Quick Review: Cystic Fibrosis

B Phillips, C Perry

Citation

B Phillips, C Perry. *Quick Review: Cystic Fibrosis*. The Internet Journal of Internal Medicine. 2000 Volume 3 Number 1.

Abstract

CF is the
most common lethal genetic disease among Caucasians with an Incidence in the United States of 1:2000 among whites; incidence is approximately 1:17000 among African-Americans; it is very rare among Orientals. CF is the major cause of severe chronic lung disease in children and is responsible for most exocrine pancreatic insufficiency during early life. It is inherited as an Autosomal Recessive Trait with a carriage percentage of approximately 5%; heterozygotes are not clinically affected. Twenty percent of patients in the US are Adults.

IN GENERAL

[Mucoviscidosis; Fibrocystic Disease of the Pancreas; Pancreatic Cystic Fibrosis]

CF is defined by the Merck Manual as:

an inherited disease of the exocrine glands, primarily affecting the GI and Respiratory systems, and usually characterized by the triad of chronic obstructive pulmonary disease, exocrine pancreatic insufficiency, and abnormally high sweat electrolytes.

CF is the most common lethal genetic disease among Caucasians with an incidence in the United States of 1:2000 among whites; incidence is approximately 1:17000 among African-Americans; it is very rare among Orientals.

According to Nelson's, CF is the major cause of severe chronic lung disease in children and is responsible for most exocrine pancreatic insufficiency during early life. It is inherited as an Autosomal Recessive Trait with a carriage percentage of approximately 5%; heterozygotes are not clinically affected. Twenty percent of patients in the US are Adults!

In general, the CF gene is most prevalent in Northern and Central Europeans and their descendents.

The basic underlying defect has yet to be identified but dysfunction of the exocrine glands is the predominant pathogenetic feature which often leads to a broad (and confusing) array of clinical manifestations.

It is known that the CF gene is localized to the long arm of Chromosome 7 (Dr. Francis Collins, U. of M - and you thought they only had a good football team) with a large domain encoding for approximately 1500 amino acids - called the “COVERT - CF Transmembrane Receptor”. This receptor is thought to act like a Membrane Regulator or an Anion Pump/Channel.

The most common gene mutation results in the deletion of a Phenylalanine residue at amino acid 508 (referred to as Delta-F 508); however, there are many more less-common mutations that have been identified throughout affected patients.

With this disease, even with the lack of a clear underlying defect, there has been 4 fundamental steps involved in the pathophysiologic process:

1. Failure to Clear Mucus Secretions
2. A Paucity of Water in Mucus Secretions
3. An Elevated Salt Content of Sweat and other Serous Secretions
4. Chronic Infection limited to the Respiratory Tract.
5. Current research is showing that the first three are related to the genetic mutation (and to each other) and that the fourth factor of Infection is a Secondary Event. A summary of the proposed process involves the Sodium and Chloride

Channels within apical membranes. These are present and functional - compared to controls, but have an altered regulation of their activity ! The product of the COVERT Gene is thought to be involved in this “altered regulation” and affects “key phosphorylation steps” in cAMP-dependent and C-kinase pathways that up-regulate and down-regulate the activity of sodium channels (which makes the channel defective in establishing the “normal” potential difference across epithelial surfaces).

A “unifying pathogenetic scheme” for the clinically-observable lung dysfunction is as follows (per Nelson's):

Apical Membrane Ion Transport is dysfunctional and leads to the production of dehydrated secretions with abnormal clearance properties - causing air flow obstruction in the lungs, duct obstruction with secondary destruction of exocrine tissue in the pancreas, and excessively sticky lumenal contents and meconium ileus in the gastrointestinal tract.

Ion Translocation Abnormalities also cause Obstructive Problems in the GU Tract, Liver, Gallbladder, among other organs. This Ion Translocation Dysfunction works “in reverse” for the sweat gland duct: usually the primary fluid generated by secretory coils passes a ductal segment which functions to Reabsorb Chloride and (secondarily) Sodium; because of the impermeability of the epithelial cell membrane to chloride (caused by the ion transport problem), this reabsorption can not occur, leading to Excessive amounts of Sodium Loss in the sweat.

Nearly all exocrine glands are affected !! However, the degree of severity and general distribution varies from patient to patient. Involved glands can be grouped into 3 types:

1. Those that become Obstructed by Viscid or Solid Eosinophilic Material in the Lumen (e.g. pancreas, intestinal glands, intrahepatic bile ducts, gallbladder, and submaxillary glands)

2. Those that produce an Excess of Histologically-Normal Secretions (e.g. tracheobronchial and Brunnuer's Glands)

3. Those that are Normal Histologically but Secrete Excessive Na and Cl (e.g. sweat, parotid, and the small salivary glands)

This summary and division into “groupings” is helpful (at least to us) in trying to correlate the clinical findings with the pathophysiologic process; if one can explain the sign or symptom as related to one of the above groups then the course of disease can be rationalized and - hopefully understood ! For example, in women fertility is decreased (not completely “shut off” - because their have been many cases of term pregnancies reported) secondarily to the large amount of viscid cervical secretions [thought to be in Group 2].

Current evidence suggests that, at time of birth, the lungs are Normal!

Pulmonary disease becomes initiated by diffuse obstruction of the smaller airways by the abnormally-thick mucus (the kind that turned our “wise and thoughtful” Clerkship Coordinator off of Pulmonology!).

This obstruction leads to Bronchiolitis and Mucopurulent Plugging of the airways, with subsequent bronchial changes seen more often than parenchymal changes. Early in the course, Staph aureus is the most common pathogen isolated from respiratory secretions but as the disease progresses Pseudomonas aeruginosa becomes the most frequent isolate. With further progression, the bronchial walls thicken, the airways remain filled with purulent and viscid secretions, areas of Atelectasis develop (in our pt, the RLL collapsed in Sept. '93), and hilar lymph nodes enlarge. Chronic Hypoxemia results in muscular hypertrophy of the Pulmonary Arteries, Pulmonary hypertension, and Right Ventricualr Hypertrophy.

Death usually results from a combination of Respiratory Failure and Cor Pulmonale !

Symptoms and Signs

Varied in type and number!

The earliest possible sign is present at birth and affects 7 - 10 % of infants: Meconium Ileus.

This is due to obstruction of the ileum by viscid meconium and is often associated with volvulus, perforation, or atresia.

In the Newborn, the Meconium Plug Syndrome may be seen; this is a transient form of distal intestinal obstruction secondary to one or more plugs of inspissated meconium in

the anus or colon. If the above conditions are not present, then classical presentation usually occurs by age 4 - 6 wks with a delay in the regaining of birth weight and inadequate weight gain.

Pancreatic insuffiency is present in 85-90% of patients with Clinical Signs include: frequent, bulky, foul-smelling, oily stools; abdominal protuberance; and poor growth pattern with decreased muscle mass - despite a good appetite (the mother states that our pt “will eat anything and is always hungry !!”). Findings of salt crystal formation on the skin and a salty taste on the skin are “highly suggestive” of CF.

50% of patients present with pulmonary manifestations consisting of Chronic Cough (which is usually the most troublesome complaint), Wheezing, Recurrent Pulmonary Infections. The cough may be accompanied by gagging, vomiting, or disruptions in Sleep.

As the disease progresses, there are noticeable intercostal retractions, use of accessory muscles of respiration, a barrel-chest deformity, digital clubbing, and cyanosis. Upper Respiratory Tract involvement includes nasal polyposis and opacification of the paranasal sinuses.

Teenagers may have retarded growth, delayed onset of puberty, and a declining tolerance for exercise.

Pulmonary Complications in adolescents and adults include:

- Pneumothorax,
- Hemoptysis,
- RHF (secondary to the Pulmonary HTN).

In 3% of patients, Insulin-requiring Diabetes develops; 4-5% will develop Multinodular Biliary Cirrhosis with Varices and Portal Hypertension (one of my favorite subjects - all of the various sequelae that are possible - and probable - make it a fascinating topic!!). Chronic and or recurrent abdominal pain may be related to Intussusception, Pancreatitis, GERD, Gallbladder disease, or episodes of partial Intestinal Obstruction secondary to abnormally-viscid fecal material.

Laboratory Findings which are helpful in distinguishing CF may begin with the Newborn Screening Test; a meconium examination looking for the abnormally-large amount of serum protein (especially albumin); however, this screening does NOT detect 10-15% of patients with normal or near-normal pancreatic function - thus it is not recommended as a universal screen.

Since 85-90% of patients will have some degree of pancreatic insufficiency, the duodenal fluid will be abnormally viscid and show an absence (or decrease) in enzyme activity and [HCO3-]. Stool Trypsin and Chymotrypsin are usually diminished or absent [a serum concentration of “immunoreactive trypsin” is being studied as a possible screening test in newborns].

Approximately 40% of patients will show a diabetic oral glucose tolerance reponse secondary to a delayed insulin release. Fasting blood levels of the carotenoids, vitamins A and E (possibly D and K - since absorption would be seriously affected, but D and K were not specifically mentioned as being diminished; direct assays of vitamins D and K may not be required - just by looking at the expected outcomes of their respective deficiencies would be a clinical guide to their possible deficiency: vitamin D - leading to a “Rickets”-type picture if long-term; vitamin K- leading to abnormal values in PTT and Bleeding Time).

Chest x-ray findings may be helpful in diagnosing CF with the earliest findings being Hyperinflation and Bronchial Wall Thickening. Subsequent changes include areas of infiltrate, atelectasis, and hilar lymphadenopathy. With further progression comes segmental or lobar atelectasis, cyst formation, bronchiectasis, and pulmonary artery enlargement with RVH.

Characteristic findings of CF include: “branching” and “finger-like opacifications” (which are due to mucoid impaction in the dilated bronchi. PFT's reveal hypoxemia, reduction in the Forced Vital Capacity, ratio of FEV1/FVC, and an increase in residual volume (with subsequent increase in the RV/TLC ratio).

Unfortunately there is no reliable test for prenatal diagnosis or for heterozygote detection. With the recent discovery of linkage markers for the CF Gene, families with a previously-affected child can undergo karyotype and genetic evaluation with prenatal evaluations !

CF is usually diagnosed in infancy or early-childhood; 10 % of patients do not become detected until adolescence or early adulthood. The diagnosis is suggested by the above clinical signs and symptoms without alternative explanations and then gets confirmed by demonstrating an elevation of Na and CL concentrations in the sweat. The ONLY reliable test is the:

QUANTITATIVE PILOCARPINE IONTOPHORESIS SWEAT TEST

The test works by pharmacologically stimulating localized sweating and then collecting the amount of sweat secreted; measurements of electrolytes are determined and NA or Cl values > 60 mEq/L confirms the diagnosis given a suggestive clinical picture or positive family history. It is estimated, that less than 1:1000 patients with CF will have a sweat chloride less than 50 mEq/L. False-negative tests are rae but can occur in the presence of edema, hypoproteinemia, or with inadequate quantities of sweat. It must be remembered that a small subset of patients (labeled "CF Variants") do exist; these people will have chronic pseudomonas bronchitis, normal pancreatic function, and intermediate values of Sweat Cl ranging from 40-60 mEq/L.

COURSE OF CF

Largely determined by the degree of Pulmonary Involvement and varies greatly from patient to patient. However, deterioration is inevitable.

- Prognosis has improved over the past few decades and is said to be mainly due to the widespread aggressive treatment before the onset of irreversible pulmonary changes.
- Median Survival is 20 yrs of age.
- Long-term survival is better for males compared to females.

One of the most important factors in this disease is the quality of Supportive Treatment - trying to make this condition more tolerable for both the patient and family (in my opinion, one of the most important responsibilities of the physicians, nurses, physical therapists, counselors, and social workers - the disease is progressive and non-curable. Most patients are able to work or attend school until shortly before death.

GENETIC COUNSELING MUST BE CONSIDERED FOR "AT-RISK" FAMILIES !

Treatment involves, ideally, a comprehensive and intensive therapy program.

The ultimate goals of therapy include:

1. Adequate Nutritional Status
2. Prevention or Aggressive therapy of Pulmonary Complications
3. Encouragement of Physical Activity
4. Provision of Adequate Psychosocial Support.

Diet therapy includes: sufficient calories and protein to promote normal growth and development (suggestion is to exceed the RDA requirements by 50%; a high-normal fat intake to increase the caloric density; multivitamins in double the recommended concentrations; supplemental Salt in times of increased sweating. Prophylaxis against respiratory infections includes the maintenance of Pertusis and Measles Immunity and annual Influenza vaccination. Since there has been no reported increase in the morbidity or mortality from Pneumococcal Infections, pneumococcal vaccine is not universally recommended.

Obstruction (in the uncomplicated Meconium Ileus or in the "Meconium Ileus Equivalent"- a partial intestinal obstruction following the newborn period) can be treated with enemas containing a hyperosmolar radiopaque contrast material or N-acetylcysteine; oral administration of N-acetylcysteine may help to prevent such problems. When pancreatic insuffiency is present (as in our pt), pancreatic enzyme replacement should be given with each meal - dosage should vary with the size of the meal. The most effective enzyme replacement consists of Pancrealipase in pH-sensitive, enteric-coated microspheres.

Treatment of Pulmonary infections includes the prevention of Airway Obstruction and subsequent control of infection. At the first sign of pulmonary involvement, chest physical therapy (postural draining, percussion, vibration, and assisted coughing) is recommended. If signs of reversible airway disease is present (as in our pt), bronchodilators may provide some benefit; oxygen is indicated for those patients with severe pulmonary insuffiency or hypoxemia - usually, assisted ventilation is not required in CF patients with chronic respiratory failure. Pneumothorax can be treated with the use of a Closed Chest Tube Thoracostomy in combination with intrapleural installation of a sclerosing agent (Quinacrine 2%, 100 mg in 50 ml NS); an alternative treatment suggested by Lawrence is Open Thoracotomy with resection of blebs and pleural abrasion. The use of aerosolized mucolytics and oral expectorants is wide and varied but, according to Nelson's has few clinical data supporting their efficacy. Tracheobronchial lavage does provide some temporary improvement in selected patients (as seen in this case, following lavage in Sept '93, the pt was asymptomatic for approximately 1 yr). Massive or recurrent

hemoptysis is treated by embolization of the involved bronchial arteries. Pts with signs of RHF should be treated with diuretics, salt restriction, and oxygen.

Surgery may be indicated for the following:

1. Localized Bronchiectasis or medically-"resistant" Atelectasis
2. Nasal Polyps
3. Bleeding form Esophageal Varices (secondary to Portal HTN)
4. Gallbladder Disease
5. Intestinal Obstruction (due to Volvulus or an Intussusception that can not be medically reduced, or that is not reducible by Barium Enema)

In symptomatic outpatients, bacterial pathogens in the respiratory tree should be treated with effective drugs as determined by C&S. For Staphylococci, penicillinase-resistant penicillins (cloxacillin) or a cephalosporin are the agents of choice. For "combination-disease" (mixed flora), other antibiotics should be instituted. For severe pulmonary infections - especially those colonized by Pseudomonas, admission to the hospital for parenteral antibiotic therapy is recommended.

Combinations of an Aminoglycoside with an anti-pseudmonas penicillin are commonly used by the IV route; some of the newer cephalosporins do carry anti-pseudomonas activity and are being used clinically. The goal of treating pulmonary infections should be to improve the clinical picture to the point that continuous antibiotic therapy is not needed; however, in some patients long-term use may be required.

CORRESPONDENCE TO

Bradley J. Phillips, MD Dept. of Trauma & Critical Care Medicine CCM 2707 One Boston Medical Center Place. Boston, MA 02118 Tel: (617) 638-6406 Fax: (617) 638-6452 Email: bjpmd2@aol.com

References

Author Information

Bradley J. Phillips, MD
Dept. of Trauma & Critical Care, Boston University School of Medicine, Boston Medical Center

Charles W. Perry, MD
Dept. of Surgery, University of Arizona