Cystic Fibrosis Diagnosis and Newborn Screening

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KEYWORDS

• Cystic fibrosis • Diagnosis • Newborn screening • Sweat chloride • Mutation

KEY POINTS

- Most new diagnoses of cystic fibrosis (CF) are now identified by newborn screening, which provides the opportunity to improve outcomes by initiating monitoring and treatments in the presymptomatic period.
- The sweat chloride measurement is still the cornerstone of CF diagnosis. It should be performed according to national guidelines. Sweat conductivity and osmolality are not acceptable substitutes.
- In the United States, newborn screening algorithms vary by state, although all involve measurement of immunoreactive trypsinogen in the dried blood spot and most involve genetic testing with a panel of CF transmembrane conductance regulator (CFTR) mutations.
- CF newborn screening inevitably identifies infants with indeterminate diagnoses (referred to interchangeably as CF-related metabolic syndrome in the United States and CF screen–positive, inconclusive diagnosis in Europe). Although most of these infants do not develop signs or symptoms of CF, they should be monitored regularly at least in the first few years of life, because some will develop evidence of CFTR dysfunction.

INTRODUCTION

The landscape of the diagnosis of cystic fibrosis (CF) has changed dramatically over the past decade, as universal screening for CF has become a reality in all 50 states in the United States since 2010. Most countries with a high prevalence of CF around the world have also implemented universal CF newborn screening. Now, instead of being diagnosed based on symptoms, typically after having endured a long, difficult, and expensive diagnostic odyssey, most individuals are diagnosed after a positive

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newborn screen. In 2013, 62% of new diagnoses in the United States were detected by newborn screening.[1] Early diagnosis affords the opportunity to improve long-term outcomes through close monitoring and appropriate interventions beginning before severe nutritional deficits or irreversible airway damage have occurred. As CF transmembrane conductance regulator (CFTR) modulator therapies that treat the basic defect in CF become available across a broad range of ages and CFTR genotypes, initiation of these therapies in infancy holds the promise of being disease modifying.

However, even in the current era of universal newborn screening, some individuals are diagnosed symptomatically, either because they were born before implementation of newborn screening or in regions in which newborn screening was not offered, or because of a false-negative newborn screen. Thus, clinicians must always maintain an index of suspicion for CF in individuals with 1 or more signs or symptoms of CF, regardless of age or newborn screening results.

Since identification of the *CFTR* gene on the long arm of chromosome 7 in 1989, it has become increasingly clear that CFTR dysfunction encompasses a wide range of phenotypes, from classic pancreatic-insufficient CF, to single-organ-system manifestations often diagnosed in adulthood, to indeterminate diagnoses in infants identified by newborn screening. Thus, although the diagnosis of CF is straightforward in most cases, with a sweat chloride level greater than or equal to 60 mmol/L and/or 2 CF-causing mutations identified, establishing the diagnosis in the minority of patients in whom these diagnostic conditions are not met can be challenging and time consuming. Newer diagnostic modalities, such as nasal potential difference and intestinal current measurements, can also be used to assess CFTR dysfunction and aid in diagnosis, but are currently only conducted at specialized centers.

ESTABLISHING THE DIAGNOSIS OF CYSTIC FIBROSIS

General Principles

The US CF Foundation has convened 3 panels of experts to establish and then refine the diagnostic criteria for CF (**Box 1**), first in 1996,[2] then in 2007,[3] and most recently in 2015. As of the writing of this article, the most recent guidelines are still in draft form. In addition, a European consensus conference established a similar diagnostic algorithm.[4] Although understanding of the heterogeneity of disease presentation and of the complexity of *CFTR* mutations has greatly increased, many of the basic tenets of establishing the diagnosis have remained virtually unchanged. The sweat chloride test remains the cornerstone of diagnosis, because it directly measures CFTR function. Proper performance of the sweat chloride test, which is crucial for the accurate diagnosis of CF, requires skill and experience. The sweat chloride test should be

Box 1
Diagnostic criteria for CF

Positive newborn screen

Or signs/symptoms suggestive of CF

Or positive family history in a parent or sibling

And:

Either a sweat chloride level greater than or equal to 60 mmol/L

Or identification of 2 CF-causing mutations in *trans*

Or nasal potential difference measurement consistent with CF