Cystic Fibrosis:
Catching up on the Fundamentals

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There are approximately 3,500 individuals with cystic fibrosis (CF) in Canada. It is one of the most common fatal genetic disorders, but its wide spectrum of presentation can make the diagnosis challenging at times. CF is classically recognized as a chronic pulmonary disease, associated with pancreatic insufficiency and an elevated sweat chloride concentration, occurring primarily in the Caucasian population; however, there are many other modes of presentation and virtually all ethnic groups can be affected.

Who is at risk?

CF is an autosomal recessive disease that occurs in 1:2,500 live Caucasian births. It has a carrier rate of 1:25 in the Caucasian population, with a significantly lower carrier rate in other ethnic groups. This results in a disease incidence of:

- 1:2,500 in Caucasians
- 1:17,000 in African Americans
- 1:90,000 in Asians

As an autosomal recessive disease, if both parents have one abnormal copy of the CF gene (*i.e.,* are carriers), there is a 25% chance their child will have CF and a 50% chance the child will be a carrier. Siblings of an affected child have a 25% chance of having the disease.

Jane's case

- Jane, 3, presents with a persistent cough and frequent stools.
- She has been on inhaled albuterol as required, and fluticasone twice daily by puffer with an aerochamber for her cough, having minimal improvement.
- Jane has four bowel movements per day.
- On examination, her height is at the 10th percentile and her weight is at the third percentile.
- She is noted to have a productive cough.
- Auscultation reveals good air entry with a few scattered crackles and no wheezes are heard.
- Her abdomen is slightly protuberant, but it is soft and benign.
- There is no hepatosplenomegaly.

What is the mechanism?

CF is caused by a defect in a single gene on chromosome 7 that results in an abnormal chloride channel conductance at the apical membrane of many cells. This results in an abnormal movement of sodium and chloride and, hence, water across cells, specifically resulting in abnormal exocrine gland secretions, causing plugging and dysfunction of many organs.

There have been more than 1,400 different mutations described in the CF gene. The most common is still ΔF508, which is present in about 70% of CF alleles in North America.

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When should you suspect CF?

Common modes of presentation include:

- Chronic respiratory complaints
  - recurrent or persistent pneumonia
  - recurrent or persistent wheezing, inadequately responding to inhalers
  - hemoptysis
  - bronchiectasis
- Meconium ileus
- Failure to thrive
- Prolonged jaundice as neonate
- Pancreatitis (in pancreatic-sufficient patients)
- Rectal prolapse
- Unexplained clubbing
- Nasal polyps
- Hyponatremic hypochloremic dehydration for infants, especially in hot weather
- Infertility in males

How is the diagnosis made?

CF is suspected on clinical manifestations or based on a positive family history. The diagnosis can be made by a sweat chloride test. The sweat test is very reliable if performed by an experienced technician in a centre that performs a sufficient number of tests on a regular basis. It is generally performed by pilocarpine iontophoresis. It can be done at any age, as long as an adequate amount of sweat is obtained.

A chloride concentration > 60 mmol/L in the presence of appropriate clinical manifestations or a positive family history indicates the diagnosis of CF. Sweat chloride results of 30 mmol/L to 60 mmol/L, with a high clinical suspicion of CF, should be evaluated further, as a small percentage of patients have sweat chloride results in this range.

Genotyping may also be performed. If two alleles known to cause CF are identified, the diagnosis of CF is confirmed. However, conventional genotyping in Canada generally assesses about 31 of the most common mutations. As stated earlier, there have been over 1,400 mutations documented. Therefore, a patient in which two alleles are not found by genotyping can still have CF.

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How is CF treated?

Unfortunately, there is no cure for CF to date. However, there are several treatment strategies available. Once the diagnosis is made or suspected, the patient should be referred to a CF clinic for full evaluation and CF care.

There are three main goals of treatment:

1) Maintain lung function
   - Regular chest physiotherapy
   - Chronic lung infections should be treated with inhaled or oral antibiotics
   - Acute pulmonary exacerbations should be treated with oral or intravenous antibiotics

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   - Regular evaluation of lung function (pulmonary function testing)
   - Regular evaluation of sputum culture and sensitivity

2) Maintain normal growth/nutrition
   - Encourage high-fat/high-energy diet
   - Replace pancreatic enzymes and fat-soluble vitamins (pancreatic-insufficient patients)
   - Consider supplemental feeds/nocturnal g-tube feeds, if necessary

3) Educate patient and family about CF

More on Jane

- Considering Jane's history of cough, frequent stools and lower growth percentiles, you decide to arrange a chest X-ray (CXR) and sweat chloride testing.
- The CXR reveals hyperinflated lungs with peribronchial thickening and mucous plugging.
- The sweat chloride is 68 mmol/L with an adequate sample of > 100 mg of sweat.
- You explain to her parents that Jane likely has cystic fibrosis (CF) and you refer them to the closest CF clinic.
- At the CF centre her family learns about CF. Jane's evaluation includes: repeat sweat chloride, evaluation of pancreatic status, throat swab/sputum culture, genetic testing, as well as a complete history and physical examination. She is reviewd by the CF multi-disciplinary team.
- Once started on treatment, her cough resolves, she only has two bowel movements per day and her weight increases significantly.

Prognosis

The median survival age for patients with CF in Canada is 38 years and has increased gradually each year. As the majority of patients with CF now live into adulthood, it introduces the issues of planning for a future, education, occupation and family.

What is the role of the family physician?

The family physician is key in having a high index of suspicion for the diagnosis of CF. The physician needs to realize that a patient cannot be too healthy to have CF. Early diagnosis enables patients to receive the appropriate treatment that will hopefully improve their symptoms and outcome. To optimize care, the family physician should work in collaboration with a regional CF clinic that is able to provide the specialized care that a patient with CF requires. Dx