CASE REPORT

CYSTIC FIBROSIS WITH NORMAL SWEAT CHLORIDE CONCENTRATION – CASE REPORT

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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 ofcystic fibrosis, broad genotyping testing was performed, showing a compound heterozygous with ΔF508 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.

DESCRIPTORS: **Cystic fibrosis. Atypical. Diagnosis. Sweat chloride. Mutations.**

Cystic fibrosis (CF) is the most common lethal genetic disease in Caucasians and is characterized by chronic and recurrent lung infections, pancreatic insufficiency, and high chloride levels in the sweat. Inheritance is autosomal recessive, and the disease is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, located in the long arm of chromosome 7. As for many other human monogenic diseases, high variability in disease expression is found among patients. The sweat test has been the diagnostic "gold standard" for CF since its description in the late 1950s, but now it is clear that a few patients (1% to 2%) may have normal or borderline sweat chloride concentrations, a condition associated with some specific mutations. Such patients have mild CF variants that include atypical clinical manifestations; therefore, it is recommended that they should be referred for CFTR genotyping[1,2]. Although nowadays this is common knowledge among CF caregivers, there are few publications of case reports of CF with normal sweat chloride levels, and general pediatricians are usually not aware of this possibility. Searching PubMed using the following keywords: [cystic fibrosis] and [normal] and [sweat chloride] and [case report] we found 21 entries. Of these entries, 8 were case reports that share some similarity to ours, but 2 cases were not confirmed by genetic testing.

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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-

lergic 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 (FEV_1) of 1.71 L (52%). Genotyping identified a ΔF508 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 ΔF508 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.

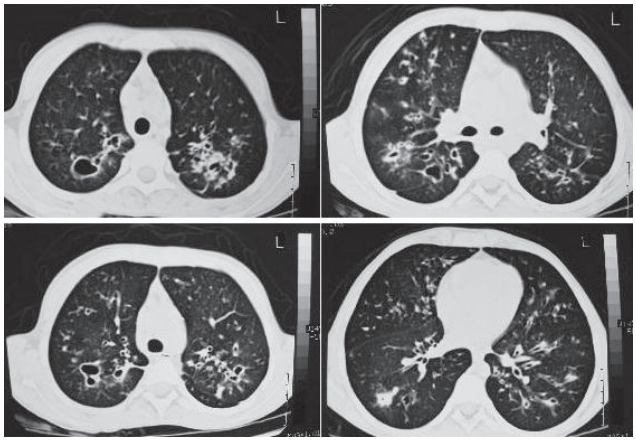

Figure 1 - High resolution computer tomography scans showing diffuse bronchiectasis and large cysts in upper lobes.

DISCUSSION

The concept of "mild" and "severe" mutations was proposed by Kerem et al.[3] 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 ΔF508 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 [2].

Highsmith et al.[4], 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[1,5]. The Cystic Fibrosis Genetic Analysis Consortium reports the relative frequency of the 3849+10kb C→T mutation to be 1.4%[1].

A classification system according to the functional properties of the gene product was proposed by Welsh and Smith[6]. 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[7]. 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→T mutation appear to have less significant pulmonary disease than patients homozygous for ΔF508, although lung disease is the most severe clinical manifestation reported[1,4]. In compound heterozygous patients, the presence of the ΔF508 allele does not necessarily confer a more severe prognosis[3].

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.

RESUMO

SILVA FILHO LVF e col. - Fibrose cística com dosagem de cloro no suor normal – relato de caso. **Rev. Hosp. Clín. Fac. Med. S. Paulo 58** (5):260-262, 2003.

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 bronquiectasias 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 ΔF508 e 3849+10kb C→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 limítrofes de níveis de cloro no suor.

DESCRITORES: **Fibrose cística. Atípica. Diagnóstico. Cloro no suor. Mutações.**

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