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**Classification of Cystic Fibrosis and  
Related Disorders**

Report of a joint WHO/ICF(M)A/ECFS/ECFTN Meeting

*Stockholm, Sweden, 3 June 2000*

## **1. Background**

Making a diagnosis of Cystic Fibrosis (CF) is not always simple.<sup>1</sup> Initially, CF was recognised as a clinical syndrome. Many diagnostic problems were resolved by the development of the sweat test in 1950.<sup>2</sup> The test remains clinically reliable for most cases,<sup>3</sup> but the occasional occurrence of false-negative and false-positive results has always been recognised. With the cloning of the gene for the CF transmembrane conductance regulator (CFTR)<sup>4,5</sup> in 1989 clinicians hoped that genetic testing for CF would be both sensitive and specific. However, the more than 900 mutations so far identified in the CFTR gene have made genetic testing for CF difficult to develop, and making a definitive diagnosis in atypical cases has become sometimes more, rather than less, difficult.

Although the rarity of most mutations has made it possible to screen by using a panel of 70 mutations with a sensitivity approaching 90% in the general population of the United States,<sup>6</sup> the complexity of the problem has been increased by recognition that some conditions caused by mutations in the CFTR gene fall short of the criteria necessary for a diagnosis of cystic fibrosis. For example, male infertility due to congenital bilateral absence of the vas deferens,<sup>7,8</sup> with or without mild sinopulmonary disease, is commonly associated with CFTR mutations. Recently it has been shown that unilateral vas deferens atresia may also be related to CFTR mutations.<sup>9</sup> Recurrent or chronic pancreatitis is another condition where a diagnosis of CF is not appropriate, but in which CFTR mutations are frequently identified. These disorders are not CF but are CFTR-related.

## **2. The role of genotype**

Genotype-phenotype correlation has proved to be inconsistent even for those specific mutations shown to be associated with "classical" cystic fibrosis. Among patients homozygous for the common deltaF508 mutation, and even within families, a variety of different clinical phenotypes and degrees of severity can be observed.<sup>10</sup> Occasional individuals carrying two "severe" mutations may have no clinical evidence of disease, at least in early life and may remain asymptomatic into the 5<sup>th</sup> decade (Warwick W, personal communication). Others, with typical CF features, may have no identifiable mutations even when their CFTR genes have been sequenced (Tsui, unpublished). This suggests that in addition to environmental factors, at least one gene at another locus (and probably more) may significantly affect the clinical picture.<sup>11</sup> It further indicates that genotype alone is an insufficient basis for the classification of clinical syndromes associated with cystic fibrosis or the CFTR gene.

## **3. The diagnosis of Cystic Fibrosis**

Features suggesting or confirming the diagnosis of CF have recently been summarised in the U.S. Consensus document 1998 (Table 1).<sup>12</sup> This statement serves well as a reference point for the majority of cases, but it does not take into account the fact that approximately 5% of otherwise typical (if usually mild) CF individuals have negative sweat tests, and the

alternative tests based on nasal, duodenal or rectal potential difference which help to resolve doubtful cases are not widely available.

### **Table 1 Phenotypic features consistent with a diagnosis of CF<sup>12</sup>**

#### 1) Chronic sinopulmonary disease manifested by

- Persistent colonisation/infection with typical CF pathogens including *Staphylococcus aureus*, nontypeable *Haemophilus influenzae*, mucoid and nonmucoid *Pseudomonas aeruginosa*, and *Burkholderia cepacia*.
- Chronic cough and sputum production
- Persistent chest radiograph abnormalities (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation)
- Airway obstruction manifested by wheezing and air trapping
- Nasal polyps; radiographic or computed tomographic abnormalities of the paranasal sinuses
- Digital clubbing

#### 2) Gastrointestinal and nutritional abnormalities including

- Intestinal: meconium ileus, distal intestinal obstruction syndrome, rectal prolapse
- Pancreatic: pancreatic insufficiency, recurrent pancreatitis
- Hepatic: chronic hepatic disease manifested by clinical or histologic evidence of focal biliary cirrhosis or multilobular cirrhosis
- Nutritional: failure to thrive (protein-calorie malnutrition), hypoproteinemia and edema, complications secondary to fat-soluble vitamin deficiency

#### 3) Salt loss syndromes: acute salt depletion, chronic metabolic alkalosis

#### 4) Male urogenital abnormalities resulting in obstructive azoospermia (CBAVD)

Another recent approach has been to regard individuals with a CF genotype but no discernable clinical disease (e.g. some infants detected by neonatal screening) as "pre-CF" using the analogy of premalignant conditions.<sup>13</sup> However, while indicating the need for such persons to be kept under clinical surveillance it begs the question of how to classify subclinical disease and is not a concept which has yet found wide acceptance.

## **4. A proposed classification for ICD-11**

All officially recognised medical diagnoses are categorised in the International Classification of Diseases (ICD) published by WHO. In the current edition (ICD 10), cystic fibrosis is placed in the section devoted to Endocrine, Nutritional and Metabolic Diseases, Chapter 4. The classification for cystic fibrosis is subdivided into four parts:

- E84.0 CF with pulmonary manifestations,
- E84.1 CF with intestinal manifestations,
- E84.8 CF with other manifestations,

#### E84.9 CF unspecified.

It would be of benefit to patients, families, health care providers, health insurers, medico-legal interests and clinicians if this classification could be revised to take account of current knowledge and diagnostic problems, and to separately designate those related conditions which are not CF, and whose diagnosis has different implications.

WHO, ICF(M)A, ECFTN and ECFS therefore convened a joint working group in June 2000 to produce a new classification suitable for inclusion in the next edition of ICD due to be published in 2002 (ICD 11).

One possibility was to classify all conditions associated with a CFTR mutation as CFTR-Related, but this would exclude patients in whom no mutation can be found, and include others in whom the mutation is not of clinical significance and not responsible for the clinical features. There are currently more than 900 mutations and more than 300 known polymorphisms in the CFTR gene, but even so using CFTR as the essential defining criterion would not cover all cases and would be open to misinterpretation.

**As ICD is a tool for clinicians, it was agreed that the diagnostic classification should be made on clinical rather than laboratory grounds, while acknowledging the importance of identifying CFTR mutations in those persons with clinical conditions such as pancreatitis<sup>14</sup> and atresia of the vas deferens<sup>9</sup> where some, but not all cases are CFTR-related.** Some of these patients may on detailed clinical and laboratory investigation, show minor and previously unsuspected features of cystic fibrosis but in others there is no evidence of multisystem disease to justify a diagnosis of atypical CF. Other conditions in which some cases appear to be aetiologically related to CFTR mutations include allergic bronchopulmonary aspergillosis,<sup>15</sup> disseminated bronchiectasis<sup>16</sup> and diffuse panbronchiolitis.<sup>17</sup> There should be appropriate cross-referencing in ICD to the same disorders located elsewhere. Where a known mutation is judged to be aetiologically related to the disease in an individual the primary diagnostic code should be assigned from the section which includes CF.

It was also agreed to include a diagnostic category for those infants with neonatal hypertrypsinogenemia who are shown to have a single CFTR mutation, the majority of whom will be healthy carriers but a few will have an undetected second mutation. There is no consensus on the management of these cases but at present there is no code for their recording to facilitate future research.

The working group agreed that the overall heading for the section should be "Cystic Fibrosis and Related Disorders" (Table 2).

## Table 2 Cystic Fibrosis and Related Disorders

- Classical CF Pancreatic-insufficient (PI)
- Classical CF Pancreatic-sufficient (PS)
- Atypical CF
- CF other specified
- CF not otherwise specified
- Isolated obstructive azoospermia\*
- Chronic Pancreatitis\*
- Allergic bronchopulmonary aspergillosis (ABPA)\*
- Disseminated bronchiectasis\*
- Diffuse panbronchiolitis\*
- Sclerosing Cholangitis\*
- Neonatal hypertrypsinogenemia\*

\*At least one CFTR mutation identified

It is likely that this classification will need further revision in the future as our knowledge and understanding of these conditions increase.

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