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When to suspect atypical cystic fibrosis

Not all patients with cystic fibrosis have abnormal sweat chloride levels, severe lung disease, or failure to thrive. These 2 cases remind us to think "outside the box."

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PRACTICE RECOMMENDATIONS

› *Don't dismiss a cystic fibrosis diagnosis just because a patient's sweat chloride levels are <60 mmol/L.* (A)

› *Suspect atypical cystic fibrosis in adults with single organ involvement, including mild lung disease, nasal polyposis, recurrent pancreatitis, biliary cirrhosis, portal hypertension, or obstructive azoospermia.* (A)

› *Consider respiratory therapies such as tobramycin, hypertonic saline, and recombinant human DNase in cystic fibrosis patients with relatively mild or atypical disease.* (A)

Strength of recommendation (SOR)

- (A) Good-quality patient-oriented evidence
- (B) Inconsistent or limited-quality patient-oriented evidence
- (C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE 1 ▸ Lauren W*

Two years ago, Lauren W, a 57-year-old Caucasian woman, sought care at our medical center after learning that her pregnant daughter tested positive during a prenatal cystic fibrosis mutation genetic screen. Lauren had clinical symptoms of malodorous and greasy bowel movements, dyspepsia, early satiety, and a history of recurrent bronchitis since childhood.

According to her history, she did not suffer from failure to thrive as a child. She'd had 5 episodes of adult-onset acute pancreatitis and had 2 surgeries for sinusitis.

On physical exam, we heard no crackles during lung auscultation. Lauren also had mild digital clubbing.

Testing: We ordered a chest x-ray, which revealed left upper lobe atelectasis, but there was no bronchiectasis.

Pulmonary function tests indicated mild obstructive lung disease with forced vital capacity (FVC) 2.39 L or 84% predicted; forced expiratory volume in 1 second (FEV_1) 1.59 L or 68% predicted; and an FEV_1/FVC of 0.66.

A sweat chloride test was positive on both arms: 77 and 83 mmol/L. Genetic testing revealed compound heterozygosity for cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations Δ F508 and R117H with a 5T allele. To test for pancreatic insufficiency, we performed a 72-hour fecal fat testing while she was on a low-fat diet; it revealed 5.5 g of fat per 24-hour period, suggesting fat malabsorption. Based on positive quantitative sweat test ≥60 mmol/L and the presence of 2 cystic fibrosis–causing mutations, we made the diagnosis of cystic fibrosis.

Treatment: We put Lauren on albuterol and recombinant human DNase respiratory treatments, pancreatic enzymes, and multivitamins with extra lipid-soluble vitamins and calcium supplements. We also continued her low-fat diet of 1500 to 1800 calories per day due to a diagnosis of coronary artery disease.

**Patients' names have been changed to protect their privacy.*

CONTINUED

Some patients with atypical cystic fibrosis seek care for idiopathic chronic pancreatitis.

CASE 2 ▸ Zack P*

Zack P, a 6-year-old Caucasian boy, was admitted to the hospital with what we suspected was acute gastroenteritis. Serum testing revealed elevated pancreatic enzymes. He had recently sustained an injury to the mid-abdomen during a soccer game and also had a history of chronic sinusitis. One month after his release from the hospital, his symptoms resolved, but his pancreatic enzymes remained elevated (amylase 130 U/L, lipase 177 U/L).

Testing: He underwent 2 sweat chloride tests, which were borderline elevated at 49 mmol/L on the right arm and 40 mmol/L on the left arm; repeat testing was 49 mmol/L on the left arm, 43 mmol/L on the right arm. Genetic testing revealed heterozygosity for CFTR gene mutation Δ F508 with the presence of 7T and 9T allele variants. Over an 8-month period, Zack remained asymptomatic, but his pancreatic enzymes were persistently elevated.

Zack's physical exam showed that his weight had dropped from the 75th to the 50th percentile. A magnetic resonance cholangiopancreatography indicated homogeneous parenchyma and normal enhancement throughout his pancreas. Similarly, we could not find evidence of acute pancreatitis or biliary or pancreatic duct dilation, and a 72-hour fecal fat study was normal. Given Zack's borderline sweat chloride, compound heterozygosity of cystic fibrosis mutations, and his phenotype of recurrent pancreatitis, he was given a diagnosis of atypical cystic fibrosis.

Treatment: Based on our diagnostic workup, pancreatic enzyme therapy was not warranted.

These 2 cases illustrate how clinically diverse cystic fibrosis can be. The cystic fibrosis phenotype can range from a patient with 2 disease-causing cystic fibrosis mutations with significant sweat gland dysfunction and childhood onset of mild cystic fibrosis symptomatology with normal growth—Lauren—to a patient who is CFTR heterozygous with pancreatitis and a borderline sweat chloride concentration—Zack. Both cases emphasize the need to think "outside the box" and not expect all patients with cystic fibrosis to come in with typical signs and symptoms.

**Patients' names have been changed to protect their privacy.*

What does the "nonclassic" cystic fibrosis patient look like?

Patients with cystic fibrosis are usually diagnosed during childhood with pulmonary disease, pancreatic insufficiency, malabsorption, malnutrition, elevated sweat chloride, and male infertility. But more recently, patients have been diagnosed in adulthood because either they lacked significant clinical symptoms in childhood or they came in with atypical signs or symptoms (pancreatic sufficiency and sweat chloride <60 mmol/L).

In the past, cystic fibrosis patients rarely lived past their second decade, but those with atypical cystic fibrosis tend to have milder disease, including less severe respiratory signs and symptoms. The good news is that often translates into a long lifespan.[1] As recently as 2005, the Cystic Fibrosis Foundation had listed a median survival age of 37.[2] Advances in respiratory, gastrointestinal, and nutritional therapies have significantly contributed to the increased survival of these patients. Unfortunately, such milder cases can easily go undetected.

Sweat chloride testing remains a gold standard for the diagnosis of cystic fibrosis. As previously mentioned, classic cystic fibrosis patients are typically diagnosed during childhood and have a sweat chloride concentration ≥60 mmol/L and more severe multiorgan involvement (sinopulmonary and gastrointestinal disease with failure to thrive).

There are 5 classes of CFTR mutations that result in compromised CFTR function: The presence of 2 severe CFTR mutations (classes I-III) completely abolishes CFTR function. It is diagnosed in childhood and usually results in the classic clinical features of pancreatic insufficiency and failure to thrive. However, patients who are compound heterozygous for the milder CFTR mutations (classes IV and V) experience partial CFTR function, which in turn results in atypical features such as pancreatic sufficiency and normal or borderline sweat chloride concentrations. That makes the diagnosis more elusive during early childhood.[1,3]

The severity of sweat gland and exocrine pancreatic dysfunction produced by a cystic fibrosis mutation depends on the class of CFTR gene mutation and the level of CFTR gene and protein expression.[4,5] In certain genetic back-

grounds, the 5T allele associated with a high number of TG (thymine/guanine) repeats found in compound heterozygosity with a disease-causing CFTR mutation acts as a "mild CFTR mutation," resulting in the nonclassic cystic fibrosis phenotype.[3] Individuals with atypical cystic fibrosis diagnosed later in life may have single organ involvement, such as mild lung disease, nasal polyposis, recurrent pancreatitis, biliary cirrhosis, portal hypertension, or obstructive azoospermia.[1]

Lauren had several classic cystic fibrosis features, including recurrent lung disease, pancreatic insufficiency, and sweat gland dysfunction, but it's likely that her relatively mild pulmonary presentation, normal body mass index, and lack of failure to thrive led to a delay in her diagnosis.

Some patients with atypical cystic fibrosis seek care for idiopathic chronic pancreatitis (ICP), and researchers have found a link between ICP and CFTR gene mutations. For instance, recent studies of ICP patients compared with geographically and ethnically matched controls revealed a higher frequency of abnormal CFTR alleles in the ICP population.[6,7] Milder CFTR mutations resulting in partial CFTR function have also been associated with ICP.[7,8]

Zack was heterozygous for Δ F508, a common CFTR mutation in the Caucasian population. Cohn et al found a higher frequency of this mutation in ICP patients from Europe (mostly English, Italian, and Czech).[9] Poly T allele variants such as 5T, 7T, and 9T have not been associated with a higher frequency of ICP.[6,7]

Although patients diagnosed with cystic fibrosis as adults are less likely to have classic clinical features, they may develop bronchiectasis and advanced lung disease.

Early detection may translate into better treatment

Although patients diagnosed with cystic fibrosis as adults are less likely to present with classic clinical features, they may develop bronchiectasis and advanced lung disease.[10,11] Those who are identified early on—including those who are asymptomatic and have normal lung function—may benefit from respiratory therapy to prevent or delay lung disease.[12] Several studies have shown that patients with mild cystic fibrosis disease and stable spirometry results have evidence of bronchiectasis on their x-rays and advanced lung disease that appears on high-resolution CT.[13,14]

Judge et al have suggested that mucus plugging occurs early in cystic fibrosis lung disease and at a milder stage of lung function impairment, and that bronchiectasis may be an end result of such abnormalities.[14] Nonclassic cystic fibrosis patients often have episodes of "bronchitis," and once the practitioner becomes concerned, the radiographic image may already show evidence of bronchiectasis. Once again, this emphasizes the importance of early detection and prompt treatment.[15]

CASE 1 ▸ Lauren

Unfortunately, Lauren was unable to benefit from early use of respiratory therapies like tobramycin, hypertonic saline, and recombinant human DNase. She began these treatments after developing advanced lung disease. Studies have shown that tobramycin, long-term inhaled hypertonic saline, and recombinant human DNase can reduce the number of pulmonary exacerbations and increase both FVC and FEV_1 values in previously stable cystic fibrosis patients.[16-18]

Similarly, because Lauren's pancreatitis was due to pancreatic insufficiency, early recognition of pancreatic insufficiency and enzyme therapy may have greatly reduced the number and severity of her pancreatic episodes.[19]

Unfortunately, over the last few years, Lauren's lung function has declined and she has been hospitalized for cystic fibrosis exacerbations and sinusitis; she has had 3 additional episodes of acute pancreatitis. Although her FEV_1 is lower than on initial evaluation, she is clinically stable.

CASE 2 ▸ Zack

Clinically, Zack is stable and his recent amylase and lipase are elevated at 92 U/L and 71 U/L, respectively. He has had no acute exacerbations.

Patients like Lauren and Zack serve to remind us of the need to recognize and closely monitor patients with nonclassic cystic fibrosis. These patients may come to the office with "asthma-like" symptoms, bronchitis, polyps, pancreatitis, cholelithiasis, constipation, abdominal bloating/flatus, and infertility. Because their symptoms may not be severe enough to be referred to a subspecialist, family physicians play a critical role in recognizing these overlooked cases early on. **JFP**

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