patients. Successful gene therapy could lead to a cure for CF.

Drugs designed to improve the function of mutant CFTR, thus correcting the ion transport problem, are currently in development. Several such drugs are in Phase 2 and Phase 3 studies. If these studies show both efficacy and safety, these drugs may lead to stabilization or improvement of CF lung disease and allow for prolonged survival.
References


Web sites of interest

Cystic Fibrosis Foundation
www.cff.org

Cystic Fibrosis Research, Inc.
www.cfri.org

United States Adult Cystic Fibrosis Association
www.usacfa.org