Review Article

Cystic Fibrosis Diagnosis and Management in Children: A Simple Literature Review

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Abstract

Background: Cystic fibrosis is a chronic inheritable disease presenting in newborns with lifelong complications. It is a common disease worldwide and in developing countries, like Saudi Arabia, a need for proper management is essential for the survival of affected children. **Objective:** The aim of this review was to evaluate the diagnostic and management approach of cystic fibrosis in the pediatric age group. **Methods:** We searched PubMed for (("Cystic Fibrosis"[MeSH]) AND (“Evaluation"[MeSH] OR "Management"[MeSH] OR "Diagnosis"[MeSH])) **Conclusion:** Complications and their prevention should be dutifully explained to parents as it would build their confidence as caretakers. Emphasis on diet and adherence to management plan would support the patient’s lifestyle. Combined treatment of Ivacaftor and lumacaftor helps reduce respiratory complications, hospitalizations, and antibiotic use in CF patients. Correct management of this illness is crucial to the child’s survival and multifactorial, with many afflicted reaching adulthood. Fortunately, there has been an improvement in the management of CF due to CFTR modulators, but most of them are for children older than 12 or 6-12 years of age and have side effects and high costs. The new era of research in this disease focuses on new and better drugs.

Keywords: Cystic Fibrosis, Diagnosis, Management

Introduction

One of the important autosomal recessive disorders is cystic fibrosis (CF), an inheritable mutation in the gene of cystic fibrosis transmembrane conductance regulator (CFTR) protein. The advances in medical research have greatly helped in the management of cystic fibrosis, a complex disease that once linked early death to young children. The current survival rate of cystic fibrosis with adequate management reaches the age of forty. This is not true for all countries, as states in developed countries are struggling with the development of health care. Cystic fibrosis is usually diagnosed early in life, on average at two months of age. This review summarizes trending and existing knowledge on cystic fibrosis, with a highlight on diagnosis and management.

Methodology

PubMed database was used for articles selection, and the following keywords were used in the MeSH: (("Cystic Fibrosis"[MeSH]) AND (“Evaluation"[MeSH] OR "Management"[MeSH] OR "Diagnosis"[MeSH])). Regarding the inclusion criteria, the articles were selected based on the relevance to the project, which should include one of the following topics; CF evaluation, and CF management and diagnosis. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint, or meta-analysis, systematic reviews, or repeated studies.

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Discussion

CF disease is a systemic and dangerously progressive lung disease that continues to be a major cause of mortality and morbidity for most patients. Over a patient-dependent and highly variable time course ranging from months to decades after birth, patients eventually develop chronic infection of the respiratory tract with a characteristic array of bacterial flora that leads to respiratory insufficiency and inevitable failure [1]. The physical and chemical abnormalities of these airway secretions result in chronic infection with phenotypically unique bacteria, particularly Pseudomonas species, with many patients requiring lung transplants [2, 3]. Other genetic factors including polymorphisms of the tumor necrosis alpha (TNF-a) gene, may increase susceptibility to P. aeruginosa infection and contribute to the clinical manifestations of CF. Primary abnormalities in fatty acid metabolism have increased tissue expression of arachidonic acid with its metabolites leading to the inflammation indicative of CF. Cystic fibrosis is common in many countries worldwide, including developed and developing countries. CFTR genetic mutations in Arabian populations is comparable to that of other races [4]. Studies have speculated the high consanguineous rate in Saudis with CF genetic mutations [5]. A retrospective study in Saudi Arabia, identified high hematocrit, low mean corpuscular volume, low mean corpuscular hemoglobin concentration, and low albumin as factors related to mortality in CF, and recommended iron supplementation even in the presence of a normal serum hemoglobin level. [6].

Pathogenesis

CF patients have abnormal transport of sodium and chloride across secretory epithelia, which results in thickened and viscous secretions in the reproductive system, intestines, pancreas, biliary tract, and bronchi. Cystic fibrosis is caused by mutations in a single large gene on chromosome 7 that encodes the CFTR protein. Moreover, to develop the full clinical picture of the diseases, mutations in both copies of the CFTR gene are required, hence the autosomal recessive pattern of inheritance. The function of this gene is as a regulator for chloride channel, and thus the activity of chloride and sodium channels at the cell surface. There are multiple ways for the mutations to occur, and they are divided by five classes (from I to V - ranging from defective protein production and protein processing to the decreased amount of functional CFTR). Additionally, some patients have gene modifiers exacerbating the severity and/or clinical manifestations of the disease. The main ones are transforming growth factor-beta (TGF-beta) and Mannose-binding lectin and approximately 20 percent of CF patients carry these variants [7].

Diagnosis

The diagnosis of CF is based upon compatible clinical findings with a biochemical or genetic confirmation. The sweat chloride test is the mainstay of laboratory confirmation, although tests for pancreatic enzyme secretion, stool fecal fat, immunoreactive trypsinogen, nasal potential difference, or specific mutations may also be useful in some cases. Overall, diagnosis is based on criteria, which imply the presence of clinical signs consistent with CF in at least one organ system plus evidence CFTR dysfunction (any elevated sweat chloride ≥60 mmol/L on 2 occasions, or the presences of 2 disease-causing mutations in CFTR, one from each parental allele, or abnormal nasal potential difference). However, this criterion is not required for newborns identified through a screening program or for siblings of patients with CF who are diagnosed by shared genotype [8]. A recent review of CF screening showed that 29 mmol/L could be the upper limit of normal, with 30-59 mmol/L suspicious of CF and require further investigation and follow-up [9].

Management Approach

When a child is diagnosed with CF, support and information should be directed towards the parents and caretakers. It would be in their favor to establish confidence in the medical team and themselves at the beginning while having supple information on taking care of their child at home. Explaining the disease, how it progresses, management routine and emergencies, and common complications with their signs all can educate the caretakers and help them stand on their feet [10]. The main aim of treatment should be to control the symptoms of the disease and prevent any further complications. CF patients require greater care when it comes to protecting their bodies from infections. Avid control of airway inflammation is achieved by NSAIDs, inhaled steroids, and cromolyn [11]. Their family and caretakers need to be aware of infection control measures early on, and this can be in the form of antibiotics including tobramycin inhaled powder and others, as to prevent unnecessary discomfort and complications to their dependants [12, 13]. The lungs in CF are viscous and filled to the brim with mucus secretions, and it is, therefore, optimal to reduce this viscosity and dilate the airways with humidified oxygen and beta-agonists while adding hypertonic saline and dornase alfa to the therapeutic mixture [14, 15]. Additionally, physiotherapy and including positive expiratory pressure (PEP) device or a high-frequency chest wall oscillation device (a percussion vest) is helpful [16].

- #### Complication Management

Complications are common in cystic fibrosis and may present as the diagnostic feature. CF newborns may suffer from meconium ileus as they develop other complications such as upper airway disease, osteoporosis, and muscle pain. CF children are often underdeveloped and malnourished with vitamin deficiencies (fat-soluble i.e. vitamins A, D, E, and K). A study in Bahrain showed that most CF patients suffer from malnourishment and that gastroesophageal reflux and low weight were risk factors for this problem [24]. When they reach adulthood, they may suffer from chronic liver disease and diabetes. Fertility is nonexistent in males and only reduced in female patients. It is common for CF patients to develop renal stones and joint pain [10]. Low water content in secretions from the respiratory, pancreatic, and biliary epithelium causes respiratory secretions to be of viscous nature. Being difficult

to clear, they would cause chronic airway obstruction and reduce bactericidal ability, developing into progressive pulmonary colonization with pathogens and formation of bacterial biofilms. Chronic infection causes an inflammatory response and tissue destruction, causing bronchiectasis. Abnormal bile and pancreatic secretions cause maldigestion and malabsorption, progressive liver and pancreatic disease, rectal prolapse, and intestinal obstruction (distal intestinal obstruction syndrome or intussusception) as aforementioned.

Lifestyle is greatly altered by disease, but actively advocating proper exercise to the patients motivates them to better lives. The participation of cystic fibrosis-affected individuals in daily exercise would benefit them with improved breathing, ease of muscle function, and decreased bone loss from non-use [10]. Although recent research has not shown significant improvement in the quality of life or forced expiratory volume, this should not discourage patients from being active [17]. Moreover, CF-affected children have lower exercise capacity than healthy children [18]. One randomized control trial in Canada has recommended the use of positive expiratory pressure devices or high-frequency chest wall oscillation devices [16]. Gastrointestinal symptoms often complicate CF disease and should be addressed early on. Oral rehydration, combined with osmotic laxatives and or enemas are utilized in the treatment and cautionary prevention of associated intestinal obstructions. Although prophylactic therapy is commonly used, it is not evidence-based [19]. Pancreatic enzyme replacement therapy contains a cocktail of proteases, lipases, and amylases that are helpful in managing the pancreatic insufficiency [20].

- ### Recent Advances

The main mechanism that stands behind CF development is the structural and functional abnormalities of CFTR protein. As a result, recent studies are focusing on solving this point. Ivacaftor, which is a recent drug used in the management of CF improves respiratory function with unprecedented alleviation of breathing symptoms, lowered rate of exacerbations, and decreased sweat chloride [20]. It works by increasing the time of channel in open state. However, it works only on G551D mutation patients, which represent 2.3% of CF patients. Fortunately, lumacaftor has shown desirable results in class II mutation, which is the most common mutation in CF patients. Lumacaftor acts on the dysfunctional processing of proteins by increasing the transport of protein to the cell surface. However, no correction of the underlying functional impairment and no significant improvement in FEV1, CFQR scores, and respiratory exacerbation rates were observed [21]. Adjunct therapy with Ivacaftor has been studied in combination with lumacaftor (Orkambi) and showed promising results in homozygous class II mutation patients older than 12 years. There was a 30-39% decrease in pulmonary complications along with better FEV1, decreased exacerbations and hospitalizations, and increased BMI and CFQR scores compared to a placebo [22,23].

Conclusion

The appropriate management of this illness is crucial to the child's survival and multifactorial, with many patients reaching the midst of adulthood. Combination treatments reducing complications and exacerbations associated with dietary and lifestyle modifications should result in improved healthcare for CF patients and the comfort of their caretakers. Fortunately, there is an improvement in the management of CF due to the CFTR modulators, but most of them are for older children either >12 or 6-12 years of age and they risk their own side effects along with the high cost. The new era of research in this disease focuses on new and better drugs. The social burden of disease on the caretakers and patients should be investigated in an effort to lighten the psychological and monetary load. Furthermore, novel gene engineering methods and molecular targeting are being explored as new therapeutic techniques that may yet to be unraveled.

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