Chapter

Introductory Chapter: Basics of Cystic Fibrosis

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1. Introduction

"Woe to the child who tastes salty from a kiss on the brow, for he is cursed and soon must die," describes European folklore and medical texts of middle ages a condition then unknown. It took several centuries for this condition to get its formal name from an American Pathologist Dr. Dorothy Anderson- cystic fibrosis [1]. While conducting an autopsy of a child apparently died of Celiac disease, she found '*cystic fibrosis of the pancreas*' and her later research for over a decade defined the characteristics of the disease that involved pancreas, lungs and intestine [2]. Dr. Paul di Sant'Agnese in 1948 New York heatwave noticed a higher concentration of salt in the sweat of dehydrated children leading to the first, most reliable and yet ubiquitously used 'sweat test' for the CF [3]. Dr. Anderson recognized that the disease is autosomal recessive, however, after half a century in 1989 Lap-Chee Tsui in Canada discovered a gene called CFTR (CF transmembrane conductance regulator), a mutation of which was responsible to cause CF [4]. Unfortunately, it was not the Holy Grail in the management of the CF as another 2000 variants of the gene mutation were found later on.

Even until the early part of the last century children affected with CF died of malnutrition. Discovery of pancreatic enzyme supplements and introduction of high-fat diet improved nutrition in CF children with many reaching to adulthood shifting the challenge to the pulmonary disease of CF. As more patients were diagnosed with the condition, a lot of organizations were founded in the western world to educate, support and treat CF. In 1965, the Royal Brompton hospital in London was the first in Europe, probably in the world to offer adult CF service [5]. Lack of knowledge and modern medicine in that era led to therapies like 'mist tent' where humidified air was delivered to liquefy mucus and 'upside-down postural drainage' to hasten expectorations. Over the decades, the discovery of various bugs affecting airways of CF patients and newer and more effective antibiotics to cull the bugs along with effective ways to deliver them including systematic inhalation saved many lives. The biggest breakthrough in the treatment of CF arrived at the beginning of the current century when gene therapy directed at fixing the defect in the gene was successfully implemented [6, 7]. Early detection and management with a well-organized nutrition plan, improved airway clearance, targeted, combination and tailored antibiotic therapy along with ever-developing gene therapy should significantly improve survival in the CF patients.

2. Pathophysiology of cystic fibrosis

In the past, CF was called as 'mucoviscidosis' and the term quite aptly underlines the pathophysiology of the disease. The CF is an autosomal recessive disorder that

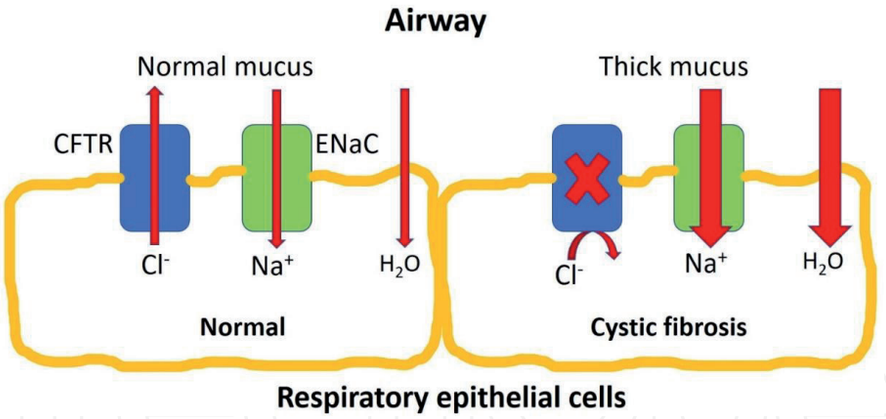

Figure 1.
Pathophysiology of cystic fibrosis.

transpires due to mutation in the CFTR gene on chromosome 7 [8]. The CFTR is an anion channel on the surface of the epithelial cells that regulate cyclic AMP-dependent and ATP energized secretion of chloride ions (Cl-) outside the cell and epithelial sodium channel (ENaC) regulated entry of Sodium ion (Na+) into the cell [9]. Simply put, the mutation in the gene leads to less secretion of chloride ion and inappropriate absorption of the sodium ion into the epithelial cells creating hyperosmolarity inside the cell and dehydration on its surface (**Figure 1**). F508del recognized by the absence of phenylalanine at position 508 in CFTR accounts for about two-thirds of mutations while the rest of the mutations measures less than 5% individually [10]. Manifestations of CF involving various systems in the body are due to this genetic defect causing epithelial surface dehydration related viscid mucus.

3. Clinical picture of cystic fibrosis

In the respiratory tract, abnormally dehydrated and thick mucus impedes normal mucociliary clearance creating a favorable environment for various organisms infect and prosper with colonies. Due to persistent mucus, the airways are colonized with several pathogens which leads to the accumulation of inflammatory mediators and increases inflammation [11]. At early stages of life, the most common bacteria detected in the sputum are *Staphylococcus aureus* and *Hemophilus influenzae*, contrary to this *Pseudomonas aeruginosa* is the most prevalent bacteria during the second and third decade of life [12]. *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, and methicillin-resistant *Staphylococcus aureus* are known to be associated with CF morbidity and mortality [13]. Persistent productive cough, breathlessness, wheeze, to begin with, leads to chronic lung infections, recurrent sinusitis and decreased exercise tolerance. Vicious cycles of infection, inflammation and mucus build-up not only cause multiple pulmonary exacerbations but slowly damage respiratory airways culminating into bronchiectasis. In later stage complications like organized pneumonia, atelectasis, hemoptysis, pneumothorax, pulmonary hypertension, chronic hypoxic and hypercapnic respiratory failure and cor pulmonale may occur [14, 15].

Abdominal manifestations of CF arise early in the course of the disease and have a severe impact on the quality of life of the patients. Dehydrated, concentrated pancreatic juices in CF patients cause a progressive obstruction and acute and chronic inflammation leading to parenchymal injury terminating into pancreatic insufficiency [16]. Clinical symptoms of pancreatic insufficiency include greasy

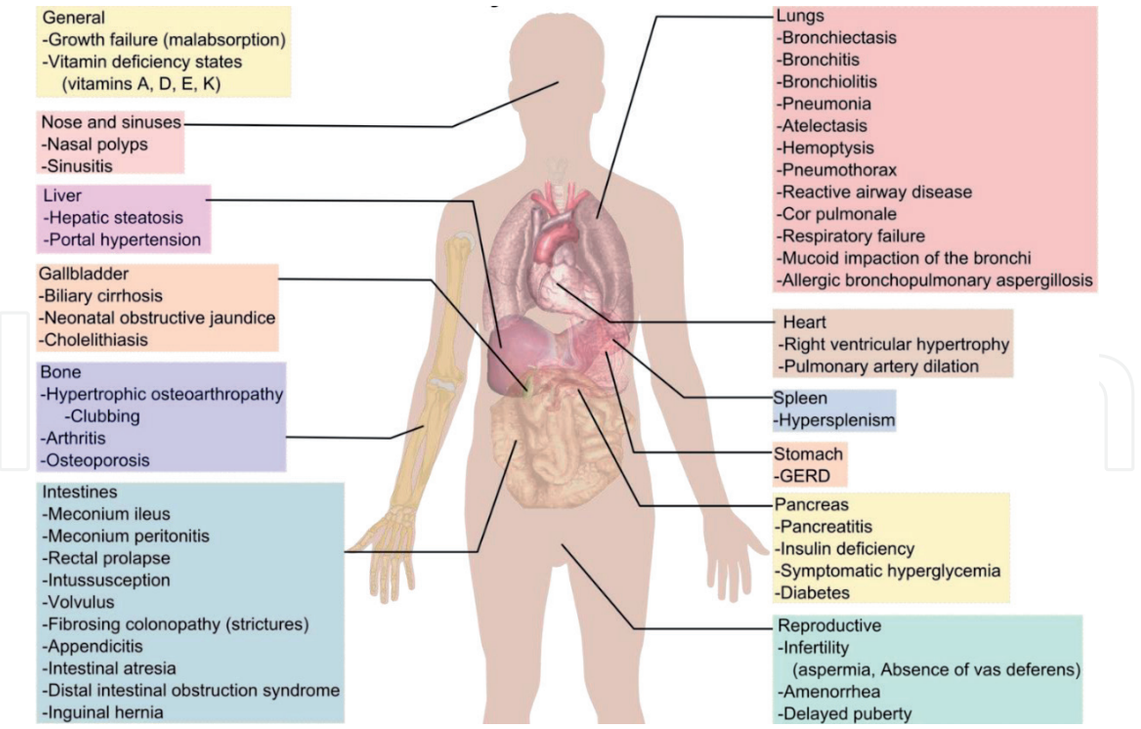

Figure 2.
Clinical presentation of cystic fibrosis (credit wikimedia.org.png).

stools, flatulence, abdominal bloating, and poor weight gain. The CF liver disease is characterized by the hyper-viscous bile causing obstructive cholangitis initially leading to focal biliary fibrosis and subsequently to biliary multinodular cirrhosis and portal hypertension [17]. Gastrointestinal manifestations of CF occur due to pancreatic insufficiency, thickened intestinal secretions, undigested food remnants, poor motility, and fecal stasis with resultant impaction of mucofeculent material in the distal ileum and right colon presented as meconium ileus in the newborn and distal intestinal obstruction syndrome in the post-neonatal life. Manifestations of CF extend beyond respiratory and gastro-intestinal symptoms to practically every system of the body as shown in **Figure 2**. A peculiar manifestation of CF that defies systemic boundaries, however, is CF-related diabetes (CFRD) that involves characteristics of both types of diabetes, that is, decreased secretion of insulin seen in type 1 due to scarring of the pancreas and decreased sensitivity to insulin seen in type 2 [18]. Incidence of CFRD increases with age and symptoms like unexplained weight loss, tiredness, increased thirst and micturition and sometimes decline in lung function can start in some patients in childhood itself. Microvascular complications like diabetic nephropathy, neuropathy and retinopathy are known to happen in untreated patients. Oral glucose tolerance test is a gold standard to detect the condition and should be performed at the age of 10 and yearly thereafter to diagnose and manage it at an early stage [19].

4. Diagnosis of cystic fibrosis

With the advent in diagnostic modalities, the CF is now diagnosed in newborns unlike a few decades ago when symptoms of CF and sometimes life-threatening CF complications prompted diagnostic procedures. However, even today false negative screening tests, migration, mild form of the disease and late presentation lets the condition undiagnosed until in the adulthood. Screening tests to clinch the diagnosis of CF at the earliest stage are offered at various levels. Carrier testing

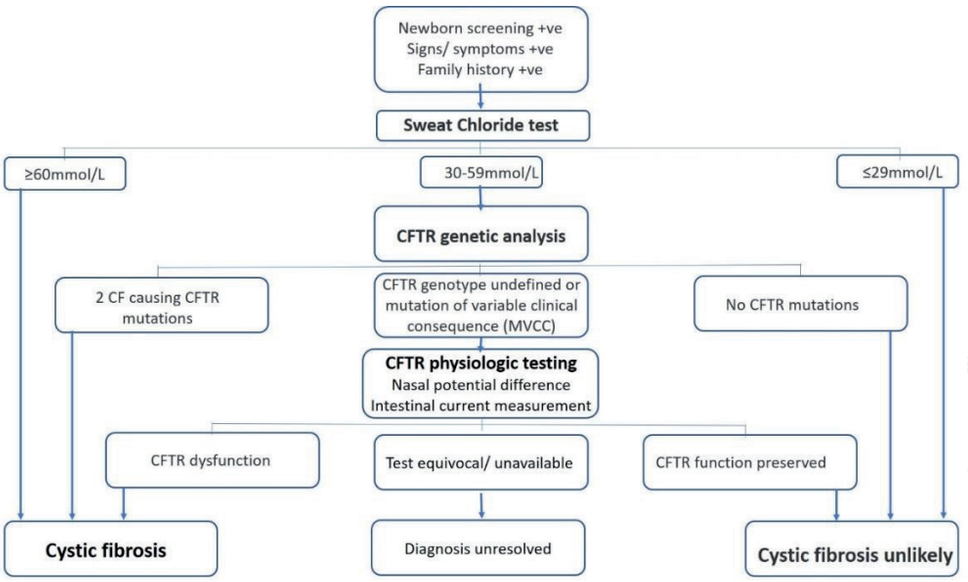

Figure 3.
Diagnosis of cystic fibrosis.

with blood or buccal mucosa analysis for common mutations in the CFTR gene is indicated in people who wants to have children and have a relative affected with the CF. Antenatal testing involves chorionic biopsy or amniocentesis for similar genetic analysis and is offered to when partners are known carriers of the disease. Newborn screening involves testing immunoreactive trypsinogen (IRT) in heel prick blood which is increased in CF due to obstructed pancreatic ductus [20]. Raised IRT mandates sweat test which measures chloride concentration in the sweat that allows categorization of patients into CF, 'CF unlikely' and 'intermediate' as shown in **Figure 3** prompting further evaluation by genetic testing in the intermediate category. In this, patients' blood is checked for the number of copies of CFTR gene affected with most common CF mutations- the inheritance of 2 copies of mutated gene confirms CF, while undefined CFTR genotype or mutation of variable clinical consequence requires CFTR physiologic testing to establish the diagnosis of CF [21]. Nasal potential difference evaluating salt transport in the nasal epithelial cells and intestinal current measurement may further help elucidating the diagnosis of CF in this group of patients [22].

5. Management of cystic fibrosis

Management of CF-related complications varies and is dependent on disease severity and rate of progression and as a result, treatment is highly individualized.

As the progression of lung disease has significant prognostic implications for patients with CF, treatment of lung disease is one of the cornerstones of CF treatment. Airway clearance is a key element of treatment and starts at birth or as soon as the patient is diagnosed. Airway clearance can be assisted by positive expiratory pressure devices and airway high-frequency chest wall oscillation techniques and should be performed daily (more frequently with advancing disease or during exacerbations) [23]. Airway clearance is assisted by treatments aimed at reducing the viscoelasticity of the mucous as thinner secretions are easier to expectorate. These involve nebulized treatment in the form of b-agonists, 3–6% hypertonic saline and dornase alpha as well as adequate levels of hydration [23, 24].

Preventing and controlling lung infections is central to the management of CF. Antibiotic regimes aim to prevent or treat exacerbations and to eradicate newly isolated pathogens. First isolation of gram-negative pathogens such as *Pseudomonas aeruginosa* should be prompt and attempt of eradication. Several eradications protocols including oral (typically ciprofloxacin) and inhaled antibiotics (typically tobramycin or colomycin) are available but details are beyond the scope of this chapter [25]. Prophylactic antibiotics aim to prevent or delay exacerbations, may be oral or inhaled and are used in conjunction with airway clearance techniques. They have been shown to reduce the frequency of exacerbations.

Pulmonary Exacerbations of CF include a combination of clinical symptoms, decline in lung function and oxygenation as well as rise of markers of inflammation. They are treated by a combination of antibiotic treatment, enhanced airway clearance and chest physiotherapy and supportive care as needed which may include oxygen supplementation or nutritional support. More severe exacerbations or exacerbations caused by more virulent and antibiotic-resistant pathogens will require intravenous antibiotics and a longer course of at least two weeks [24].

Haemoptysis and spontaneous pneumothorax are common complications of CF-related lung disease. Haemoptysis is often related to an infective exacerbation and treatment may be controlled with conservative measures such as treating the underlying infection and may require bronchial artery embolization or even lung resection. Repeated episodes of significant haemoptysis not controlled by embolization may be an indication for lung transplantation [26].

Treatment of gastrointestinal manifestations of CF includes treatment of pancreatic insufficiency and management of CF-related diabetes as well as prevention and treatment of intestinal blockage. Pancreatic insufficiency is treated with pancreatic enzyme replacement as well as nutritional support with high-calorie fat diet, vitamin supplementation and sodium chloride supplementation. Intestinal blockage prevention and treatment requires oral hydration, osmotic laxatives and hyperosmolar contrast enemas as needed [27, 28].

CF is a multisystem disease and therefore patients may also require treatment of other organs and systems such as complications from sinuses, urogenital complications as well as metabolic disorders such as reduced bone mineral density.

5.1 CFTR modulators – targeted treatment in CF disease

In recent years targeted therapy in the form of CFTR modulators has revolutionized the treatment of patients with CF. Oral, small molecules were developed that target the CFTR protein and have proven to be clinically successful in correcting the defect of the CFTR protein in vivo [29]. They are extremely efficacious and are transforming the care of patients living with CF - a chronic, progressive, multiorgan disease- in an unprecedented way. A detailed description of CFTR modulators is beyond the scope of this chapter. The first CFTR modulator -ivacaftor- was suitable for a relatively small percentage of patients with CF. There are currently four single or combination therapies available (with more being investigated) and they have revolutionized the management of patients with CF. Numerous CFTR modulators are currently being tested as well as gene engineering techniques aimed directly at the different mutations of the CF gene [30].

5.2 Lung transplantation in patients with CF

CF is a chronic progressive disease. Patients gradually develop structural changes in the lung parenchyma such as bronchiectasis. As the lung disease progresses the

frequency of exacerbation increases as well as the likelihood of complications such as pneumothoraces and haemoptysis both of which are associated with advanced disease. Patients eventually develop respiratory failure. In these cases, lung transplantation presents a definitive treatment. Patients with reduced lung function (expressed as an FEV1 of <30% predicted), increasing frequency of exacerbations and/or increase in symptom burden as well as patients with life-threatening haemoptysis not controlled by embolization or with persistent recurrent pneumothorax should be considered for lung transplantation. Median survival after lung transplantation remains modest (7–8 years), however, it improves the quality of life and prognosis of patients with end-stage lung disease [26].

6. Conclusion

CF is a chronic, progressive, multiorgan disease caused by different mutations of the gene responsible for the CFTR protein. The involvement of lung disease is central in the clinical manifestations of the disease and carries significant prognostic implications for patients with CF. Early diagnosis and aggressive management with airway clearance and antibiotic treatment of lung disease as well as vigorous management of extrapulmonary complications have significantly improved the quality of life and survival of patients with CF. Lung transplantation remains a definitive treatment in patients with end-stage lung disease. However, the management of CF disease has entered an exciting era with CFTR modulators targeting the defective CFTR protein and have revolutionized the management and prognosis of CF.

Future studies are looking at gene engineering to target CFTR gene mutations which will hopefully provide new therapeutic targets.

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