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A Mini Review on Clinical Aspects of Cystic Fibrosis

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Abstract

Cystic fibrosis (CF) is a multisystem disorder among children, caused by mutations of the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR). In the present article, a comprehensive literature review is performed on, the clinical and genetic characteristics of cystic fibrosis in children. Classical cystic fibrosis is characterized by chronic pulmonary infection and inflammation, pancreatic exocrine insufficiency, male infertility, and might include several comorbidities such as cystic fibrosis-related diabetes or cystic fibrosis liver disease. This autosomal recessive disease is diagnosed in many regions following the newborn screening, whereas in other regions, diagnosis is based on a group of recognized multiorgan clinical manifestations, raised sweat chloride concentrations, or CFTR mutations. Management strategies, including augmenting mucociliary clearance and aggressively treating infections, have gradually improved life expectancy for people with cystic fibrosis. However, restoration of CFTR function via new small molecule modulator drugs is transforming the disease for many patients. Clinical trial pipelines are actively exploring many other approaches, which will be increasingly needed as survival improves and as the population of adults with cystic fibrosis increases. This review provides a general update on CF, including screening and current and future treatment.

Key words: Cystic fibrosis, chronic lung disease, CFTR, clinical feature, *P. aeruginosa*

1. Introduction

Cystic fibrosis is an autosomal recessive inherited disease affecting multiple body systems. Recorded observations of children with this disease from the 1940–50s resulted on pancreatic, damage leading to severe malabsorption, wasting, and childhood mortality [1]. Children were noted to be at risk of lung infections, although the pathogenic links between

these disparate disease processes were unclear A heatwave in 1948 in New York, NY, USA, which resulted in many children with cystic fibrosis developing severe hyponatremic dehydration, led to the discovery of salt loss through sweat and the development of diagnostic testing via sweat sodium and chloride testing[2].Since 1989, the discovery of the CFTR gene that causes cystic fibrosis has underpinned substantial increases in the understanding of pathophysiology[3]. Over time, cystic fibrosis has become a model for the harmonization of research development and clinical advances, wherein scientific progress in pathophysiology and cellular biology has led to therapeutic advances directly linked with major improvements in patient care and survival. Such examples are nutritional supplementation including pancreatic enzyme supplementation, airway clearance, and long-term antimicrobial treatment for the suppression of airway infection [1, 4-6]. The development of small molecules to improve CFTR protein function, termed CFTR modulators, has substantially benefitted people with cystic fibrosis. The resultant changing epidemiology of cystic fibrosis creates new challenges, which might require different approaches to health-care delivery. In the present article, a comprehensive literature review is performed on, the clinical and genetic characteristics of cystic fibrosis.

2. Clinical features of cystic fibrosis

CF is caused by dysfunctional transport of chloride and/or other ions (such as sodium and bicarbonate) that leads to generation of thick, viscous secretions (such as mucus) in the lungs, pancreas, liver, intestine, and reproductive tract and increased salt content in sweat gland secretions. Ultimately, progressive lung disease is the main cause of CF complications and patient mortality. The course of disease varies greatly and can begin from a few months after birth to decades after birth, with many patients exhibiting mild or atypical symptoms. Therefore, clinicians should take care to avoid excluding CF as a possible diagnosis in cases where patients exhibit only a few typical CF signs and symptoms [7, 8].

2.1 Respiratory tract involvement

Typical respiratory manifestations of CF include a persistent productive cough, hyperinflation of lung fields on chest radiograph, and pulmonary function test findings indicative of obstructive airway disease. As the disease progresses, repeated infections associated with inflammatory cell accumulation and release of cell contents damage bronchial walls, leading to loss of bronchial cartilaginous support and muscle tone and eventual bronchiectasis. Disease progression includes acute exacerbations of cough, tachypnea, dyspnea, increased sputum production, malaise, anorexia, and weight loss. These acute events are associated with acute, transient loss of lung function that improves with treatment but that often progresses to permanent loss of lung function over time. Although CF patients often vary, transient airway infection with pathogenic bacteria often first occurs early in life. After years of CF disease, chronic airway infection with either *Staphylococcus aureus* or *Pseudomonas aeruginosa* often becomes established and is often detected based on

radiographic evidence of bronchiectasis. In addition, airways of CF patients can be colonized or infected by other species of microbes, including *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Burkholderia cepacia* complex, nontuberculous mycobacteria (especially *Mycobacterium avium* complex and *Mycobacterium abscessus*), and the filamentous fungus *Aspergillus fumigatus* [7]. Continuous airway colonization and infection by bacteria (especially *Pseudomonas aeruginosa*) can enhance the inflammatory response by triggering neutrophils to release large amounts of DNA and matrix proteins into airways. These substances, coupled with CF-induced impaired airway clearance functions and chronic inflammation, increase airway mucus viscosity. Current research efforts are underway to identify additional bacterial species in CF patient airways, including obligate anaerobes that may be identified using next-generation sequencing technology [8, 9].

2.2. Sinus disease

The majority of CF patients develop sinus disease [10]. Sinus disease can present with chronic nasal congestion, headaches, cough caused by chronic postnasal drip, and sleep disturbances. Sinus infections can trigger lower respiratory exacerbations in some patients, although organisms found in sinuses do not always match those recovered from lungs. Meanwhile, some individuals with isolated chronic rhinosinusitis have signs and symptoms suggestive of CFTR dysfunction that do not satisfy CF diagnostic criteria, prompting clinicians to refer to this affliction as CFTR-related disorder. Notably, in one case control study, the single CFTR mutation rate for a group of chronic rhinosinusitis cases was significantly higher than the corresponding rate for the general population (7% versus 2%) [11]. The other clinical features of cystic fibrosis are consisting, digestive system diseases, reproductive system diseases and nutrition and growth disorders.

3. Diagnosis of cystic fibrosis

3.1. Clinical diagnosis

Updates to diagnostic consensus guidelines were published in 2017 by the Cystic Fibrosis Foundation in collaboration with global partners [12–15]. In regions without newborn screening programmers, diagnostic criteria are suggestive clinical features, or family history and evidence of CFTR dysfunction, or family history and detection of two disease causing *CFTR* mutations [14].

Genotypes of varying clinical consequence require a diagnostic sweat chloride or advanced electrophysiological testing for a firm cystic fibrosis diagnosis. Sweat testing, done in an accredited clinical laboratory, remains the gold standard test of CFTR function: chloride concentrations of more than 60 mmol/L are diagnostic; concentrations between 30–59 mmol/L are in the intermediate range; and concentrations less than 30 mmol/L are considered normal [16].

3.2. Newborn screening

Several newborn screening strategies are in use, most of which use an initial biochemical screen (commonly immunoreactive trypsinogen measurement from dried blood spot) followed by genetic testing or sweat chloride testing, or both. The selection of CFTR mutations included in newborn screening panels is based on local population prevalence, in general, seeking to detect as many patients with cystic fibrosis as possible while trying to minimize false positives. Benefits of newborn screening for people with cystic fibrosis and their families have been numerous, with positive effects to both physical and psychological health [17]. Future health benefits from highly effective CFTR modulator therapies might prove synergistic with newborn screening, as new animal uterine studies and postnatal therapy show disease attenuation [17, 18].

4. Treatment

Treatment regimens for CF should be evaluated, improved, and administered in combination with close monitoring to achieve early, active intervention to manage CF. In order to achieve these goals, prospective CF patients should be hospitalized until additional test results and other findings are obtained to support or exclude a CF diagnosis. Once a CF diagnosis has been made, clinicians should immediate initiate patient treatment and educate patients and their families to effectively manage the disease.

Treatment for CF lung disease includes administration of mucus thinner, airway clearance, and antibiotics. To thin mucus, inhalation therapy consisting of hypertonic saline is administered to hydrate thick mucus within CE patient airways. The high osmotic pressure of the solution draws water out of airway epithelial cells to reconstruct the water-containing surface layer that is absent in CF patients. To address retention of purulent secretions in CF patients that obstruct airflow and damage airways, chest physiotherapy based on postural drainage and percussion is the standard method for clearing secretions, with bronchoscopy lavage also used for this purpose. Although antibiotics are essential for treatment of chronic infections and acute CF exacerbations, long-term oral antibiotics are generally not recommended for controlling infection. However, long-term azithromycin use is recommended for many CF patients, due to its anti-inflammatory and/or antibacterial properties, while long-term treatments with aerosolized antibiotics against *P. aeruginosa* (eg tobramycin and aztreonam) are recommended due to their beneficial effects on lung function [19].

Notably, the main CF airway pathological feature is severe neutrophil inflammation. In past years, inflammation was considered necessary for preventing spread of infection, but accumulating evidence suggests that excessive inflammation is generally harmful. Thus, in clinical practice, azithromycin is recommended for all CF patients older than 6 years of age with clinical evidence of airway inflammation (such as chronic cough) or any decrease in

FEV1, regardless of the status of *P. aeruginosa* infection. To further support CF patient growth and nutrition, patient diets should be supplemented with pancreatic enzymes, calories, and fat-soluble vitamins [19].

To further support CF patient growth and nutrition, patient diets should be supplemented with pancreatic enzymes, calories, and fat-soluble vitamins. At present, several new types of drugs are under development, of which some are well-tolerated by patients, including drugs to restore normal function of defective CFTR protein and drugs that have a direct impact on mucociliary clearance. CFTR modulators, such as ivacaftor (Kalydeco), lumacaftor/ivacaftor (Orkambi), tezacaftor/ivacaftor (Symdeko), target different potential CFTR protein defects caused by different gene mutations, thus rendering these drugs effective only for people with specific mutationsn [19-22]. Trikafta (tezacaftor plus elexacaftor and ivacaftor) is the third drug approved by FDA that rescues defects caused by F508del, which is superior to its predecessors. Trikafta is also effective in CF patients with one copy of F508del-CFTR mutation. It demonstrates safety and sustained efficacy for 24 weeks or longer in people with CF and one or more F508del alleles [22].

4.1. Newer therapies and clinical trials pipelines

Until the group of small molecule drugs, now termed CFTR modulators, was developed, all available therapies targeted symptoms and downstream consequences of CFTR dysfunction rather than the root cause itself. The goal of treating disease by restoring CFTR activity was considered to be game changing, but was challenging in the early stages. Two main groups of molecules have been developed: potentiators that improve the function of CFTR at the cell surface, and correctors that aid trafficking of CFTR to the cell surface. In 2020, amplifiers, which increase the amount of CFTR mRNA (and thus protein) within the cell, entered clinical trials [23].

5. Conclusion

Although cystic fibrosis is currently incurable and greatly reduces life expectancy, the average CF survival age has increased significantly over the past 50 years and now exceeds 40 years of age. Thus, CF is no longer viewed solely as a childhood disease, but now is recognized as a disease of children and adults. Currently more than half of CF patients are adults as old as 60 years of age, indicating that active treatment can improve prognosis, increase quality of life, and prolong lifespan. Time to diagnosis and treatment, severity of lung disease, nutritional and general conditions, and mental state are key factors that influence prognosis. With regard to pediatric CF patients, attention should be paid to improving awareness and compliance of family members to prevent infection, actively treat acute exacerbations, and comply with recommended care instructions to maximize quality of life and long-term survival.

Conflict of Interest

The authors have no conflict of interest.

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