

Atypical cystic fibrosis

Identification in the primary care setting

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Abstract

Objective To review the diagnosis of patients with atypical cystic fibrosis (CF).

Sources of information A comprehensive search of MEDLINE (1950 to the third week of May 2009), MEDLINE In-Process and Other Non-Indexed Citations and Cases (1950 to the third week of May 2009), and EMBASE (1980 to the fourth week of March 2009). The Cystic Fibrosis Canada website was also reviewed and the most recent patient data registry report was consulted.

Main message Atypical CF is a milder form of the CF disorder, which is associated with mutations of the cystic fibrosis transmembrane receptor gene. Instead of having classic symptoms, individuals with atypical CF might only have mild dysfunction in 1 organ system and might or might not have elevated sweat chloride levels. Atypical CF is a very diverse disorder affecting different organ systems to varying degrees. The symptoms patients experience can also fluctuate over time; however, certain clinical signs and symptoms affecting the respiratory, gastrointestinal, endocrine and metabolic, and genitourinary systems should alert physicians to the possibility of CF. Patients with atypical CF often have fewer hospitalizations during childhood than those with classic CF do, and the disorder can remain undiagnosed for many years, at times into adulthood.

Conclusion Although patients diagnosed with atypical CF have longer life expectancies than individuals with classic CF, the long-term expected outcome for many individuals with atypical CF is unknown. It is important to counsel patients about the possibility of future illness. Education about CF can help patients understand their symptoms, modify their lifestyles to optimize health, reduce the incidence of complications, and receive family planning counseling when appropriate.

With a carrier rate of up to 1 in 25 among the people with northern European ancestry,¹ virtually all family physicians in Canada will encounter patients who possess a recessive gene for cystic fibrosis (CF). Abnormalities of the cystic fibrosis transmembrane receptor (CFTR) primarily affect the respiratory, gastrointestinal, endocrine and metabolic, and genitourinary systems.²⁻⁵ Although most people with classic CF in Canada will have the disorder detected through newborn screening or symptoms in early childhood, atypical forms of CF are increasingly being recognized in older children and adults. Unlike classic CF, atypical CF might only affect 1 organ system^{3,6,7} and symptoms might not develop until late childhood, adolescence, or adulthood.^{3,6,7} When symptoms do develop, most people with atypical CF will seek the advice and care of their family physicians. Identification of patients with atypical CF is of particular importance for family physicians because appropriate referral and treatment can substantially affect quality of life and life expectancy. In addition, identification and counseling of family members about this common recessive disorder is important for additional case detection and reproductive planning.

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KEY POINTS Cystic fibrosis (CF) affects about 1 in 2500 Canadians; the incidence of atypical CF is unknown and debatable. The carrier frequency of cystic fibrosis transmembrane receptor gene mutations is up to 1 in 25. Atypical cystic fibrosis (CF) is not uncommon, and individuals with atypical CF can have normal sweat chloride levels. Atypical CF can affect the respiratory, gastrointestinal, endocrine and metabolic, and genitourinary organ systems. Cystic fibrosis is diagnosed through newborn screening or, when suspected clinically, through sweat chloride testing with or without genetic analysis. Patients with atypical CF might or might not have elevated sweat chloride levels; sweat chloride testing, nasal potential difference, and genetic analysis in combination can be beneficial to confirm or refute a diagnosis. After an index case is diagnosed, family members should be offered screening for the disorder. With appropriate treatment, patients diagnosed with CF will suffer less acute and long-term morbidity and mortality and can receive family planning counseling, if appropriate.

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Case

A 43-year-old white woman (Ms M.) presented with chronic productive cough, occasional wheezing, and recurrent lower respiratory tract infections. She had smoked 1 pack of cigarettes per week for more than 20 years and had been exposed to second-hand smoke since childhood. Her medical history was relevant for asthma, chronic sinusitis, septorhinoplasty, environmental allergies, and infertility. Seven years previously, Ms M. saw a respirologist after a visit to the emergency department for pleuritic chest pain, sputum production, and hemoptysis. Bronchoscopy results were positive for *Staphylococcus aureus*, *Haemophilus influenzae*, and light-growth *Escherichia coli*. A computed tomography scan revealed bronchiectasis in both upper lobes. Ms M. was diagnosed with pneumonia and her symptoms resolved with antibiotic treatment.

Ms M. later presented for a complete physical examination. At that time, the practice in which she was a patient was involved in a study examining pulmonary function in people older than 40 years of age with a history of smoking. Ms M. participated in the study. She underwent spirometry, reversibility, lung volume, and diffusion testing and was found to have hyperinflation with substantial airway obstruction, normal diffusion capacity, and no change in obstruction following bronchodilator use. Owing to these findings, the lead respirologist involved in the study assessed Ms M. and found that she had wheezing, increased forced respiratory time, and digital clubbing.

The differential diagnosis included immotile cilia syndrome and CF. The patient underwent a computed tomography scan of the sinuses and chest and sweat chloride testing, which was performed at the Hospital for Sick Children in Toronto, Ont. Results of sweat chloride testing and subsequent genetic analysis were both positive for CF. Her family history was relevant for recurrent sinusitis in Ms M.'s father but was otherwise unremarkable.

Sources of information

A comprehensive search of MEDLINE (1950 to the third week of May 2009), MEDLINE In-Process and Other Non-Indexed Citations and Cases (1950 to the third week of May 2009), and EMBASE (1980 to the fourth week of March 2009) was performed to capture as many articles as possible focusing on cases of atypical CF, CF diagnosed in adulthood, and cases of CF identified in family practice. Cystic Fibrosis Canada was also contacted for their most recent patient data registry report.

Altogether, the initial search produced 908 titles and abstracts, which were reviewed when available; 127 met the initial inclusion criteria. Full-text copies of 119 articles were obtainable, and these were closely assessed,

along with the Cystic Fibrosis Canada patient data registry report, for quality, relevance, originality, and importance to primary care practice in Canada. A total of 38 articles, including the Cystic Fibrosis Canada website and patient data registry report (www.cysticfibrosis.ca/en/aboutCysticFibrosis/NBS.php), were reviewed in this study. These consisted of review articles of CF, atypical CF, or CF diagnosed in adulthood,^{1,2,5-8} 2 primary research studies on CF diagnosis,^{9,10} 1 diagnostic review article,⁴ 1 diagnostic consensus guideline,¹¹ 1 review article focusing on the dermatologic effects of CF,¹² 1 primary research study on atypical sinusitis,¹³ 1 primary research study on bronchiectasis and pulmonary infection,¹⁴ 3 primary research studies on fertility in CF,¹⁵⁻¹⁷ 3 epidemiologic studies,¹⁸⁻²⁰ 2 qualitative studies on the effects of diagnosis on individuals,^{21,22} adolescent and adult case studies selected based on originality,²³⁻³⁶ and 3 comprehensive database and chart reviews.^{3,37,38}

Main message

Cystic fibrosis is an autosomal recessive disorder characterized by impaired chloride transport across the apical membrane of cells as a result of mutations of the CFTR gene.⁸ It is the most common recessive disorder among people of northern European ancestry, with a carrier rate of approximately 1 in 25 to 1 in 28.¹ Although less common, CF is found in virtually all ethnic populations.⁴ Therefore, every family physician in Canada will come into contact with patients who are carriers of CF-causing gene mutations, some of whom might potentially have an atypical form of the disorder. In 2000, the CF birth rate in Canada was 1 in 3600.¹⁸

Classically, CF is a childhood disease characterized by chronic lung disease, sinusitis, nasal polyposis, pancreatic insufficiency causing diarrhea and malnutrition, meconium ileus, rectal prolapse, and elevated sodium and chloride concentrations in sweat.^{3,5,7} Since the 1960s, a milder form of CF with atypical features has been known to exist²⁴; it is often not diagnosed until adolescence or adulthood.^{2,24} Individuals with mild or atypical symptoms of CF pose a diagnostic challenge to clinicians and can suffer substantial morbidity as a result of not receiving appropriate diagnosis and treatment.

What is atypical CF? Atypical CF is a milder form of the CF disorder, which is a result of mutations of the CFTR gene. Individuals with atypical CF usually have 1 severe mutation and 1 less common mutation²⁵ or abnormality of trinucleotide repeats on their other CFTR gene.²⁶ Instead of having classic symptoms, individuals with atypical CF might only have dysfunction in 1 organ system and of a much milder degree than those with 2 severe mutations.^{3,4,6,14} They might or might not have elevated sweat chloride levels.^{3,14} As a result, these

individuals often have fewer hospitalizations during childhood than those with classic CF do,²¹ and the disorder can remain undiagnosed for many years, at times into adulthood.^{3,4,6,14} Individuals as old as 70 years have been diagnosed.²⁷ Over time, individuals with atypical CF can develop additional symptoms²³ or discover that other pre-existing health issues are symptoms of CF that were not properly identified as such.³⁰

What signs or symptoms should make me suspect atypical CF in my patients? Atypical CF is a very diverse disorder affecting different organ systems to varying degrees. The symptoms patients experience can also fluctuate over time; however, certain clinical signs and symptoms affecting the respiratory, gastrointestinal, endocrine and metabolic, and genitourinary systems should alert physicians to the possibility of CF.

The respiratory system is the primary system physicians associate with CF. In classic CF, patients suffer from chronic and recurrent sinus and respiratory infections, nasal polyposis, bronchiectasis, digital clubbing, and symptoms of progressive respiratory obstruction beginning in childhood.^{2,7} In atypical CF, respiratory symptoms are often more mild and might not begin until adulthood but still include recurrent pneumonia, progressive obstruction possibly identified as asthma or chronic obstructive pulmonary disease, chronic sinusitis, or nasal polyposis.^{2,13,14,20,37}

One of the earliest signs of CF is meconium ileus in infancy, and a history of this should always alert the clinician to the possibility of the diagnosis.² Other gastrointestinal manifestations of classic CF include exocrine pancreatic insufficiency causing steatorrhea, fat-soluble vitamin deficiency, difficulty gaining weight,^{2,38} cirrhosis, portal hypertension, and rectal prolapse.²⁸ In atypical CF, however, gastrointestinal effects can be subtle and include chronic constipation or diarrhea,^{28,37} and chronic or recurrent pancreatitis with mild or no respiratory symptoms.^{29,30,34}

The endocrinologic and metabolic effects of CF overlap with the gastrointestinal effects through pancreatic dysfunction. Endocrine pancreatic dysfunction can be

the primary presentation of CF.³¹ In addition, individuals with CF can also present with electrolyte abnormalities, primarily hyponatremia, hypokalemia, and metabolic alkalosis, which most commonly occur in the context of dehydration or heat stroke.^{25,32,36}

The genitourinary manifestations of CF are primarily related to fertility and are often not apparent until an individual is trying to conceive. For men, suspicion of CF might arise after the finding of azoospermia on semen analysis as a result of congenital bilateral absence of the ductus deferens^{1,2,6,23,35}; the abnormality occurs in approximately 97% to 98% of men with classic CF.³⁵ Women with CF are usually fertile but tend to have more difficulty conceiving than women without CF. This is most often attributed to thickened cervical mucus,^{16,17} although there is also evidence of abnormal ovarian cycling and reduced ovarian reserve.¹⁵ Other less common presentations of CF include dermatitis secondary to nutritional deficiencies, early aqueous wrinkling, and angitis.¹² **Table 1** summarizes the systems affected in and symptoms of atypical CF.

How is CF diagnosed? Cystic fibrosis is routinely screened for at birth in Alberta, Ontario, Saskatchewan, British Columbia, and Manitoba (www.cysticfibrosis.ca/en/aboutCysticFibrosis/NBS.php). Although screening will identify a substantial number of infants with CF, there was no screening in Canada before 2007 and this, in addition to high immigration rates and a lack of a natural screening program, means most individuals in Canada have not been screened for the disorder. Further, it is possible that infants with negative screening results for CF might later develop symptoms. The diagnosis should not be overlooked simply because of previous screening results negative for CF.⁴

Case identification requires a high index of suspicion for the disorder, and individuals with CF can be diagnosed in 1 of 3 ways: 1) newborn screening, 2) clinical suspicion based on symptoms, or 3) screening of family members of individuals who have been diagnosed, including possible prenatal testing. When suspected, physicians should begin with sweat chloride testing at

Table 1. Affected systems and symptoms in atypical CF

SYSTEM	SYMPTOMS
Respiratory	Chronic sinusitis, nasal polyposis, poorly controlled obstructive lung disease, recurrent pneumonia, digital clubbing
Gastrointestinal	Meconium ileus, rectal prolapse, atypical acute pancreatitis or chronic pancreatitis, diarrhea, constipation, weight loss or poor weight gain, nutritional deficiency
Endocrine and metabolic	Diabetes mellitus, hyponatremia, hypokalemia, metabolic alkalosis
Genitourinary	Azoospermia in men, reduced fertility in women
Other	Dermatitis secondary to nutritional deficiencies, unexplained anemia, early aqueous wrinkling

CF—cystic fibrosis.

a CF reference centre, followed by genetic analysis or nasal potential difference (NPD) testing if required to clarify the diagnosis.²⁰ Results of sweat chloride tests in adults are considered positive for CF when the chloride level is greater than or equal to 60 mmol/L.^{4,11} At a level of 70 mmol/L or greater, the sensitivity and specificity of the test both approach 100%.¹⁰ Chloride levels between 40 and 59 mmol/L are considered intermediate, and at values of 39 mmol/L or less, CF is unlikely.¹¹ Follow-up and repeat testing at 6- to 12-month intervals is appropriate until a definitive diagnosis is made.¹¹

While most individuals with CF will have positive sweat chloride test results, there are cases, particularly with atypical CF, in which individuals with 2 genetic mutations for the disorder will have sweat chloride test results negative for CF.^{6,14,20} In patients with atypical CF, NPD test results might be positive for CF or have values between those of unaffected individuals and individuals with CF.⁹

At present, more than 1500 CFTR mutations have been identified, but most of these are not associated with the disease.¹¹ Twenty-three genes have been identified as conferring substantial dysfunction to produce CF, and 2 of these are identifiable in about 85% of those with the disorder.¹¹ This means that genetic analysis might not provide a definitive diagnosis in approximately 15% of patients with CF.¹¹ Therefore, sweat chloride testing, NPD, and genetic analysis in combination can be beneficial to help confirm or refute a diagnosis in some instances.²⁰ **Table 2** summarizes these diagnostic tools.

What are the benefits and implications of diagnosis for my patients? It is important to diagnose CF for patients as well as for their families, but the diagnosis

is not benign. Individuals and families might react differently on receiving a diagnosis, ranging from relief at having an explanation for symptoms³⁷ to anger, family stress, and concern regarding potential economic consequences.²² It is important to explore some of the possible psychosocial effects that might result when the disease is suspected and the diagnosis is pursued both for the individual and for family members who might be affected or be carriers of the disorder. Ultimately, how a person comes to be diagnosed has a substantial effect on his or her emotional response to diagnosis and compliance with medical care.²¹

Delays in diagnosis can result in substantial morbidity and hospitalizations that might otherwise have been avoided.³⁸ It is important to recognize that there are excellent treatments for the various symptoms of CF, including chest physiotherapy, antibiotic therapy, diet modification, and pancreatic enzyme replacement. With these interventions the course of the disease can be favourably modified.^{20,26,37} In addition, close follow-up with specialists can help identify complications and exacerbations early and allow for appropriate treatments proven effective for CF to reduce morbidity and mortality. Although adults diagnosed with atypical CF have longer life expectancies than individuals with classic CF,³ the long-term outcome for many individuals with atypical CF is unknown,³⁵ and it is important to counsel patients about the possibility of future illness. Finally, education about CF can help patients understand their symptoms, modify their lifestyle to optimize health, reduce the incidence of complications, and receive family planning counseling when appropriate.^{13,29} It is important to remember that there are wide variations in phenotypes of CF among individuals and family


Table 2. Diagnostic investigations in CF

TEST	POSITIVE RESULTS FOR CF	ADVANTAGES AND DISADVANTAGES OF TEST	
		ADVANTAGES	DISADVANTAGES
Sweat chloride levels	≥ 60 mmol/L indicative of CF ≤ 39 mmol/L unlikely to be CF 40-59 mmol/L considered intermediate	A high sweat chloride level is very strong evidence for CF	It is possible to have CF and intermediate or low sweat chloride levels; intermediate levels are common in atypical CF and require repeat sweat chloride level testing or further testing of NPD or genetic analysis
NPD	≥ 30 mV suggestive of CF Relevant response to zero-chloride perfusate with isoproterenol might help rule out CF	Can add strength to diagnosis of atypical CF or help rule out CF	Not definitive for diagnosis alone owing to overlap between normal values and values in CF
Genetic analysis	Presence of 2 CFTR gene mutations known to cause disease in <i>trans</i> arrangement on 2 separate chromosomes (<i>cis</i> arrangement on the same chromosome is not associated with disease)	Identification of 2 known CFTR gene mutations provides strength to diagnosis	Up to 15% of individuals with CF have rare or unidentified CFTR gene mutations

CF—cystic fibrosis, CFTR—cystic fibrosis transmembrane receptor, NPD—nasal potential difference.

members, even with the same genotype.^{33,34} Therefore, individualization of diagnosis, treatment, and expected outcome is crucial to best meet unique patient needs.

Conclusion

Atypical CF is not a commonly considered differential diagnosis in family practice, but most family physicians in Canada will see 2 to 3 cases of CF during their careers (assuming a patient population of 1800 and 5% patient variability per year). Atypical CF can present as chronic symptoms within the respiratory, gastrointestinal, endocrine and metabolic, or genitourinary systems. Understanding CF and identification of atypical cases is important because diagnosis and treatment can substantially improve quality of life and life expectancy for those affected and their families. 

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Competing interests

None declared

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