CASE FIVE

Short case number: 3_7_5
Category: Respiratory System
Discipline: Medicine
Setting: Emergency Department
Topic: Cystic fibrosis [SDL]

Case

Michael Seaver, aged 18 years has cystic fibrosis and presents to the emergency department with a flare up of the usual. He is worried as last time he cultured a resistant organism and required triple therapy.

Questions

1. What further history and examination would you undertake?
2. What are the complications of cystic fibrosis?
3. What are the clinical features of cystic fibrosis?
4. How would you manage this case?
5. What is the role of somatic gene therapy?
6. Define the following terms used in respiratory medicine: FEV1, FVC, VC, PEF, TLC, FRC, RV, TLco, Kco.

Suggested reading:

Innes JA, Reid PT. Respiratory disease. In: Boon NA et aal. Davidson's Principles and Practice of Medicine 20th Ed. Churchill Livingstone, London, 2006 PP647-737.

ANSWERS

1. What further history and examination would you undertake?

A correlation may be made between the mutation and the patient's clinical condition. Based on current knowledge of the association between genotype and phenotype, the clinical characteristics of patients with cystic fibrosis (CF) are divided into severe, milder than severe, and variable phenotypes.
The affected organs include:

- Respiratory tract

Ask about cough, chronic or recurrent cough, which can be dry and hacking at the beginning and later mucoid (early) and purulent (later) sputum. Other respiratory symptoms may include wheezing, recurrent pneumonia, atypical asthma, pneumothorax, hemoptysis, and digital clubbing are all complications and may be the initial manifestation. Check for increasing shortness of breath.

- Pancreatic dysfunction

Check for use of pancreatic supplements and the adequacy of replacement. Steatorrhea is characterized by frequent, poorly formed, large, bulky, foul-smelling, greasy stools that float in water. Check for weight loss, recurrent abdominal pain, and abdominal distention.

- Hepatobiliary

Check for symptoms of biliary dysfunction such as nausea, vomiting, dark urine, bleeding. Patients may present with a history of jaundice or gastrointestinal tract bleeding.

- Urogenital tract manifestations

Males are frequently sterile because of the absence of the vas deferens. Undescended testicles or hydrocele may exist.

Physical examination includes:

- Nose (Rhinitis, nasal polyps)
- Respiratory system (tachypnea, degree of distress, wheeze or crackles, cough, sputum, diameter of chest, clubbing, cyanosis, crackles).
- Gastrointestinal tract (abdominal distention, hepatosplenomegaly, rectal prolapse)

2. What are the complications of cystic fibrosis (CF)?

Respiratory - Infective exacerbations of bronchiectasis - Spontaneous pneumothorax - Haemoptysis - Nasal polyps - Respiratory failure - Cor pulmonale - Lobar collapse due to secretions
Gastrointestinal - Malabsorption and steatorrhoea - Distal intestinal obstruction syndrome - Biliary cirrhosis and portal hypertension - Gallstones
Others - Diabetes (25% of adults) - Delayed puberty

- Male infertility
- Stress incontinence
- Psychosocial problems
- Osteoporosis
- Arthropathy

3. What are the clinical features of CF?

The lungs are macroscopically normal at birth, however bronchiolar inflammation and infections usually lead to bronchiectasis in childhood.
The lungs become infected, most commonly with *Staphylococcus aureus.* Later, the majority of patients have *Pseudomonas aeruginosa* infection by the time they reach adolescence. Recurrent exacerbations of bronchiectasis, initially in the upper lobes but subsequently throughout both lungs, cause progressive lung damage resulting ultimately in death from respiratory failure.
Other clinical manifestations of the gene defect include intestinal obstruction, exocrine pancreatic failure with malabsorption, diabetes and hepatic cirrhosis.
Most men with CF are infertile due to failure of development of the vas deferens, but microsurgical sperm aspiration and in vitro fertilisation are now possible.
The genotype is a poor predictor of severity of disease in most individuals; even siblings with matching genotypes may have quite different phenotypes. This suggests that other 'modifier genes' (as yet unidentified) influence clinical outcome.

4. How would you manage this case?

Chest physiotherapy;

Treat infections;
While infections with *Staph. aureus* can often be managed with oral antibiotics, intravenous treatment is needed for *Pseudomonas* species.
Nebulised antibiotic therapy, mainly with colomycin or tobramycin is used between exacerbations in an attempt to suppress chronic *Pseudomonas* infection
Unfortunately, the bronchi of many CF patients eventually become colonised with pathogens which are resistant to most antibiotics.
Resistant strains of *P. aeruginosa, Stenotrophomonas maltophilia* and *Burkholderia cepacia* are the main culprits, and may require prolonged treatment with unusual combinations of antibiotics.
Aspergillus and 'atypical mycobacteria' are also frequently found in the sputum of CF patients, but in most cases these behave as benign 'colonisers' of the bronchiectatic airways and do not require specific therapy.
Treat co-incidental airways diseases such as asthma if present.

Nebulised RNA;
Treatment with nebulised recombinant human deoxyribonuclease (DNase) has been available since 1994.
The aim of this is to liquify the sputum by breaking up the excess viscous DNA derived from disintegrated inflammatory cells. Careful monitoring of response to treatment is appropriate as this treatment is very expensive.

Non-respiratory aspects of CF must be considered;
There is a clear link between good nutrition and prognosis in CF.

Malabsorption is treated with oral vitamins and pancreatic enzyme supplements and the increased calorie requirements of CF patients are met by supplemental feeding including nasogastric or gastrostomy tube feeding if required.
Diabetes will eventually appear in about 25% of patients and often requires insulin therapy.
Osteoporosis secondary to malabsorption and chronic ill health should be sought and treated

Long term treatments;
For advanced CF lung disease, home oxygen and non-invasive ventilation may be necessary to treat respiratory failure. Ultimately, lung transplantation can produce dramatic improvements but is limited by donor organ availability.

5. **What is the role of somatic gene therapy?**

The discovery of the CF gene and the fact that the lethal defect is located in the respiratory epithelium (which is accessible by inhaled therapy) presents an exciting opportunity for gene therapy. Manufactured normal CF gene can be 'packaged' within a viral or liposome vector and delivered to the respiratory epithelium to correct the genetic defect. Initial trials in the nasal and bronchial epithelium have shown some effect, and further trials of nebulised bronchial delivery are planned. Improved gene transfer efficiency is needed before this will become a practical clinical treatment.

6. **Define the following terms used in respiratory medicine: FEV1, FVC, VC, PEF, TLC, FRC, RV, TLco, Kco.**

Abbreviation	Stands for
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
VC	Vital capacity (relaxed)
PEF	Peak (maximum) expiratory flow
TLC	Total lung capacity
FRC	Functional residual capacity
RV	Residual volume
TL_{CO}	Gas transfer factor for carbon monoxide
K_{CO}	Gas transfer per unit lung volume