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GPs Meet Rare Lung Disorders Task Force factsheet: cystic fibrosis

Definition

Cystic fibrosis (CF) is a complex autosomal recessive disease caused by a mutation in a gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein, the main function of which is to regulate liquid volume on epithelial surfaces through chloride secretion and inhibition of sodium absorption. The disease mainly affects the upper and lower airways, but also the pancreas, bowel, liver and reproductive tracts. Lung disease, the cause of death in 85% of affected subjects, begins early in life and is characterised by impaired mucociliary clearance and consequent chronic airway inflammation and bacterial infection.

Prevalence

The prevalence of CF varies from country to country. It is most common in white populations of northern-European descent, in which it occurs in approximately 1 in 2500 births. CF is uncommon in Africa and Asia. In Europe, about one in 25 individuals carries a mutated CFTR gene but carriers do not have symptoms of the disease.

Clinical manifestations

CF manifests in many organs and, depending on the type of CFTR mutation and other factors, with different severity. The main symptoms of CF, which often appear in infancy and childhood, are fatty stools, poor growth and weight gain despite normal food intake, frequent chest infections, coughing and shortness of breath. In newborn babies, bowel obstruction due to meconium ileus can occur. Males can be infertile due to congenital absence of the vas deferens.

Diagnosis

The diagnosis of CF should be considered in any child or adult who presents with the signs or symptoms listed in the table. CF can be diagnosed by sweat testing. People with CF have increased amounts of sodium and chloride in their sweat (>60 mmol·L^{-1} diagnostic; 40–60 mmol·L^{-1} intermediate; <40 mmol·L^{-1}, normal). The test needs to be performed by trained and experienced staff. CF can also be diagnosed by genetic testing for CFTR mutations, of which more than 1500 have been identified. The most common F508del mutation occurs in about 70% of CF patients' chromosomes. In cases where these methods fail to establish a diagnosis, advanced electrophysiological studies of nasal and rectal mucosa can be performed in selected tertiary CF centres.

Once CF diagnosis has been confirmed, all siblings need to be screened for the disease, as it may have been unrecognised so far. Asymptomatic adult relatives should be offered screening for carrier status to enable them to make informed choices about prenatal

Table 1. *Main symptoms and findings of CF according to typical age of onset*

Neonatal	Meconium ileus causing bowel obstruction (10% of cases), obstructive jaundice, bleeding disorders due to vitamin K malabsorption, salty tasting skin
Childhood	Fatty stools and failure to thrive (exocrine pancreas insufficiency in 85% of cases), chronic sinusitis and nasal polyps, dehydration and electrolyte disturbance, recurrent respiratory symptoms (chest infections, cough, wheeze), digital clubbing, pseudo-Bartter's syndrome, distal intestinal obstruction syndrome, rectal prolapse, acute or chronic pancreatitis
Adolescents, adults	CF-related diabetes mellitus, liver disease, portal hypertension, osteoporosis, arthritis, male infertility (congenial bilateral absence of the vas deferens)

screening. Couples planning a pregnancy can have themselves tested for CFTR mutations to determine the risk that their child will have CF, although this option may not be available in all countries. During pregnancy, testing for CFTR mutations may also be performed (chorionic villi sampling or amniocentesis).

In several countries, CF is nowadays diagnosed shortly after birth as part of newborn screening programmes. The newborn screen usually measures raised blood concentrations of immunoreactive trypsinogen. Infants with an abnormal newborn screen are referred to a CF centre to confirm or exclude CF diagnosis.

Treatment and follow-up

CF treatment is aimed at restoring and maintaining organ function and consequently quality of life as far as possible, based on early detection and vigorous treatment of complications. Cornerstones of CF management are the substitution of pancreatic enzymes and vitamins, good hypercaloric nutrition, proactive treatment of airway infection and other complications of the disease, psychological support and an active lifestyle.

Management of CF lung disease involves aggressive treatment of upper and lower airway infections by antibiotics, use of anti-inflammatory agents, inhalation therapy (*e.g.* hypertonic saline, recombinant human deoxyribonuclease) and airway clearance by combinations of physiotherapy and physical exercise. Lung transplantation is the ultimate therapeutic option for patients with end-stage lung disease. Newer treatments such as gene therapy and small molecule based treatments aimed at curing some of the effects of CF are under development.

As CF is a complex multi-organ disease, it is best managed in a multidisciplinary setting coordinated by a tertiary centre for CF, and tailored to the individual. A team consisting of specialists in paediatric respiratory medicine, gastroenterology, endocrinology, and otorhinolaryngology, as well as nurses, nutritionists, respiratory physiotherapists, social workers and psychologists is necessary to provide adequate care. A main challenge for CF patients is finding the time to comply with prescribed time-consuming treatments while balancing a normal life.

Prognosis

The outlook for people with CF has improved substantially in the past 20 years, due to earlier diagnosis of the disease, better treatment and access to healthcare. Patient compliance is a major factor, with patients following better treatment recommendations living longer. Currently, the life expectancy of CF patients is 38 years but the predicted median survival for babies born today is now more than 50 years.

Key messages

- Think about CF if your patient has failure to thrive and has chronic respiratory symptoms.
- CF is an important cause of progressive lung disease and our key aim is to establish an early diagnosis and institute treatment strategies prior to the onset of irreversible lung damage.
- Refer the patient to a centre with experience in CF diagnostic studies (*i.e.* sweat testing, genetic analysis).
- If feasible, follow your patient through the years in shared care with the team at the reference centre.

Patient case

A girl born at full term with normal height and weight was breast fed and gained weight normally. The father had several food allergies and the girl developed allergies against cows' milk and egg. She was followed by a general paediatrician.

Having had several airway infections with wheezing and was diagnosed with asthma at the age of 2 years. She was prescribed inhaled steroids (by the general practitioner: budesonide 100 µg daily and 800 mg daily for three days) at the start of an airway infection. During the summer she did not need the inhaled steroids but every autumn, she began coughing and was again prescribed inhaled steroids.

At the age of 3 years, the girls's father asked the paediatrician about the girls' protruding stomach and stomach aches. The girl often had around eight loose stools per day. Her weight was -1 SD of the mean and she was pale but very active. A blood test for gluten intolerance, blood counts and the food allergies were performed and the doctor added a note in her medical record that a sweat test should be performed afterwards; however, the next appointment was scheduled for half a year later.

The next appointment was postponed and the girl came to the paediatrician a year later, at the age of 4 years. She had no lung symptoms during summer but lots of coughing during the rest of the year, especially during the night. She had often been prescribed bronchodilators and other cough medicine by the general practitioner. Her asthma medication was increased and she was given montelukast orally. Her weight had decreased to -2 SD of the mean and her stomach was still protruding but she had only a couple of stools per day of a normal consistency. She was advised to use lactose-reduced food. Two months later, at follow-up, her condition had improved with no coughing, no stomach aches after lactose-reduced food and she had gained weight.

At the next follow-up, at the age of 5 years, the girl recorded peak expiratory flow (PEF) before and after jumping on a trampoline. After jumping, the girl had a lot of sputum and coughing but an increased PEF value. She had gained weight but still had stomach ache and loose stools (*e.g.* after eating ice cream). Genotyping of the lactase gene polymorphism nucleotide 13910 was performed and showed the polymorphism 13910 C/T with a low probability of lactose intolerance.

Over the next couple of years, the girl continued to see the general paediatrician once or twice a year with the same, but not increased, symptoms. At the age of seven years, her stomach ache worsened and she was admitted to the emergency room twice in a short period of time due to constipation. During one of these consultations, a urine sample showed glucosuria, so she was sent to the paediatric endocrinology department and diabetes examinations were begun. The endocrinologist remarked that although the girl's height was only -1.5 SD of the mean, this was -2.5 SD below her target height. At the same time as she was followed up for hyperglycaemia, she again had severe stomach ache and constipation. A paediatrician at the emergency room noticed "watch-glass" nails (digital clubbing) and, because of the girl's symptoms, suspected cystic fibrosis and ordered a sweat test.

Comments

- If you think of CF or a sweat test, always do the sweat test (to exclude CF). In this case the girl would have had the right diagnosis at the age of 3 years instead of 7 years.
- Always do a sweat test to exclude CF if an asthma patient continues to cough or has sputum problems even though maximum asthma treatment is given. The asthma diagnosis may be wrong.
- Ask how often the parents hear the child cough. Is the child coughing when doing physical exercise (as in this case)?
- Often do sweat test if there is a patient with asthma and some stomach symptoms (for example stomach ache, loose stools, constipation).
- Look for digital clubbing and watch-glass nails.
- Not all CF patients have pancreas insufficiency from birth, so their failure to thrive may come after some years.
- Ask what loose stools look like and how they smell. Are they pale yellow/white, voluminous? Does the child have stomach ache at the same time? Is it after more fatty food (for example after pizza, cheese or ice cream)?
- CF children are often active and happy. You seldom think it is a child with a severe chronic disease until they are very ill.

Further reading

1. O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet* 2009; 373: 1891–1904.
2. The European Cystic Fibrosis Society (www.ecfs.eu).
3. The Cystic Fibrosis Foundation, USA (www.cff.org).