Cystic Fibrosis: A Review Article

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Abstract

Cystic Fibrosis is considered one of the most common autosomal recessive diseases that is associated with a decrease in the length of age in a Caucasian population. Also, it is considered as one of the most common life-shortening diseases in the white population in the United States. Cystic fibrosis affects around 30,000 people in the United States and more than 80,000 people worldwide. The incidence rate of this disease is 1 out of 3,500 births per year in the white population in the United States, while the incidence rate of the person becoming a carrier is 1:25 in the Caucasian population, the incidence of the disease is 1:2,500. The main cause for this disease is the mutation in Fibrosis Transmembrane Conductance Regulator (CFTR) gene. This disease is considered a life-threatening genetic disease that causes a buildup of thick, viscous mucus secretions in organ systems. Cystic Fibrosis is considered a multiple system disease, but in most cases, the disease gets worse and mortality increases because of respiratory manifestations such as bronchiectasis. Also, pancreatic damage in children is followed by severe wasting, malabsorption, and mortality is one of the recorded observations in children. This article aims to provide a brief introduction and the clinical picture of the disease, Etiology, Pathophysiology, Epidemiology, Nutrition, Prevention, and good practice management advice.

Keywords: Cystic Fibrosis, Bronchiectasis, Review Article, Airway Clearance Therapy, Fibrosis Transmembrane Conductance Regulator gene.

Introduction

Cystic Fibrosis is considered one of the most common life-limiting autosomal recessive genetic diseases which are spread mostly in Europe, North America, and Australia. Cystic Fibrosis has been associated with a decrease in the length of age in the Caucasian population (1, 2). Also, it is considered as one of the most common life-shortening diseases in the white population in the United States (3). Cystic Fibrosis is mainly diagnosed early during infancy (4). The most common technique used to diagnose Cystic Fibrosis is Sweat Testing Technique (5). The Sweat Testing Technique works by analysis of electrolyte concentration in the content of sweat. Mainly this technique measures Chloride and sodium concentration after 48 hours of birth because sweat start rises over the first 24 hours of the infant's life. If the chloride level is very high this indicates the presence of Cystic Fibrosis (6, 7). Patients with Cystic Fibrosis may present acutely to their local hospital with a variety of complaints but the prominent respiratory component, bronchiectasis, is responsible for most of the morbidity and, eventually, the mortality. The main cause for this disease is the mutation in Fibrosis Transmembrane Conductance Regulator (CFTR) gene. This gene has a major role in encoding epithelial ion channel which is responsible for transporting the chloride and bicarbonate ions, therefore mutation in this gene will lead to impaired mucus hydration and clearance (8). This disease considers a life-threatening genetic disease that affects epithelial cells and causes a buildup of thick, viscous mucus secretions in various organ systems, most commonly the gastrointestinal, pulmonary, and genitourinary systems (9). Cystic Fibrosis consider a multiple system disease, but in most cases, the disease worsens and mortality increases because of the respiratory manifestations such as bronchiectasis. (8, 10). This article aims to provide a brief introduction and the clinical picture of the disease, Etiology, Pathophysiology, Epidemiology, Nutrition, Prevention, and good practice management advice.

Epidemiology

Cystic fibrosis affects around 30,000 people in the United States and more than 80,000 people worldwide. The incidence rate of this disease is 1 out of 3,500 births per year in the white population in the United States (3). While the incidence rate of the person becoming a carrier is 1:25 in the Caucasian population, the incidence of the disease is 1:2,500 (1).

Pathophysiology

Pathophysiology of Cystic Disease starts with the mutation in Fibrosis Transmembrane Conductance Regulator (CFTR) gene (11). Mainly this gene controls the encoding epithelial ion channel which is responsible for transport and movement of the chloride and bicarbonate ions across the epithelial cell membrane (11-13). When the mutation occurs in one or multiple copies of this gene, the ion transport across the epithelial cell membrane will be affected and defective (13, 14). Consequently, a thick mucus membrane will build up throughout the body cavities, leading to respiratory insufficiency with other fetal systemic obstructions and abnormalities (15, 16). Also, the combination of altered ions transportation, accumulation of mucus, and decreased mucociliary clearance will permit organism colonization especially bacteria (17). The most common Bacteria which colonize include Pseudomonas, Haemophilus influenza, and staphylococcus aureus. Less common bacteria which colonize include Burkholderia, Stenotrophomonas, Achromobacter, Pandorea, and Ralstonia (17-25). Mainly these organisms will affect the respiratory tract and will cause severe repetitive inflammation. Consequently, Repetitive inflammation and chronic infection by these organisms will lead to respiratory destruction (26, 27).

Diagnosis

Most cases of cystic fibrosis are diagnosed during early infancy (4).

1. Sweat Testing Technique

The loss of Fibrosis Transmembrane Conductance Regulator (CFTR) gene function in Cystic Fibrosis patients will lead to elevating the levels of sodium and chloride in the sweat gland secretions because of poor reabsorption of these electrolytes in the ducts of glands. The sweat test technique is the analysis of electrolyte concentration in the content of sweat because chloride is more dependent on CFTR function and sodium flux can be mediated by CFTR independent pathway. But, sweat chloride is the main ion analyzed. Some institutions measure sodium to evaluate quality control. Also, the large discrepancy between sodium and chloride may give the alarm that there is a measurement error. Unaffected individuals have a sweat chloride less than 40 mmol/L. Values between 40 to 59 mmol/L are considered indeterminate and need further evaluation. This measurement should be obtained after 48 hours because sweat electrolytes rise over the first 24 hours of the infant's life. Sweat chloride levels rise over days after birth. The normal maximum limit of the level of chloride sweat in infants aged less than 3 months is 30 mmol/L. Finally, the patient is diagnosed with Cystic Fibrosis if the sweat chloride level is higher than 60 mmol/L (6, 7).

2. Newborn screening

Cystic Fibrosis newborn screening (NBS) started in Colorado (1982) then continued in Wisconsin (1985) (28). In (2003), The Centers for Disease Control and Prevention convened a workshop devoted to reviewing the outcomes of Cystic Fibrosis newborn screening and the potential benefits and risks. The final results of this workshop were that Cystic Fibrosis newborn screening is justified and the potential benefits outweigh the risks. Nowadays, several states in the United States have started performing this screening of newborn neonates, and in the future, all states in the United States will have this screening test (7).

Gene Expression

Cystic fibrosis is the result of a mutant gene located on chromosome 7 (29, 30). Cystic fibrosis is caused by mutations in the transmembrane conductance regulator (CFTR) gene (31, 32). Cystic Fibrosis transmembrane conductance regulator (CFTR) is located in the membranes of most of the cell lines and is responsible for chloride ion conduction. In addition, CFTR influences the expression of several other gene products (33). More than 2,000 different CFTR mutations have been reported (12), but there are six common classes of mutation and the most common one is class 2 mutation which is a protein processing abnormality and it includes F508del which accounts for 70% of all mutations (34).

Nutrition

Cystic fibrosis is the most common association with energy deficiency in children and adults. Chronic malnutrition will lead to failure to thrive, wasting, and stunting of linear growth. Nutrition and survival are strongly related to cystic fibrosis. Cystic Fibrosis can be considered as an energy imbalance. The most common specific nutrient deficiencies in Cystic Fibrosis are the deficiency in fat-soluble vitamins such as vitamin A, Vitamin D, Vitamin E, and Vitamin K. Recent studies highlight the problems with bone density and prevalence of fat-soluble vitamins deficiency. Management of problems related to nutrition can be complex (35-38).

Management

1 Bronchodilator

Cochrane Review 2005 guidelines recommended the use of both short-acting and long-acting b2-adrenergic receptor agonists because they provide better outcomes, such as decreased exacerbations or increase the quality of life (QOL) (39).

2 Mucolytic Agents

Nowadays, there are two drugs given through aerosol that have been used to treat abnormal pulmonary secretions in Cystic Fibrosis patients such as N-acetylcysteine and dornase alfa. Both drugs have the same mechanism of action which is to act by disrupting the disulfide bonds in mucus (NAC) or enzymatically breaking down DNA (dornase alfa) in airway secretions (40).

3 Anti-Infectives

3.1 Azithromycin can be used in individuals with persistent Pseudomonas aeruginosa in airway cultures. Cochrane Review 2005 guidelines highlight the efficacy for improving lung function and reducing exacerbations (41).

3.2 Inhaled Aztreonam attacks Pseudomonas aeruginosa which is the most common pathogen that affects the respiratory tract inpatient with Cystic Fibrosis. It is used to improve FEV1 by (6.3 – 10.3) percentage. The dose of inhaled aztreonam ranges from 75 mg up to 225 mg, administered three times daily for 28 days (42, 43).

4 Steroids

Steroids can be given to patients with bronchial hyperreactivity which is a common feature of cystic fibrosis. Patients with intermittent or persistent wheezing have little or no response to inhaled ipratropium bromide, disodium cromoglycate, or inhaled steroids. Some patients respond to bronchodilators alone, but if not, then oral steroids are effective. The suggestion is that prednisolone given on alternate days may help lung function in mildly affected patients (44, 45).

5 CFTR modulators

Utilization of CFTR modulator therapies such as Ivacaftor by a dose of 50-75 mg given twice daily, have been shown to be safe in children 2-5 years of age with CFTR gating mutations. After using Ivacaftor the sweat chloride concentration decreased by a mean of 47 mmol/L and weight, height, and body mass index improved during treatment. After 24 weeks of treatment, the FEV1 increased by (5.5) percentage points and body weight increased by 3.3 kg (46, 47).

6 Lung Transplant

Lung disease is considered a primary cause of death in cystic fibrosis disease; in around 80% of patients (1, 10). Around 14% of all lung transplants are for patients with Cystic Fibrosis. A lung transplant may be under consideration if the Forced Expiratory Volume (FEVI) falls below 30% and the function becomes limited. Some important points should be mentioned before preparation and assessment of patients for transplantation, such as (Optimal Nutrition, Body Mass Index [BMI] less than 17, bone density, control of extrapulmonary manifestations such as Diabetes and liver, and the psychological status because it may affect the adherence to therapy). Additionally, Post-transplant management is very complex and needs good communication between the patient and the transplant center. Also, patient adherence to their immunosuppressant medications is one of the major complications of lung transplantation (10, 48-50).

7 Novel Therapy

Gene Therapy for selective gene mutation has become one of the options that can treat patients who suffer from Cystic Fibrosis, Furthermore, this type of treatment is designed to treat lung disease only (29). Also, new small-molecule agents that aim to facilitate defective CFTR function of processing have now been developed. Ivacaftor is a new agent that has recently been investigated in patients carrying the G551D mutation (6% of all CF patients) (51).

Monitoring

Monitoring of bacterial pathogens should be done regularly (monthly) through throat swabs or specimens of sputum to detect the right antibiotic treatment. A routine following with a health care unit every 1.5 to 3 months is recommended to detect any prognosis and check the medication compliance. Additionally the monitoring includes weight, height, and lung function (including chest radiograph every 6 months). An abdominal ultrasound

development of the condition, such as enlargement in the spleen and gallstone. Finally, it is important to educate and counsel the patient and their family on how to manage the disease (52-54).

Multisystem Co-morbidities

1 Endocrine, and bone mineral.
Cystic fibrosis has a strong relation with reduced bone mineral density (BMD) and an increased incidence rate of fracture (55). The most common endocrine disorder in Cystic Fibrosis patients is Cystic Fibrosis related diabetes (CFRD) (56).

2 Gastrointestinal Health/Nutrition
It is a very important component of Cystic Fibrosis patients' care to achieve an optimal nutritional status and reduce gastrointestinal morbidity. There are specific nutritional parameters that can help in continuing to improve growth in the Cystic Fibrosis population. Also, early diagnosis in pancreatic insufficient patients may lead to increase in adult height and magnitude of growth in a person in a long-term follow-up (57).

3 Thrombosis
Thrombosis is considered a major complication in patients with Cystic Fibrosis. This thrombosis may be for a short duration (weeks) or long duration (years) (58).

4 Mental Health
Depression and anxiety are consider some of the most common important targets of Cystic Fibrosis because research demonstrates that there is a high increased prevalence of Cystic Fibrosis compared to the general population and this can adversely affect other health outcomes (59).

Prevention

1 Mucolytic Agents
Chronic endobronchial sepsis and profuse airway have strong relation with Cystic Fibrosis, So, mucolytic agents are considered one of the good option treatments for Cystic Fibrosis patients. Mucolytic treatment helps in reducing the acute exacerbations. The evidence related to the usage of these drugs is still limited and needs further investigation (60).

2 N-Acetylcysteine
In 1999, a Systematic review article highlighted the use of inhaled N-acetylcysteine as treatment of Cystic Fibrosis, but the finding shows there is no benefit on lung function in short-term and long-term trials. Also, no evidence shows the efficacy in reducing the severity of respiratory exacerbations or the number of episodes in patients who have Cystic Fibrosis (61).

3 Hypertonic saline
Usage of Inhaled hypertonic saline has been shown to increase mucociliary clearance and produce improvements in lung function in people with Cystic Fibrosis in short-term trials (62).

Special Cases

1 Pregnancy
In Cystic Fibrosis, the percentage of premature birth is common, especially in reduced lung function, low body mass index, Cystic Fibrosis-related diabetes, chronic microbial colonization, and transplanted lungs. In this case, the optimization of treatment is recommended during pregnancy planning (63-65).

2 Children
Cystic fibrosis used to be considered a fatal disease of childhood. With improved treatments and better ways to manage the disease, many people with cystic fibrosis now live well into adulthood. Adults with cystic fibrosis experience health problems affecting the respiratory, digestive, and reproductive systems. Also, there are related GIT disturbances in infants with CF dysfunction (66, 67).

Conclusion

As we mentioned before Cystic Fibrosis is considered one of the most common autosomal recessive diseases that is associated with a decrease in the length of age in the Caucasian population and also, it is considered one of the most common life-shortening diseases in the white population in the United States. But, nowadays, the improving state of Cystic Fibrosis has became predominant and the outlook is bright thanks to novel small molecule pharmacological treatments.

DEFINITIONS, ACRONYMS, ABBREVIATIONS
CFTR: Fibrosis Transmembrane Conductance Regulator

Authors' Contributions
'H. Karrar' supervised the team and direct the research. 'M. Nouh' wrote the nutrition, epidemiology, complication, and Conclusion paragraph. 'A. Alanzi' Wrote the Special Cases paragraphs. 'S. Alharbi' and 'R. Alhendi' will revise the article. 'F. Almutairi Wrote the diagnosis paragraph. 'H. Alhammad' Wrote the Monitoring paragraph. 'A. Sadeeg' Wrote the Special Cases paragraph. 'M. Alsheikh' Wrote the Introduction paragraph. 'W. Alshaikh' Wrote the Gene Expression paragraph. 'M. Alyahya' Wrote the Pathophysiology paragraph. 'W. Makki' Wrote the Treatment paragraph. 'H. Alhazmi' Wrote the Prevention paragraph. 'A. Almutairi Wrote the Gene Expression paragraph. The authors had full access to the data and take full responsibility for the integrity of the data. All the authors gave their approval for the submission of the final manuscript.

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