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Cystic Fibrosis and its Management

Ruchika Singh*, Keerti Phalswal, Parul Saini,Kavita Pillai
Dept. of Medical Surgical Nursing, Faculty of Nursing, SGT University, Gurugram, Haryana

ABSTRACT

An obstructive lung illness, cystic fibrosis is an autosomal recessive disorder. Due to mucus stasis, cystic fibrosis sufferers have difficulty exhaling. As a result, the amount of leftover air in the lungs increases even after expiration.[1] The alveoli fully expand, but because of thickened mucus and decreased airflow, air is retained in the lungs and lung volume increases. The cystic fibrosis transmembrane conductance regulator gene (CFTR) mutations that cause cystic fibrosis (CF) induce inadequate mucous secretion clearance, progressive pancreatic and pulmonary dysfunction, significant disability, and early mortality.[2] Among Caucasians, CF is thought to be the most prevalent, deadly. The chance of survival is low, but it has significantly increased rate of medical treatments, attention to maintaining strict pulmonary cleanliness, quick treatment for lung infections, and appropriate nutritional management. The CFTR gene, which is found on chromosome 7, has a mutation that is the cause of it. The CFTR (Cystic Fibrosis Transmembrane Conductance Receptors) gene codes for a protein with 1480 amino acids.[11] Cystic fibrosis has been managed using a variety of therapy techniques such as nebulization with 7% hypertonic saline, uses of antibiotics and recently developed technique-Human recombinant DNA technology approach have shown better outcomes.[5]

Keywords:*CF-Cystic Fibrosis,CFTR-Cystic Fibrosis Transmembrane Conductance Receptors,COPD-Chronic Obstructive Pulmonary Disease,GIT- Gastro-Intestinal Tract,RAAS- Renin-Angiotensin-Aldosterone System*

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INTRODUCTION

Cystic fibrosis is an autosomal recessive disorder and is a type of obstructive lung disease. The patients with cystic fibrosis have a problem in exhaling air due to stasis of mucous. This results in increased amount of residual air in the lungs even after expiration. The alveoli inflate fully but due to thickened mucous and reduced airflow the air is trapped in lungs and lung volume increases other conditions with a similar picture are COPD, Asthma and Bronchiectasis [1].

Cystic Fibrosis is a genetically acquired condition in which secretions of the body i.e. mucous becomes very thick, this thickened mucous leads to various manifestation. As due to change in the genetic makeup of the individual the resultant mucous produced has increased viscosity and it leads to blockage of pancreatic ducts, intestines and often bronchi.

Mucoviscidosis is referred to a condition when cystic fibrosis affects the secretions in relation with the pancreas wherein the secretions become very thick and contribute to various manifestations. The patients which have their pancreas affected by cystic fibrosis are bound to have type II diabetes mellitus in the future [2].

When this condition has the propensity to involve the exocrine glands then it is known as exocrinopathy.

Definition

Cystic fibrosis is an inherited life threatening disorder which causes damage to the lungs and the digestive system. Cystic fibrosis primarily affects the cells which produce mucous, sweat and digestive juices.[3] It causes the affected fluids to become thick and sticky which in turn leads them to plug up the tubes, ducts and passage ways [3].

The affected fluids are otherwise thin and slippery but due to a faulty gene affecting a movement of salt and water across the cells these secretions thickens occluding the body's tube and passages mainly the lungs and digestive system [4].

Pathogenesis

Cystic fibrosis is an autosomal recessive condition. It is caused by a mutation in CFTR gene which is located on chromosome seven. The CFTR gene has 1480 amino acids sequences which code for CFTR **(Cystic Fibrosis Transmembrane Conductance Receptors)** protein [5].

In cystic fibrosis the amino acid phenyl alanine which is present at 508th position is deleted hence the mutation is known as F508 mutation [6].

The resultant CFTR Protein malfunction leads to several manifestations the chloride channel is defective as a result of which chloride/Bicarbonate/water transport does not take place across it. Due to this periciliary dehydrations occurs and mucous becomes highly viscid and thick.

The root cause of this condition is :-

1) Low water content of PCL(Periciliary fluid)
2) Acidic environment of periciliary fluid which results due to defect in bicarbonate release.
3) Mucociliary clearance is reduced which results in stasis of mucous. As a results of this the inhaled bacteria i.e. staphylococcus aureus, Pseudomonas, burkholderia undergo mucoid transformation. This can result in formation of a biofilm which is impervious to antibiotics.

ORGAN SYSTEMS INVOLVED

Cystic fibrosis affects multiple organ systems in the body leading to a wide range of clinical manifestations important organs involved in this conditions are:

1. **Lungs**

   The lungs are the first organs to be involved in cystic fibrosis, the mutated gene leads to a thickened mucous being produced in the bronchi, bronchioles and other parts of upper respiratory tract.

   The follicular plugging in airway by thick tenacious secretions leads to stasis of airflow in bronchioles resulting in bronchiolitis. This in turn leads to inflammation of bronchus leading to bronchitis and individual develops bronchiectasis and has large dilated airways filled with pus. This condition ultimately leads to recurrent pneumonia and causes death of the individuals (before first year of life in India).[7]

   Upper respiratory tract can also present with nasal polyps or recurrent sinusitis.

2. **GIT**

   The main part of GIT which is affected in cystic fibrosis is the pancreas. The pancreas becomes decreased in size gradually and the pancreatic secretions become thick and viscid. It can also be replaced by fibro fatty tissue [8]. This in turn leads to development of diabetes mellitus in the second decade of life. The levels of amylase as well as lipase drop significantly and the individual suffers from malabsorption syndrome hence resulting in failure to thrive.

3. **LIVER**

   The individual suffering from cystic fibrosis ends up having secondary biliary cirrhosis. The individual presents with obstructive jaundice and prolongation of physiological jaundice. The individual can also present with absence of cystic duct and ORGAN TRANSPLANTATION is required in these individuals.[9]

   The esophageal and duodenal glands(Brunner's) are filled with thick mucus and are unable to secrete their own secretions hence the acid from stomach is not neutralized which leads to duodenal development of duodenal ulcers.

4. **GENITO URINARY SYSTEMS**

   Females:-In females the formation of thick cervical mucus plug causes conception issues which leads to infertility. It can be managed by ART.[10]In such individuals whether the pregnancy occurs or not depends on the individual's lung function status. The lungs which are shrunken with decreased lung volume are a contraindication to pregnancy. Such individuals are managed by regular tobramycin nebulization.

   Males:-In males with cystic fibrosis the sexual function i.e. ejaculation and erection are normal. The individual suffers from agenesis of vas deferens and epididymis. The individual gradually develops azoospermia and infertility.

CLINICAL FEATURES

The individual suffering from cystic fibrosis exhibit a wide variety of symptoms clinically. Some of the peculiar clinical features encountered are:-

1. **Chronic cough**

   The individual suffers from chronic cough which is purulent in nature. A foul smelling pus is present and the individual experiences shortness of breath. The individual also develops non-cardiogenic edema and right ventricular failure. A lung transplant might be needed in severe cases. The AP diameter of the lungs is increased and the chest becomes hyper resonant.[11] Clubbing is exhibited by the individual and in some cases sudden deterioration occurs due to pneumothorax and massive hemoptysis resulting in fall in BP and severe hypotension. The individual presents with nasal stuffiness.

2. **Meconium ileus**
   The individual presents with abdominal distension and delayed passage of meconium (normally it occurs within 48 hours).The investigation best suited in these conditions is GASTROGRAFFIN enema which serves both diagnostic and therapeutic purposes as it softens the stools [12].
3. **GIT**
   The individual exhibit osmotic diarrhea due to poor and viscid pancreatic secretions. The individual also suffers from steatorrhea and protein energy malnutrition with failure to thrive.
4. The levels of vitamin E and vitamin K are decreased in the body thus resulting in hemolytic anemia with formation of acanthocytes. The individuals also develops bleeding manifestations due to deficiency of vitamin K.[13]
5. The patient develops liver cirrhosis gradually showing ICTERUS and ascites. The individual also develops hypersplenism, esophageal varices and CAPUT medusae.
6. The individual suffering from cystic fibrosis also develops INFERTILITY due to agenesis of vas deferens and epididymis in males and due to thickening of cervical mucus in females.
7. The sweat glands of individual are also affected in cystic fibrosis.Both sodium and chloride reabsorption is inhibited hence these individuals suffer from SALTY BABY SYNDROME.[13]Due to increased amounts of sodiumchloride and water in sweat the RAAS system is activated which leads to increased amounts of aldosterone in kidney which leads to hypochloremia, hypokalemia and metabolic acidosis.

Work Up

One of the major investigations used in the diagnostic workup of cystic fibrosis is the sweat chloride test. The method used in sweat chloride test pilocarpine iontophoresis [5]. A positive test is considered when the value of chloride concentration in sweat comes out to be more than 60 mEq per liter on two consecutive occasions.

A false positive sweat chloride test can be seen in individuals with anorexia nervosa, Addison disease, the individuals having congenital adrenal hyperplasia and the patients suffering from nephrogenic diabetes insipidus. On the other hand a false negative report comes in individuals suffering from malnutrition and edema. An equivocal report is considered in cases where the value of sweat chloride concentration is more than 60 on one occasion and less than 60 on other occasion [8]. A second sweat chloride test is repeated if the first one is non-confirmatory.

Some other tests used in the diagnostic workup of cystic fibrosis are:-

1. Trans epithelial nasal potential test is done in cases with equivocal sweat chloride concentration reports.
2. A DNA testing can also be done which shows at least two mutations in the genomic sequence.
3. The individual can also undergo fecal elastase level testing to identify the malabsorption component of the disease. Further the pulmonary function testing of the individual reveals an obstructive pattern in the lungs during earlier part of the disease whereas it shifts to restrictive pattern in the later part of the disease. A chest XRAY or a HRCT of chest shows dilated airways in the lungs [11].

The sputum culture of the individual shows the growth of staphylococcus aureus and also pseudomonas in some cases. A HbA1C value of more than 6.5% is noticed which in turn is an indicator of secondary diabetes mellitus due to the pancreatic component of the disease [16].

Diagnostic Criteria: The diagnostic criteria used for cystic fibrosis is as follows:-

1. Presence of typical clinical features in the patient:-

Respiratory - COPD, Bronchiectasis
Gastrointestinal -Meconium ileus, Malabsorption(ranging from osmotic diarrhea to steatorrhea) in addition to vit E & vit K deficiency[9]
Genitourinary – Infertility
Or
A history of cystic fibrosis in a sibling
Or
A positive screening test in a new born + laboratory evidence for CFTR

2. Dysfunction:

Two elevated sweat chloride levels obtained on two consecutive tests on two separate days[10]
Or
Identification of two CF mutations by DNA sequencing
Or
An abnormal nasal potential difference measurement.

Treatment

Various treatment modalities have been used in the management of cystic fibrosis .A quite recent approach in the management of cystic fibrosis involves human recombinant DNA technology.The enzymes DNAase & DORNase are used in this process.[11] This helps to decrease the viscosity of sputum so as to facilitate antibiotic penetration and the clearance of sputum by coughing becomes relatively easy. In another approach N-acetyl cysteine is administered followed by beta2 agonist nebulization [12]. This causes the individual to cough vigorously resulting in the expectorant sputum to come out.

Other additional treatment modalities are also used to aid the individual with cystic fibrosis. Nebulized hypertonic saline 7% is used which draws the water into the periciliary mucus thus making it less viscid and thick thereby easing its clearance [13]. In addition to this nebulized TOBRAMYCIN/AZTREONAM weekly reduces the chances of colonization of mucus by various bacteria. Chest percussion or physiotherapy and usage of hand held oscillometer devices which causes vibrations help to mobilize the secretions [14]. These thick and viscid secretions once mobilized are cleared thereby providing symptomatic relief to the individual.

Certain bacterial infections can also occur due to stasis of secretion and their colonization by some bacteria. Specific antibiotics are used for particular bacteria to omit chances of further infection. For example, if the individual encounters an infection by BURKHOLDERIA CEPACIA Treatment regime is to use MEROPENEM as an antibiotic of choice. Sometimes patients encounter allergic bronchopulmonary aspergillosis and hence a combination of oral corticosteroids with anti-fungal medications is used this this particular scenario [15]. These individuals have their upper airway colonized by aspergillus and show highlighted features of chronic bronchiectasis. In this condition serum precipitin antibody against aspergillus is quite useful.

In individuals with cystic fibrosis there is CFTR G551 mutant protein formation which results in loss of chloride ion conductance. A prenatal diagnosis of cystic fibrosis with chorionic villi sampling or amniocentesis has proven to be quite useful. Hence IVACAFTOR drug is used in a dosage of 150 mg twice daily to improve chlorine ion conductance [16]. This has an added advantage of increase in FEV1 which causes significant reduction in pulmonary exacerbation thus providing symptomatic relief to the individual by improving pulmonary function.

CONCLUSION

Cystic fibrosis is an autosomal recessive disorder and is a type of obstructive lung disease. The patients with cystic fibrosis have a problem in exhaling air due to stasis of mucous. This results in increased amount of residual air in the lungs even after expiration. In cystic fibrosis the amino acid phenyl alanine which is present at 508th position is deleted hence the mutation is known as F508 mutation.[6]

The resultant CFTR Protein malfunction leads to several manifestations the chloride channel is defective as a result of which chloride/Bicarbonate/water transport does not take place across it. Due to this periciliary dehydrations occurs and mucous becomes highly viscid and thick which will cause varieties of symptoms such as difficulty in breathing, shortness of breath etc. Individual shows wide variety of symptoms which will lead to multiple organ involvement, Hence if treated on time can prevent multiple organ damage. Various antibiotics regimen have shown wide variety of symptoms relief.

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