

CYSTIC FIBROSIS

Cystic fibrosis (CF) (OMIM database No. 219700)⁷⁰ is a hereditary disease that has primary effects on the lungs, pancreas, intestine, liver, sweat glands, and male reproductive tract as well as important secondary effects on growth and nutrition.⁷¹ The clinical course is variable, but most patients succumb to lung disease in early adulthood.

Incidence

The incidence of CF is approximately 1 in 3500 in white newborn infants. The incidence in black and Hispanic newborn infants (approximately 1 in 15000 and approximately 1 in 7000, respectively) is higher than previously suspected. There is a low incidence in Asian infants.

Clinical Manifestations

CF usually presents in infancy. Meconium ileus, a neonatal intestinal obstruction, occurs in approximately 17% of infants with CF. Beyond the perinatal period, CF presents as failure to thrive secondary to exocrine pancreatic insufficiency, chronic respiratory symptoms, or both. Nutritional deficits can be severe at presentation and may lead to edema and hypoproteinemia from protein-calorie malnutrition. Infants may present with hyponatremia from sweat salt loss. The most common chronic respiratory symptoms are cough and wheeze. If infants are not diagnosed in the newborn period, they often undergo months of illness with concomitant stress on the parents. Patients are prone to chronic endobronchial infections with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and other characteristic bacteria throughout childhood. Many of these patients suffer from recurrent intestinal blockages, and a small percentage of patients have severe liver disease. Diabetes is increasingly common during adolescence and young adulthood. Fifteen percent of these patients have mutations that do not lead to exocrine pancreatic insufficiency. They are at risk of recurrent pancreatitis, however. The median predicted age of survival is 33 years.⁷²

Pathophysiology

CF results from abnormalities in the CF transmembrane conductance regulator (*CFTR*) protein, a membrane glycoprotein that regulates ion flux at epithelial surfaces. Abnormalities in *CFTR* cause thick secretions that obstruct pancreatic ductules, leading to exocrine pancreatic destruction. In the airway, dehydration of airway surface liquid leads to chronic infection and neutrophil-dominated inflammation. Bronchiectasis and progressive obstructive lung disease then follow.

Inheritance

CF is autosomal recessive. More than 1000 mutations in the *CFTR* gene have been described, but one mutation, $\Delta F508$, accounts for more than 70% of affected chromosomes in individuals of European ancestry. Several-dozen mutations have been characterized as pancreatic sufficient or insufficient on clinical grounds. The American College of Medical Genetics has developed standards and guidelines for population-based CF-carrier screening that include a panel of 25 mutations.⁷³

Rationale for and Benefits of Newborn Screening

The principal benefit of newborn screening and early diagnosis is improved height and weight at least through adolescence, demonstrated in a well-controlled clinical trial.⁷⁴ Improvement in height and weight likely occurs from early institution of pancreatic enzyme, fat-soluble vitamin and salt supplementation, as well as the general nutritional follow-up that is part of care at a CF center. In addition, it is likely that early diagnosis and attention to nutrition can help patients avoid severe nutritional complications of infancy, although this has not been shown in a controlled trial. Severe nutritional complications of CF in infancy include anemia from vitamin E deficiency, zinc deficiency, linoleic acid deficiency, hyponatremia, and protein-calorie malnutrition. In addition, vitamin E deficiency at symptomatic diagnosis of CF is associated with cognitive deficits. Thus, early diagnosis through newborn screening is likely to improve developmental outcome. Observational studies support improved pulmonary outcome after newborn screening. In addition, height in CF is correlated with improved pulmonary outcome. Thus, the increase in height in patients identified through screening also may be beneficial. Another benefit of screening is that parents of children identified through screening have been shown to have greater trust in the medical establishment than parents whose children are identified only after symptoms appear.⁷⁵

Screening Methodology

Determination of immunoreactive trypsinogen (IRT) concentrations from dried blood spots serves as the basis for the first tier in all newborn-screening programs for CF. IRT concentration is high in the blood of infants with CF, presumably from leakage of the protein into the circulation after exocrine pancreatic injury. Two approaches can be taken if the IRT concentration is high. The more common approach is to perform mutation analysis from the dried blood spot for a set of CF mutations. Another approach is based on persistent elevation of IRT concentration, which requires a second dried blood spot taken 2 to 3 weeks after birth.

The value at which the initial IRT concentration is considered abnormal varies from program to program. If mutation analysis is performed from the first dried blood spot, a second specimen is not required. Thus, the IRT cutoff can be set to include a substantial fraction of the newborn population. In some programs, the top 5% of all IRT concentrations are considered abnormal and mutation analysis is performed. In other programs, the cutoff is set at the top 1%.

Programs that are based on persistent elevation of IRT concentration require a second dried blood spot taken at 2 to 3 weeks of age in infants with a high concentration on the first specimen. These programs set the cutoff value for IRT at a higher concentration (0.5% of newborn infants) than programs that perform mutation analysis. Diagnosis through persistent elevation of IRT concentration can identify infants with CF who do not carry mutations included in most mutation-analysis panels.

Timing

Because IRT concentration is frequently high immediately after birth, specificity is improved if the test is performed after the first day of life.

Sensitivity and Specificity

The sensitivity of most CF screening programs, whether based on genotyping or persistent elevation of IRT concentration, is approximately 95%. The specificity of programs that rely on persistent elevation of IRT concentration without genotyping is approximately 99.5% after the first measurement of IRT concentration. The specificity of programs that perform genotyping after the initial elevation of IRT may be as high as 99.9%.

Follow-up and Diagnostic Testing (Short-term) Timeline

For programs that perform mutation analysis, the diagnosis of CF can be made if 2 mutations are identified from the dried blood spot. If only one mutation is identified from the dried blood spot, then sweat testing, the definitive diagnostic test, should be performed as soon as possible. In programs that do not perform mutation analysis, sweat testing should be performed within a few days of the repeat IRT test. There is some urgency to making the diagnosis. Many patients are pancreatic insufficient in the first weeks of life and are at risk of severe nutritional complications. Pancreatic enzyme-replacement therapy, fat-soluble vitamin supplementation, and salt supplementation should be initiated very soon after diagnosis in pancreatic-insufficient infants.

Test and Procedures

Sweat testing should be performed at more than 1 week of age. Almost all term infants will have adequate sweat amounts by that time.⁷⁶ Sweat collection amounts may be inadequate in preterm infants; in such a case, mutation analysis can be performed.⁷⁷ Currently, a sweat chloride value of more than 40 mmol/L is required for the diagnosis of CF in the newborn period; infants with values more than 30 mmol/L, however, require follow-up.⁷⁸ In programs that perform mutation analysis, confirmatory sweat testing should be obtained even in infants who test positive for 2 mutations.

Brief Overview of Disease Management

Nutrition is an important focus of management beginning in infancy. A recently developed test for fecal elastase may allow convenient determination of need for pancreatic enzyme supplementation. Pancreatic enzyme, fat-soluble vitamin, and salt supplementation will be started in most infants at diagnosis. Outpatient regimens become increasingly complex with age and often include several inhaled medications, nutritional supplements, attention to secretion clearance, and a number of ongoing oral medications to be taken daily. Patients with pulmonary exacerbation require hospitalization to receive intravenous antibiotic therapy and intensive secretion clearance. Every effort should be made to have the infant and family cared for at centers accredited by the Cystic Fibrosis Foundation.

Current Controversies

Three controversies have surrounded newborn screening for CF. One issue has been whether the growth and nutritional benefits of early diagnosis are sufficient to justify screening. Very recently, however, the Centers for Disease Control and Prevention has determined that newborn screening for CF is of benefit.⁷⁹ Follow-up studies of pulmonary and cognitive outcomes may further address this issue. A second issue is carrier detection, which occurs in all programs that use mutation analysis as part of the screening. It is not known for sure whether identification of otherwise well infants as carriers of CF may do harm, but studies suggest that this is not the case. A third issue is that approximately 5% of newborn infants identified will have borderline sweat tests (sweat chloride levels of 30–40 mmol/L) and "mild" mutations. It is not clear yet how many of these infants will have important medical problems. Follow-up studies are underway.

Counseling

Parents will require education on all aspects of CF. The care team consists of the primary pediatrician and the CF center staff. Genetic counseling should be arranged for all families.⁸⁰

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