Practice guidelines

ELSEVIER

Received:
27 May 2017
Accepted:
4 July 2017

Guidelines for the clinical management and follow-up of infants with inconclusive cystic fibrosis diagnosis through newborn screening

Recommandations pour la prise en charge et le suivi des nourrissons pour lesquels un diagnostic de mucoviscidose n'a pu être conclu après dépistage néonatal

I. Sermet-Gaudelus[a,b,*], J. Brouard[c], M.-P. Audrézet[d], L. Couderc Kohen[e], L. Weiss[f], N. Wizla[g], S. Vrielynck[h], K. LLerena[i], M. Le Bourgeois[a], E. Deneuville[j], N. Remus[k], T. Nguyen-Khoa[a], C. Raynal[l], M. Roussey[m], E. Girodon[b,n]

[a] *Cystic fibrosis center, Necker-Enfants-Malades hospital, 75015 Paris, France*
[b] *Inserm U1151, 75993 Paris, France*
[c] *Cystic fibrosis reference center, hôpital de la Côte-de-Nacre, 14033 Caen, France*
[d] *Molecular genetic laboratory, CHRU de Brest, 29609 Brest, France*
[e] *Cystic fibrosis reference center, Charles-Nicolle hospital, 76000 Rouen, France*
[f] *Cystic fibrosis reference center, Hautepierre hospital, 67200 Strasbourg, France*
[g] *Cystic fibrosis reference center, Jeanne-de-Flandres hospital, 59000 Lille, France*
[h] *Cystic fibrosis reference center, child and mother hospital, 69677 Lyon, France*
[i] *Cystic fibrosis center, university hospital, 38700 Grenoble, France*
[j] *Cystic fibrosis center, CHU de Rennes, 35000 Rennes, France*
[k] *Cystic fibrosis center, Créteil intercommunal hospital, 94000 Créteil, France*
[l] *UMR 5535, molecular genetic institute, 34293 Montpellier, France*
[m] *Association française pour le dépistage et la prévention des handicaps de l'Enfant, 75015 Paris, France*
[n] *Molecular genetics laboratory, Cochin hospital, 75014 Paris, France*

Summary

Neonatal screening for cystic fibrosis (CF) can detect infants with elevated immunoreactive trypsinogen (IRT) levels and inconclusive sweat tests and/or *CFTR* DNA results. These cases of uncertain diagnosis are defined by (1) either the presence of at most one CF-associated *cystic fibrosis transmembrane conductance regulator* (*CFTR*) mutation with sweat chloride values between 30 and 59 mmol/L or (2) two *CFTR* mutations with at least one of unknown pathogenic potential and a sweat chloride concentration below 60 mmol/L. This encompasses various clinical situations whose progression cannot be predicted. In these cases, a sweat chloride test has to be repeated at 12 months, and if possible at 6 and 24 months of life along with extended *CFTR* sequencing to detect

Résumé

Les cas d'hypertrypsinémie au dépistage néonatal pour lesquels le diagnostic reste non conclu sont définis soit (1) par l'association d'une mutation au plus du gène *CFTR* associée à la mucoviscidose avec une concentration de chlorure sudoral intermédiaire entre 30 et 59 mmol/L, soit (2) par l'association de 2 mutations de *CFTR*, dont au moins une est de pathogénicité indéterminée avec une concentration de chlorure sudoral inférieure à 60 mmol/L. Ces situations regroupent des formes cliniques différentes dont il est impossible de prévoir l'évolution. Ceci impose de refaire un test de la sueur à 12 mois et si possible à 6 et 24 mois et de rechercher les mutations rares du gène *CFTR*. En l'absence de conclusion, des explorations fonctionnelles visant à établir une dysfonction de CFTR peuvent être proposées. Les

DOI of original article: https://doi.org/10.1016/j.arcped.2017.01.019
* Corresponding author at: Cystic fibrosis center, Necker–Enfants-Malades hospital, 75015 Paris, France.
e-mail: isabelle.sermet@aphp.fr (I. Sermet-Gaudelus).

https://doi.org/10.1016/j.arcped.2017.07.015 Archives de Pédiatrie 2017;xxx:1-14
0929-693X/

rare mutations. When the diagnosis is not definite, CFTR functional explorations may provide a better understanding of CFTR dysfunction. The initial evaluation of these infants must be conducted in dedicated CF reference centers and should include bacteriological sputum analysis, chest radiology, and fecal elastase assay. The primary care physicians in charge of these patients should be familiar with the current management of CF and should work in collaboration with CF centers. A follow-up should be performed in a CF reference center at 3, 6, and 12 months of life and every year thereafter. Any symptom indicative of CF requires immediate reevaluation of the diagnosis. These guidelines were established by the "neonatal screening and difficult diagnoses" working group of the French CF society. Their objective is to standardize the management of infants with unclear diagnosis.

nourrissons concernés doivent avoir une évaluation initiale au sein d'un centre de ressources et de compétences pour la mucoviscidose (CRCM) comprenant une étude bactériologique des sécrétions bronchiques, une radiologie de thorax et un dosage de l'élastase fécale. Le praticien libéral référent doit être informé des particularités de la prise en charge et travailler en collaboration avec le CRCM. L'enfant doit être revu à 3, 6 et 12 mois, puis tous les ans au CRCM. L'apparition de symptômes évocateurs de mucoviscidose justifie une réévaluation. Ces recommandations établies par le groupe « Dépistage et formes de diagnostic difficile » de la Société française de la mucoviscidose visent à uniformiser les pratiques dans les CRCM pédiatriques français pour un suivi rationnel adapté et éthique.

1. Introduction

A key objective of newborn screening for cystic fibrosis (CF) is early diagnosis and prompt initiation of specialized care from a pediatric team of CF specialists to delay nutrition impairment and pulmonary complications and improve long-term outcomes. Current screening methods include immunoreactive trypsinogen (IRT) in dried blood spots and common *CFTR* (*cystic fibrosis transmembrane conductance regulator*) gene mutation analysis in infants with IRT levels $\geq$ 65 μg/L [1]. In newborns with presumptive CF, a sweat chloride testing is carried out to rule out or confirm a diagnosis. A diagnosis for CF is confirmed when the sweat chloride concentration is $\geq$ 60 mmol/L and the presence of one CF-causing mutation inherited from both parents has been established. These abnormalities result in loss or altered function of the CFTR protein and are associated with a high probability of developing clinical manifestations of CF later in life [2–5]. However, diagnosis for CF can be challenging in some subjects with intermediate sweat chloride results between 30 and 59 mmol/L and only one to no CF-causing mutation [3,4,6–10]. In those individuals with an atypical presentation, reliable predictions for disease progression are difficult. A subset of these infants will develop classic CF [3,4,6–11], sometimes later in life [12], while some might never exhibit any symptoms [13]. In others, clinical features associated with CFTR dysfunction might not develop until adolescence or adulthood, which is associated with better prognosis than classic CF. These forms may affect multiple organ systems and are usually characterized by mild pulmonary disease and the absence of exocrine pancreatic insufficiency. They may also involve a single organ with evidence of CFTR-related pathology such as enlarged airways (bronchiectasis), recurrent acute or chronic pancreatitis, or obstructive azoospermia with congenital bilateral absence of vas deferens in boys [14]. The prevalence of such cases is highly variable across populations, ranging from 1 to 6% in Australia and Canada [3,9], up to 10% in the US [6,15], and even 21% in California [16]. In France, the proportion of patients with uncertain diagnosis for CF is 1 in every 6.3 confirmed diagnoses, accounting for 184 children between 2002 and 2009 [17,18]. These patients are usually clinically asymptomatic (9% versus 63% of the children with established diagnosis according to the French CF newborn screening report) [18]. In some cases, these patients can present symptoms consistent with CF, but this is at a later stage than in individuals with confirmed diagnosis due to the mild clinical course of the disease (26% before 35 days of age and 70% before 56 days of age in patients with an inconclusive diagnosis versus 53% and 88% in patients with confirmed CF) [18]. This delay illustrates the challenge to ensure proper diagnosis management of these patients. Moreover, a wide variability of management approaches for these patients with inconclusive diagnosis across CF centers in France adds to the diagnostic dilemma. A survey conducted by the authors of this consensus has shown that 12 French CF care teams provided support and reassurance to parents, two others recommended routine follow-up visits similar to classic CF, while 11 teams scheduled spaced-out follow-ups and 13 did not have any defined strategy.

Parents of CF children face a great deal of anxiety about their infant's prognosis and uncertain future. Moreover, the desire for future pregnancies raises the indication of prenatal DNA diagnosis with the possible option of terminating the pregnancy if a genetic test proves positive for CF mutations in the fetus. It is therefore fundamental to clarify this situation by establishing adapted and homogenous diagnostic management and follow-up throughout France. The "Screening and uncertain diagnosis of cystic fibrosis" working group of the French cystic fibrosis society consists of physicians, biochemists, geneticists, nurses, and psychologists at CF centers. Their objective is to provide a standard of care for CF patients harmonized with international guidelines [19]. This group previously published recommendations for management and follow-up of newborns diagnosed with typical forms of CF [20,21]. The goal of the present recommendations is to