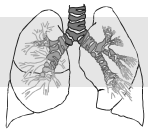

Reaching the Diagnosis of Cystic Fibrosis — the Limits of the Spectrum

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Abstract

Background: Cystic fibrosis is the most common life-limiting autosomal recessive genetic disorder in Caucasians. Typically it is a multisystem disease diagnosed by increased chloride levels on sweat testing, with mortality due mainly to progressive respiratory disease. The clinical spectrum of CF has recently been much expanded. Genetic testing for mutant CF transmembrane regulator has revealed atypical cases where sweat test results are borderline or normal. In other patients, genetic mutations cannot be identified but abnormal CFTR function is shown using nasal potential difference measurement.

Objectives: To highlight the diagnostic and therapeutic dilemmas in cases of atypical cystic fibrosis.

Methods: We reviewed patients with atypical CF and widely varying phenotype who are managed at Schneider Children's Medical Center of Israel.

Results: Two patients had severe lung disease but little expression in other organs. Accurate diagnosis was essential to enable aggressive therapy in a specialized center. Four other patients are in excellent general health but have symptoms limited to male infertility, heat exhaustion, pancreatitis or transient liver dysfunction, while lung disease is minimal. For these patients, careful counseling is needed to avoid unnecessary upheaval, inappropriately aggressive management, and the psychosocial implications of a CF diagnosis. These dilemmas have increased considerably in our center, as in others worldwide.

Conclusion: It is our obligation as clinicians — at the level of both primary physician and referral center — to maintain an ever higher index of suspicion for CF, tempered by a rational program of counseling and management appropriate to the individual.

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CF = cystic fibrosis
CFTR = CF transmembrane regulator

Cystic fibrosis is the most common life-limiting genetic disorder in Caucasians. It is an autosomal recessive disease caused by mutations of the gene for cystic fibrosis transmembrane conductance regulator that regulates transport of sodium and chloride across epithelial cell membranes [1]. Classic CF is a generalized exocrine disease of the respiratory, gastrointestinal, hepatobiliary and reproductive systems. Mortality is due mainly to progressive respiratory disease.

According to a recent consensus statement [2], the diagnosis of CF is based on at least one characteristic clinical feature as well as laboratory evidence of abnormal CFTR. The latter is usually demonstrated by repeatedly elevated sweat chloride (>60 mEq/L) using pilocarpine iontophoresis sweat tests carefully performed by an experienced technician [3]. In atypical cases with borderline or normal sweat tests, the clinical spectrum of CF has been vastly expanded by the ability to detect genetic mutations in CFTR [4,5] and by the demonstration of abnormal CFTR function using nasal potential difference measurement [2].

In the past, clinicians were confronted with diagnostic dilemmas of patients with CF-like severe lung disease but only partial phenotypic expression in other organs. Indeed, about 10% of CF patients have adequate pancreatic function and about 5% have normal function of sweat glands [6]. In these patients it is now often possible to reach an accurate diagnosis of CF, enabling appropriate therapeutic interventions in specialized centers, prognostic and genetic counseling, and access to disability aid. Where there is significant lung involvement, early implementation of aggressive treatment can markedly increase life expectancy [7].

In other atypical patients, clinical symptoms affect only one organ, such as the pancreas, vas deferens or sweat gland, and the patient is otherwise healthy [2]. In these cases a diagnosis of CF leads to major upheaval, which

Table 1. Clinical features and evaluation of patients with atypical cystic fibrosis

Origin	Case 1 Turkish-Moroccan	Case 2 Turkish-Iraqi	Case 3 Turkish-Polish	Case 4 Ashkenazi	Case 5 Ashkenazi	Case 6 Ashkenazi
Sex/age at diagnosis	M/6 wk	M/34 yr	M/9 yr	M/20 yr	M/24 yr	M/46 yr
Presentation	Respiratory failure, *Pseudomonas*	Infertility	Recurrent pancreatitis	Abnormal liver enzymes	Heat exhaustion	CF-like lung disease
Chest X-ray, CT	Large cysts resolved	Normal	Normal	Normal	Normal	Bronchiectasis
Sinus radiography		Normal	Normal	Maxillary polyps	Normal	Sinusitis
Pulmonary function tests		Mild, reversible obstruction	Normal	Mild, reversible obstruction	Mild, reversible obstruction	Severe, irreversible obstruction
Pancreatic function	Sufficient	Insufficient	Sufficient	Sufficient	Sufficient	Sufficient
Sweat tests						
Cl^- (mEq/L)	52–66	33–49	32–52	36–40	80–95	111–123
Na^+(mEq/L)	47–59	43–59	34–54	45–49	97–115	102–117
Cl^-:Na^+ ratio	>1	<1	<1	<1	<1	>1
Mutation	ΔF508/ 3849+10 Kb C-T	D1152H/ D1152H	W1282X/ 5T	W1282X/ 5T	?	W1282X/ ? D1152H
NPD	–	–	Abnormal	Normal	Abnormal	Normal

NPD = nasal potential difference

adversely affects the patient and his or her family emotionally and financially. Due to the stigma of CF as a severe life-limiting disease, the patient's self-perception is severely altered and problems frequently arise with regard to employment, marriage and insurance [8]. In Israel, exclusion of these patients from conscription to the Israel Defense Forces may not be justified. Most importantly, the time-consuming standard management of CF patients, including daily physiotherapy from the time of diagnosis and frequent courses of antibiotics, may not be necessary. When counseling these families it is difficult to predict the future course of the disease [9].

The recent and rapid increase in the diagnosis of atypical CF has made the problems outlined above a daily dilemma. The spectrum of disease in atypical patients is shown in Table 1. We describe six such patients and discuss the diagnostic and management concerns.

Patient Histories

Case 1. A 6-week-old infant of Turkish-Moroccan Jewish origin presented with increasing dyspnea and fever. He was admitted with a diagnosis of bronchiolitis but over the next week developed respiratory failure necessitating mechanical ventilation. Chest X-ray showed multiple large cysts in the left lower lobe. At bronchoscopy, secretions were extremely viscid and cultures were positive for *Pseudomonas aeruginosa* and *Stenotrophomonas maltiphilia*. Serology for parainfluenza virus type 3 rose from 1:8 to 1:128. The child was treated with amikacin and imipenem. His condition improved gradually and he was extubated after 6 days. Due to the viscid airway secretions and culture results, two sweat tests were performed, which revealed Na^+ 47 and 59 mEq/L and Cl^- 52 and 66 mEq/L. Genetic testing was positive for the two CFTR mutations ΔF508 / 3849+10 Kb C-T.

A diagnosis of CF was made and appropriate treatment instituted, which resulted in marked improvement in respiratory status. By age 3 months his respiratory rate and oxygen saturation were normal; the chest was clear on auscultation, and chest X-ray showed complete resolution of lung cysts with residual mild peribronchial thickening. A 72 hour fecal fat collection showed 95% coefficient of fat absorption, consistent with pancreatic sufficiency. At age 4 months sweat tests were repeatedly normal: Cl^- 28–36 mEq/L, Na^+ 27–31 mEq/L, but Cl^-/Na^+ ratio >1. Immunoglobulins were normal.

The child is now 4 years old and thriving. Lung disease is generally mild, but severe exacerbations due to viral respiratory infections require hospitalization. Sputum cultures for *Pseudomonas* were sterile until 2 years ago.

Had the sweat test been performed only when the child was clinically stable, he would not have been diagnosed with cystic fibrosis. CFTR function is variable in patients with the 3849+10 Kb C-T mutation [10], and viral infections might cause a transient decrease in function in both the lung and sweat gland epithelium. In view of the unusual sputum organisms and viscid secretion, a high index of suspicion was essential in order to perform a sweat test and genetic analysis and institute appropriate therapy as early as possible.

Case 2. A 34-year-old Jewish man of Turkish-Iraqi origin was evaluated for infertility and found to have congenital bilateral absence of vas deferens. On direct questioning, he complained of mild dyspnea on exertion, and productive cough for 2–3 weeks following colds. He avoided fatty foods to avoid indigestion. A diagnosis of Gilbert's disease was made based on transient elevation of liver enzymes. Physical examination was normal and he was well nourished. Chest X-ray was normal as was chest CT. Sputum

was sterile. Pulmonary function tests revealed mild reversible obstruction of small airways, but cardiopulmonary exercise test was within normal limits. Sweat test results were borderline: Cl^- 33–49 mEq/L and Na^+ 43–62 mEq/L. Fecal elastase was low: 166 μg/dl, consistent with pancreatic insufficiency. Genetic evaluation for CFTR mutations showed him to be homozygous for D1152H.

The vas deferens is the tissue most dependent on normal CFTR function and thus the first to be affected by mutations. Hence 99% of males with classic CF suffer from infertility due to CBAVD. Conversely, patients with the mildest mutations, e.g., 5T at intron 8, may have CBAVD alone or very mild disease in other organs [11]. All males with CBAVD, even if an isolated problem, require evaluation at a CF center.

In this case, homozygosity for D1152H enabled a definitive diagnosis of CF as well as genetic counseling. Further evaluation revealed slightly abnormal lung function, pancreatic insufficiency and borderline sweat tests. In addition, CF liver disease may result in recurrent transient elevation of liver enzymes.

As our patient had previously regarded himself as 'healthy', we emphasized that his outlook was excellent. However, since the life-long prognosis of lung disease in atypical CF is unknown, he was advised to present with any respiratory infections or cough and he was trained in chest physiotherapy for these episodes. Low dose pancreatic enzymes and fat-soluble vitamin supplements were recommended. As a treatment for infertility, he will attempt assisted reproduction using sperm aspiration and in vitro fertilization with intracytoplasmic sperm injection [12].

Case 3: A 9-year-old Jewish boy of Turkish-Polish origin was evaluated for recurrent acute pancreatitis over the past 3 years. The child had no history of sinopulmonary disease. Physical examination was normal other than abdominal tenderness during the attacks and an impalpable epididymis. Chest X-ray and pulmonary function tests were normal. Sweat tests were borderline: Cl^- 32–52 mEq/L, Na^+ 34–54 mEq/L. Fecal elastase and 72 hour fecal fat collection were normal. Genetic testing revealed two CFTR mutations: W1282X and 5T. Since the 5T allele has partial penetrance, nasal potential difference was assessed. This was consistent with a diagnosis of CF. He began to take low dose pancreatic enzyme supplements to preserve residual pancreatic function and reduce retrograde secretion of enzymes with resultant pancreatitis. As in the previous case, recommendations were made for continued follow-up of pulmonary status and aggressive management of respiratory infections.

Recurrent pancreatitis in CF patients with pancreatic sufficiency [13] may be the only expression of CFTR disease, particularly with the 5T mutation.

Case 4. A 20-year-old Ashkenazi man presented with repeated transiently abnormal liver function tests. A diagnosis of Gilbert's disease had been made in the past. He reported occasional productive cough in the morning. Physical examination was normal. Sweat test results were borderline-normal: Cl^- 36–40 mEq/L and Na^+ 45–49 mEq/L. Pulmonary function tests showed mild reversible airways obstruction. Chest X-ray and CT were normal, but sinus tomography showed mucosal polypoidal hypertrophy. Nutritional state and pancreatic function were normal. Genetic analysis revealed W1282X/5T. However, nasal potential difference was normal.

This patient may be at the extreme of the clinical spectrum of CF. The mild, transient abnormalities in liver function led to his diagnosis and may be due to CF. He had very mild sweat gland, airway and sinus involvement. He is unwilling to undergo fertility investigation at present. Surprisingly, nasal potential difference was within the normal range despite two genetic mutations. Mutations such as 5T, with partial penetrance, may not always result in clinical disease [13]. At present, follow-up alone has been recommended.

A different clinical presentation in this case and the preceding one, despite identical mutations, is intriguing. The role of modifier genes and environmental influences in determining CF phenotype has gained increasing interest over recent years [14].

Case 5: A 24-year-old man of Ashkenazi origin and the father of two presented with recurrent heat exhaustion. All investigations were normal other than repeatedly positive sweat tests of Cl^- 80–95 mEq/L and Na^+ 97–115 mEq/L. He described prolonged episodes of productive cough following upper respiratory infections and occasional episodes of shortness of breath. There was a family history of asthma but he did not suffer from allergies. Examination was normal and he was well nourished. Chest X-ray was normal but high resolution chest CT revealed bilateral marked peribronchial thickening. Sinus X-ray was normal. Pulmonary function tests showed mild reversible obstruction. Pancreatic function was normal as assessed by a fecal elastase level of 701 μg/g stool. Challenge tests excluded hypoaldosteronism. He did not wish to undergo fertility tests since his wife had not had trouble conceiving. Although of Ashkenazi origin, where genetic testing has a diagnostic sensitivity of 97% [1], no mutations for CF were found. Nasal potential difference measurements showed low basal level and no response to isoproterenol on two separate studies, excluding pseudohypoaldosteronism and suggesting atypical CF.

This case demonstrates phenotypic expression affecting mainly the sweat gland in an otherwise healthy young man.

Case 6: This 46-year-old man of Ashkenazi origin, also a father of two, presented with chronic severe irreversible obstructive lung disease and bronchiectasis. A right upper lobectomy performed when he was 19 years old showed the lobe to be filled with viscid green secretions and abscess-like bronchiectasis. He was a non-smoker. Follow-

CBAVD = congenital bilateral absence of vas deferens

Table 2. Clinical features and diagnosis of genetic mutations in atypical CF

Clinical features	+ CF mutation	- CF mutation
+	CF	CF?
–	CF?	Normal

Table 3. Nasal potential difference and genetic mutations in clinically atypical CF

NPD	+ CF mutation	- CF Mutation
Normal	CF?	Normal?
Abnormal	CF	CF?

ing positive sputum cultures for *Pseudomonas aeruginosa*, he underwent repeated sweat testing that revealed Cl^- 111–123 mEq/L and Na^+ 102–117 mEq/L. On examination he was obese, had nasal obstruction and markedly decreased breath sounds bilaterally. Spirometry showed severe irreversible airways obstruction with forced expiratory volume in 1 second of 39% predicted. Genetic analysis revealed W1282X/D1152H. Nasal potential difference measurements were within the normal range on a single examination. To date he has not agreed to repeat the test.

This patient is an example of severe CF lung disease and abnormal sweat test, but with pancreatic sufficiency. CFTR function, as measured by nasal potential difference, was normal. He is apparently fertile and does not wish his children to undergo genetic analysis at present. Thus, expression of CFTR appears to vary greatly in different organs. We have recommended aggressive management for severe CF lung disease, which in this case determines his prognosis.

Discussion

The broader spectrum of disease in cystic fibrosis is becoming evident worldwide [8]. An atypical CF phenotype often consists of CF-like severe lung disease with preserved pancreatic function and a borderline or normal sweat chloride concentration [5,10]. In some patients there is a single clinical feature, such as recurrent pancreatitis, liver disease, sinusitis, and nasal polyps or obstructive azoospermia [2]. In these patients it is important to carry out a comprehensive clinical, radiographic and laboratory evaluation, which may well reveal additional features associated with CF. As the lifetime pulmonary prognosis is unknown, continued surveillance is essential even in cases where lung examination and tests are normal.

In an attempt to define CF in an era of "medical guidelines" and limited insurance policies, reviews of current opinions were recently compiled [2,15]. In patients with at least one clinical feature of CF but borderline or normal sweat tests, it was agreed that laboratory criteria for the diagnosis of CF should be expanded to include genetic identification of two CFTR mutations [Table 2]. Unfortunately, despite over 700 CFTR mutations described to date, genetic probes used clinically have varying sensitivity in different ethnic groups. This is highlighted in Israel where sensitivity varies from 97% in Ashkenazi Jews to 60% in Israeli Arabs [16,17]. In those cases where CF mutations are not identified, or are associated with an unusual clinical picture, abnormal nasal potential difference typical of decreased CFTR function could establish the diagnosis [Table 3]. However, as demonstrated by our cases, there remains a gray zone where available diagnostic tools are inconclusive. It is clear that definitions will change rapidly, as research and understanding of genotype-phenotype correlation, CFTR function and its measurement in various organs, and the effects of modifier genes [14] are unraveled. Meanwhile, it is our obligation as clinicians, at both the level of primary physician and referral center, to maintain an ever higher index of suspicion for CF, tempered by a rational counseling and management program appropriate for the level of clinical disease in each individual patient.

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Only those who dare to fail greatly can ever achieve greatly.

Robert F. Kennedy

Capsule

Medical magicians: making one disease into many

A recent article by S. Wessely et al. discusses the myriad of functional somatic syndromes. Each is described by specialists according to their specialty; for example, gastroenterologists diagnose irritable bowel syndrome, while rheumatologists diagnose fibromyalgia. Other syndromes, such as multiple chemical sensitivity, are controversial. In this study the authors attempted to test if indeed there are many individual somatic syndromes or if there are fewer (or even one general syndrome). They examined four hypotheses:

- That case definitions (criteria) of the syndromes overlap
- That patients may frequently fit the diagnostic criteria for multiple somatic syndromes
- That patients with different functional syndromes share nonsymptomatic characteristics
- That all functional syndromes respond to the same therapies.

The authors found that:

There is frequent overlap of diagnostic criteria between the "different" functional syndromes. For example, abdominal pain is a symptom of six somatic syndromes.

A review of clinical research confirms that patients frequently fit the diagnostic criteria for "multiple" functional syndromes. For example, patients with chronic fatigue syndrome frequently have symptoms fitting fibromyalgia, tension headache, food allergy, PMS, and irritable bowel syndrome.

Most people with somatic disorders are females with emotional psychological/emotional distress, a history of childhood abuse, and interpersonal relationship difficulties (including the doctor-patient relationship). Many syndromes share a common physiological mechanism and CNS dysfunction. There are many common treatment modalities shared by the "different" syndromes including antidepressant treatment, psychological therapy and other drug courses.

Based on the similarities between the various functional somatic syndromes the authors conclude that the current system of multiple classifications is flawed. They propose reclassifying the syndromes into groups based on different criteria, such as symptoms (case definitions), epidemiology, psychiatric classification, and a multi-axial approach including all three.

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