From the Children’s Institute, Hospital das Clínicas, Faculty of Medicine, University of São Paulo – São Paulo/SP, Brazil; Genetika Laboratory – Paraná, Brazil and Federal University of Medicine, São Paulo/SP, Brazil. 

Received for publication on August 30, 2002.

Luiz Vicente Ferreira da Silva Filho, Maria Helena de Carvalho Ferreira Bussamra, Cleyde Miriam Aversa Nakaie, Fabiola Villac Adde, Joaquim Carlos Rodrigues, Salmo Raskin and Tatiana Rozov


Cystic fibrosis is a genetic disease usually diagnosed by abnormal sweat testing. We report a case of an 18-year-old female with bronchiectasis, chronic P. aeruginosa infection, and normal sweat chloride concentrations who experienced rapid decrease of lung function and clinical deterioration despite treatment. Given the high suspicion of cystic fibrosis, broad genotyping testing was performed, showing a compound heterozygous with ∆F508 and 3849+10kb C→T mutations, therefore confirming cystic fibrosis diagnosis. Although the sweat chloride test remains the gold standard for the diagnosis of cystic fibrosis, alternative diagnostic tests such as genotyping and electrophysiologic measurements must be performed if there is suspicion of cystic fibrosis, despite normal or borderline sweat chloride levels.


In Brazil, CF is an underdiagnosed condition that is primarily treated at specialized centers, usually university hospitals. The Pediatric Pulmonology Unit of the Children’s Institute is a general pediatric pulmonology clinic that treats approximately 120 CF patients. Cystic fibrosis is routinely diagnosed by clinical symptoms and sweat testing; genotyping was not routinely performed before 1998 except for selected or atypical cases. We report a case of a female with symptoms suggesting CF but with normal sweat chloride levels who underwent genotype testing that confirmed the CF diagnosis.

CASE REPORT

An 18-year-old female was referred to our service in 1997 with a previous history of atopic symptoms, such as al-
Cystic fibrosis with normal sweat chloride concentration
Silva Filho LVF et al.

Allergic rhinitis and angioneurotic edema, as well as nasal polypectomy at age 9. There was no history of pneumonia, although she presented several upper airway infections, treated with antibiotics, expectorants, and antihistamines. Her brother was healthy, and no relative had experienced similar symptoms. She was well until age 16, when adynamia, chronic cough, and dyspnea during exercise ensued. Her pulmonary symptoms worsened, and the cough became productive. During this period, salivary gland lithiasis was diagnosed, with spontaneous resolution. The patient was referred for evaluation showing mild malnutrition without clinical steatorrhea, finger clubbing, and diffuse inspiratory crackles at pulmonary auscultation. A chest X-ray revealed hyperinflation and bronchiectasis, confirmed by chest CT scan. Sweat chloride measurements by pilocarpine iontophoresis ranged from 23 to 47.5 mEq/liter (5 samples). A sputum culture was positive for *Staphylococcus aureus*. Pulmonary function testing revealed an obstructive disorder, with a forced vital capacity (FVC) of 2.28 L (68%) and a forced expiratory volume in the first second (FEV₁) of 1.71 L (52%). Genotyping identified a ∆F508 mutation in 1 allele. Pancreatic function was assessed by a 72-hour fecal fat study and was found to be preserved.

The patient developed chronic *S. aureus* and intermittent *Pseudomonas aeruginosa* pulmonary infection. Acute pulmonary exacerbations were treated with oral or intravenous antibiotic therapy. Despite aggressive treatment, pulmonary function testing revealed a massive decrease in FVC and FEV₁ (0.82 L (25%) and 1.30 L (32%), respectively) after 2 years. A new chest CT scan was performed and showed widespread bronchiectasis and large cysts, mainly in the upper lobes (Fig. 1). Since the clinical presentation suggested CF, in spite of repeatedly normal sweat chloride values, a new broader genetic testing including infrequent mutations was performed. The new genotyping showed that the patient was a compound heterozygous, with ∆F508 and 3849+10kb C→T mutations, which confirmed the diagnosis of CF. The basic treatment of CF was maintained with nutritional support, frequent courses of systemic antibiotics, and continuous inhaled gentamycin; however, lung function decline persisted, and the patient is now waiting for a lung transplantation.

**DISCUSSION**

The concept of “mild” and “severe” mutations was proposed by Kerem et al. as an explanation for the clinical heterogeneity of CF. However, because of the high clinical variability and the large number of identified mutations, it is very difficult to characterize genotype-phenotype correlations in CF, except for the most common mutations. The ∆F508 mutation is usually associated with a more severe clinical presentation and higher sweat chloride levels, while a few other mutations are associated with a mild phenotype. Patients carrying at least 1 mild mutation may present symptoms with later onset, better nutritional status, pancreatic sufficiency, and lower sweat chloride levels.

Highsmith et al., studying 23 patients with pulmonary disease characteristic of CF but with normal sweat testing, identified a point mutation in intron 19 of the CFTR gene, termed 3849+10kb C→T. Published data show mild phenotypic characteristics among CF patients who are homozygous for this mutation. The onset of pulmonary disease was delayed in most of them, but then became severe in some, as was the case for our patient. Male patients can have normal sperm count, sweat Cl⁻ values are usually in the intermediate or normal range, and sufficient exocrine pancreatic function is reported. The Cystic Fibrosis Genetic Analysis Consortium reports the relative frequency of the 3849+10kb C→T mutation to be 1.4%.

A classification system according to the functional properties of the gene product was proposed by Welsh and Smith. Class V mutations result in reduced synthesis of normally functioning CFTR because of defective processing or alternative splicing sites, resulting in decrease of normal messenger ribonucleic acid (mRNA) transcripts. The 3849+10kb C→T mutation produces an alternative splicing site, and decreased amounts of CFTR.
mRNA can be detected\(^4\). Minor disease manifestations are probably associated with some production of normally functional protein. Patients with the \(3849+10kb\) \(C\rightarrow T\) mutation appear to have less significant pulmonary disease than patients homozygous for \(\Delta F508\), although lung disease is the most severe clinical manifestation reported\(^1\)\(^-\)\(^4\). In compound heterozygous patients, the presence of the \(\Delta F508\) allele does not necessarily confer a more severe prognosis\(^1\)\(^-\)\(^4\).

Although in most patients with CF all major diagnostic criteria are present, variation in severity of involvement of the different organs is well known. Chronic pulmonary disease, even in the absence of pancreatic insufficiency and abnormal sweat electrolyte values, can suggest CF if other clinical manifestations like nasal polyposis, azoospermia, or mucoid \(P. aeruginosa\) colonization is present. For more than 30 years, the sweat chloride test has been used to confirm the diagnosis of CF and remains the gold standard\(^8\). However, once there is a clinical suspicion of CF but normal or borderline sweat chloride levels, alternative diagnostic tests such as genotyping and electrophysiologic measurements must be performed to confirm diagnosis.

**REFERENCES**


**RESUMO**


A fibrose cística é uma doença genética usualmente diagnosticada através de teste anormal de dosagem de cloro no suor. Os autores descrevem o caso de uma paciente de 18 anos com bronquiteciasas e infecção crônica por *P. aeruginosa* mas com dosagens de cloro no suor normais que evoluiu com rápido declínio da função pulmonar e piora clínica, a despeito do tratamento. Dada a forte suspeita de fibrose cística, realizou-se um teste de genotipagem amplo, evidenciando a presença de mutações \(\Delta F508\) e \(3849+10kb\) \(C\rightarrow T\), deste modo confirmando o diagnóstico de fibrose cística. Apesar da dosagem de cloro no suor ainda ser considerada o padrão ouro para o diagnóstico de fibrose cística, testes diagnósticos alternativos como genotipagem e medidas eletrofisiológicas devem ser empregados se há suspeita de fibrose cística, mesmo com níveis normais ou limitrosos de níveis de cloro no suor.