Review Article

The pathological features of cystic fibrosis and the diagnostic techniques and treatments involved

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ABSTRACT

Cystic fibrosis is a disease found predominantly in Caucasians. It is caused by an autosomal recessive mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The mutation(s) lead to defective CFTR proteins, or transmembrane cyclic adenosine monophosphate (cAMP)-dependent chloride channels found on the surface of epithelial cells. The respiratory system is most impacted by this abnormal phenotype, and lung disease can bring about the majority of the various issues that a cystic fibrosis patient has to deal with. Even so, due to the excess amount of mucus that is secreted, individuals diagnosed with cystic fibrosis experience complications in other organs as well. Today, newborn screening is widely used as a means of early diagnosis of cystic fibrosis, and there are also multiple other novel technologies that aim for accurate diagnosis and prevention of the disease. In addition, while traditional treatment programs are based on curing the symptoms that the patients exhibit, new regimens are directed at correcting the error that occurred at the molecular level. With improvements made in the medical field, cystic fibrosis patients are able to live longer and have a better quality of life. This review article serves as a compilation of the current knowledge on the causes of cystic fibrosis, the physiological processes associated with the disease, the techniques for diagnosis of the disease, and finally the recent and upcoming therapeutics for the disease.

KEY WORDS: Cystic Fibrosis; Cystic Fibrosis Transmembrane Conductance Regulator; Cystic Fibrosis Pathology; Cystic Fibrosis Diagnosis; Cystic Fibrosis Treatment

INTRODUCTION

Back in the ancient days, cystic fibrosis was a disease that led to shortened life spans and children who had the disease were said to be cursed. In the 18th century, a poem referred to cystic fibrosis in the child whose brow tastes salty.[1] Only in relatively modern times did scientists begin to understand that the major characteristic of cystic fibrosis is elevated sweat salt concentration[1] – in 1949, Lowe *et al*. suggested that cystic fibrosis is a genetically inherited autosomal recessive disease.[2] Multiple researchers proposed hypotheses regarding the abnormality of the electrolyte transport system from the sweat glands as well as the faulty chloride channels on the surface of the lungs.[2] In the modern day, it is now understood that cystic fibrosis is a metabolic disease with an autosomal recessive pattern of inheritance.[3] The condition is due to a mutation that leads to dysfunctional exocrine glands and reduced chloride ion transport, causing an overall multiorgan disorder, particularly affecting the respiratory and digestive tracts.[4]

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ETIOLOGY

Cystic fibrosis is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which is located on the long arm of chromosome 7.[3] This gene codes for the CFTR protein, which is a transmembrane cAMP-dependent chloride channel located at the respiratory, digestive, reproductive, and sweat epithelium.[2,5] The

protein's main function is to regulate liquid volume on epithelial surfaces through chloride secretion and inhibition of sodium absorption.[6]

There are approximately 2000 types of mutation in the CFTR gene that could cause cystic fibrosis. These mutations are classified into six classes, the first three of which cause severe disease involvement in early childhood, and the latter three of which cause minor severe disease in the same age range.[7] Classes III and IV result in decreased function of the CFTR protein, while the rest of the classes result in a smaller number of the proteins.[8] Defects in the transport protein result in dehydrated mucus, impaired mucus clearance, and mucus adhesion to airway surfaces.[9]

EPIDEMIOLOGY

With modern diagnostic criteria and treatment methods, the epidemiology of cystic fibrosis has improved over the years.[8] Cystic fibrosis occurs most frequently in Caucasians and is rarely found in individuals of other races.[5] The incidence rate ranges from roughly one in 3500 births in North Americans and Northern Europeans[2] to one in 1400 in persons of Irish descent.[10] In Latin Americans, the rate is only one in 4000–10,000, and in African Americans, it is one in 15,000–20,000. The incidence rate is even smaller in people of Asian background.[11]

Many countries have reported that over one-half of their cystic fibrosis population is over the age of 18, meaning that the age of the patient population has increased.[8] Furthermore, the overall median age of survival is increasing, whether in patients who were diagnosed before or after the age of 15, patients with mild or serious symptoms, and patients with or without lung disease or other complications.[8] Newborn screening is also being applied for use throughout the world, supporting early diagnosis of the disease, and improved molecular genetic diagnostics has allowed for better identification of patients who exhibit non-classical presentations of cystic fibrosis as well.[12] As the chances of survival are increasing with better technology, some data suggest that the prevalence of cystic fibrosis could be increasing even though the incidence rate is at a decline.[8]

PATHOGENESIS

Each of the six categories of mutations involves different cellular mechanisms that lead to the disease phenotype of cystic fibrosis at varying severities.[8]

1. Class I is caused by large deletions, nonsense, frame shift, or splice site mutation that lead to a premature stop codon in the mRNA.[13,14] This eventually brings about the translation and formation of a shortened protein that degrades rapidly, and the outcome is that the functional CFTR protein is absent from the apical cell membrane. This type of mutation is usually associated with severe cases.[14]
2. Class II results from an issue in the processing of the CFTR protein after it has been translated.[2] During wild-type CFTR translation, the products are normally inserted into the endoplasmic reticulum to be glycosylated with two sugar groups.[1] However, due to the mutation, the protein does not mature into the glycosylated form.[14] Since the processing step is very important for the proper intracellular transit of the protein, the partially functioning protein is unable to be transported to the correct location, and only a small amount of the protein reaches the apical membrane.[2,14]
3. Class III is characterized by a normal, functioning CFTR protein that is present at the apical membrane. The opening time of the channel protein, however, is significantly reduced due to the decreased protein activity in response to intracellular signaling.[2,14] The reasoning behind this is that the mutation interferes with the binding and hydrolysis of adenosine triphosphate (ATP) at the nucleotide-binding domains on the channel protein.[1]
4. Class IV indicates a complication in the conductivity of the channel protein.[14] There is a decline in the rate at which chloride ions flow through the channel as well as the duration of channel activation after stimulation.[2] This mutation is associated with pancreatic insufficiency and milder phenotypes.[14]
5. Class V is identified by an abnormal splicing or ineffective transport of the protein, lessening the synthesis of fully active CFTR proteins. Similarly to category IV mutation, this type of mutation is connected to pancreatic insufficiency and milder phenotypes.[14]
6. Class VI is due to altered stability of the mRNA of an otherwise fully functional CFTR protein. Cellular processes quickly degrade the protein, thus lowering the concentration of the CFTR proteins at the cell membrane.[2]

The most common mutation that leads to cystic fibrosis is the deletion of the amino acid phenylalanine, also known as the ΔF508 mutation, which occurs in about 70% of patients.[6] This type of mutation is sorted as the second class (defective protein processing) since it generates an unusual structure of the CFTR protein, bringing about premature destruction of the protein in the Golgi apparatus and thus decreasing its expression at the cell surface.[2,15] The protein channels that do arrive at the apical membrane do not open often. Those who are homozygous for the recessive allele with this mutation, therefore, have very little channel activity and consequently have severe symptoms.[15]

PATHOPHYSIOLOGY

All types of mutations lead to a lack of functional CFTR protein that leads to a deficiency of cAMP-dependent

chloride and bicarbonate secreted into fluids rich in mucus and other proteins, which are found among tissues lining the airways.[16] The decreased secretion of chloride leads to increased reabsorption of sodium ions – to maintain a balance of the charges – thus increasing the reabsorption of water and eventually leaving thick mucus on the epithelial linings along with the viscous secretions from the exocrine tissues.[2] Moreover, as the mucus remains attached to the bronchial surfaces, it lowers the fluid pH. A possible consequence of this acidification is defects in the host antibacterial defenses.[16] The organs that are most frequently affected by the thickened mucus comprise the sinuses, lungs, pancreas, biliary and hepatic systems, intestines, and sweat glands.[2] Other affected areas include the bones and the reproductive tract.[6] In addition, once the organs become obstructed, they could become infected with pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Burkholderia cepacia*, causing chronic airway inflammation, tissue destruction, and respiratory insufficiency.[16]

The Sinuses and Lungs

Bacterial colonization almost always leads to impaired sinus secretion clearance and chronic sinusitis. The risk of cystic fibrosis patients having chronic rhinosinusitis, whether with or without nasal polyps, approaches 100%.[17] Thick mucus secretion could also result in the plugging of the bronchioles; when the lungs are obstructed, the environment in the airways becomes perfect for bacterial growth.[2] Inflammatory responses against the infectious agents in the airways then inevitably lead to the positive feedback loop of mucus secretion and progressive bronchiectasis, or an irreversible airway abnormality[2,4,18] that comes with the secretion of thick and/or purulent sputum.[19] At this point, patients usually have clubbed fingers.[5] Eventually, bronchiectasis, along with pulmonary fibrosis and pulmonary hypertension, could lead to death due to failure of lung ventilation or cardiac failure.[1,2]

These respiratory problems are found in over 90% of all patients diagnosed with cystic fibrosis.[5] Although the disease manifests in many organs, most notably the upper and lower airways, pancreas, bowel, and reproductive tracts, for most patients, lung disease is the most important problem of all when the symptoms and treatments are considered.[6]

The Pancreas

Cystic fibrosis of the pancreas often involves reduced water content of the pancreatic secretions since the CFTR protein that is normally expressed in the ductal epithelial cells is missing. With increased viscosity, the luminal content then obstructs the pancreatic ductules.[14] As food materials enter the duodenum, the exocrine glands of the pancreas must secrete enzymes into the lumen of the small intestine. The presence of these enzymes, along with the thickened secretions, obstructs the ductules and inhibits the enzymes from being released into the duodenum. This pancreatic manifestation is known as pancreatic exocrine insufficiency, a condition in which the amount of secreted pancreatic enzymes is insufficient to maintain normal digestion.[20]

In addition, because a smaller amount of bicarbonate can be secreted by the pancreas, the acidic chyme in the stomach undergoes less neutralization, and thus duodenal hyperacidity is caused.[21] For this reason, any of the pancreatic enzymes that do reach the small intestine becomes degraded in the acidic environment.[2] This maldigestion, in turn, contributes to malabsorption of nutrients, specifically a malnutrition of fat-soluble Vitamins A, D, E, and K, antioxidants, and other micronutrients.[20]

A more severe pancreatic manifestation due to cystic fibrosis is pancreatitis or inflammation of the pancreas when it undergoes autodigestion as the enzymes destroy the pancreatic tissues. The reasoning behind this is that acidification of the pancreatic lumen can lead to a loss of tight junction integrity, allowing the leakage of digestive enzymes into the pancreatic duct lumen and interstitial space.[22] In addition, a decrease in pH within the ductal lumen is also associated with acceleration of trypsinogen autoactivation into trypsin, initiating the early stages of autodigestion of the pancreas by pancreatic enzymes.[22] The impact is endocrine pancreatic failure, in which the islets of Langerhans become digested by the enzymes. This can then result in type 1 diabetes mellitus.[2]

The Biliary and Hepatic Systems

Normally, the CFTR protein is expressed in the epithelial cells of the biliary duct and regulates acid-independent bile flow.[14] CFTR dysfunction significantly affects the function of the epithelial cells and causes an alteration in the bile composition, leading to impaired secretion and deposition of thick, viscous bile with reduced alkalinity, as well as chronic damage of the biliary epithelium.[23,24] The abnormal bile increases the activity of free radicals and heightens the susceptibility to infectious agents and other toxic compounds secreted with the bile. The accumulation of hydrophilic, toxic bile acids may also damage a hepatocyte directly.[24]

Moreover, without the CFTR protein, the thickened bile may plug the biliary ductules and cause obstructive liver disease, progressing to multilobular biliary cirrhosis and post-hepatic jaundice. Other than that, portal hypertension could also result in esophageal varices, splenomegaly, and hypersplenism.[2] Gallbladder disease is also likely to occur as a common complication of cystic fibrosis.[25]

The Intestines

Meconium ileus is often seen as the first manifestation of cystic fibrosis in neonates.[26] Meconium that is thicker

and stickier than usual physically blocks the ileum and the small intestine proximal to the obstruction, then becomes dilated with additional meconium, gas, and fluid.[26] This is likely caused by the increased fluid absorption due to the faulty CFTR protein channel, leading to dehydration of the intestinal contents and constipation.[2] Chronic blockage would eventually bring about inflammation, scars, and constriction; fecal impaction or intussusception could occur later in life as well.[2]

The Sweat Glands

Under normal conditions, the flow of chloride ions in sweat glands is opposite to that in all other tissues with the CFTR protein channels.[2] Sweat glands transport chloride ions from the extracellular fluid into the intracellular space, thus reabsorbing sodium and water back into the body as well. However, when the CFTR channel fails to function properly, chloride ions, and consequently sodium and water, are not reabsorbed; this results in a loss of sodium and fluid on the surface of the skin.[27] This explains the particular characteristic of having salty skins in patients diagnosed with cystic fibrosis. In severe cases, or if left prolonged, hyponatremic dehydration may follow.[2]

The Bones

The chronic inflammatory state associated with cystic fibrosis impacts the hypothalamic-pituitary-growth axis and the insulin-like growth factor 1 (IGF-1).[28] When the hypothalamus releases growth hormone-releasing hormone, the anterior pituitary secretes growth hormone as a signal for the liver to produce IGF-1. The IGF-1 hormone targets the long bones, influencing the cartilaginous epiphyseal plates of the bones and increasing the body's long axis. Whereas growth rates are normally highest during utero, infancy, and puberty, children diagnosed with cystic fibrosis often have delayed pubertal growth spurt with reduced velocity; those with severely affected lungs experience greater delays.[28]

This effect has been partly attributed to lower IGF-1 levels, and the suppression of the GH-IGF-1 axis has been blamed on malnutrition and pulmonary inflammation.[29] However, studies on humans and pigs with cystic fibrosis have shown that growth defects cannot be a direct consequence of malnutrition or pulmonary inflammation. Instead, the CFTR protein plays a role in the secretion of growth hormone from the pituitary. Loss of the protein's function has a more direct effect on the reduced production of growth hormone.[29]

Bone defects are found in approximately 20–35% of cystic fibrosis patients.[30] These patients show low bone mineral density at dual-energy X-ray absorptiometry and are at risk of osteopenia, osteoporosis, and vertebral fractures.[14] Cystic fibrosis-related bone disease may develop depending on various factors such as malnutrition, low body mass index, severity of lung disease, poor mobility, reduced absorption of Vitamin D, low levels of Vitamin K, use of steroids, circulating inflammatory cytokines, and increased bone turnover.[14]

The Reproductive Tract

Mutations in the CFTR gene affect both male and female fertility. Nonetheless, not all cystic fibrosis patients are infertile.[31] Although most men with cystic fibrosis have significant physical abnormalities of the reproductive tract that lead to infertility, most women have anatomically normal reproductive tracts, and up to half of them could be able to conceive spontaneously.[31] Congenital bilateral absence of the vas deferens (CBAVD) is detected in up to 90% of males diagnosed with cystic fibrosis,[32] while females often have vaginal yeast infection and stress urinary incontinence.[6]

DIAGNOSIS AND EVALUATION

The key clinical features of cystic fibrosis are defects in the secretion of chloride, sodium, and water, followed by the formation of hyperviscous mucus in the respiratory, digestive, and reproductive systems. Insufficiency in the reabsorption of these ions at the level of sweat glands is of secondary significance.[5]

For the majority of patients, diagnosis of cystic fibrosis is straightforward with a clear clinical picture. Cystic fibrosis patients most frequently come with chronic respiratory symptoms, malabsorption, a sweat chloride value of over 60 mmol/L, and two known disease-causing mutations in the CFTR gene. Still, diagnosis of the disease can be complicated in those who exhibit milder symptoms (<5% of all patients). With these patients, initial diagnostic tests may be inconclusive if the concentration of chloride in sweat is in the intermediate range (40–60 mmol/L) and/or there are fewer than two CFTR mutations. For patients whose diagnostic criteria are not met, they are often diagnosed with a CFTR-related disorder (CFTR-RD).

CFTR-RDs may include disseminated bronchiectasis, CBAVD, and acute or recurrent pancreatitis.[33]

After reviewing common screening protocols for cystic fibrosis, the Cystic Fibrosis Foundation has recommended that for optimum results, all diagnoses should be done by demonstrating CFTR protein channel dysfunction. This can be done initially with a sweat chloride test and potentially bioassays of CFTR function such as nasal potential difference measurement or intestinal current measurement to directly assess altered salt transport.[34] There are, however, many limitations to the sweat chloride test. The test does not produce a diagnostic value in infants under 7 days of age or in infants weighing under 3000 g, as well as in patients

diagnosed with edema or eczema. Furthermore, borderline or slightly increased chloride concentrations can be detected in other pathological conditions such as untreated adrenal insufficiency, ectodermal dysplasia, glycogenosis type 1, hereditary nephrogenic diabetes insipidus, hypothyreosis, hyperparathyroidism, mucopolysaccharidosis, fucosidosis, and severe malnutrition. The results can also be false under conditions of pyrexia, dehydration, high salt consumption, and diuretic therapy.[5]

Cystic fibrosis newborn screening, using the Guthrie blood spot test,[6] has been introduced to numerous countries across the globe, and for babies who screen positive, the diagnosis of cystic fibrosis must be confirmed with a sweat chloride test that results in a sweat chloride concentration that is greater than 60 mmol/L. Newborn screening is not, however, foolproof: Some babies with cystic fibrosis may be missed and some diagnoses may be uncertain.[33]

Another modern method of cystic fibrosis diagnosis is DNA analysis, but most can detect only common mutations. Other values used for diagnosis are high levels of immunoreactive serum trypsinogen, high contents of fat in stool, pathological pancreozymin secretin test, and low fecal elastase levels.[5] Depending on the symptoms a patient exhibits, additional diagnostics may be assigned as well to evaluate and monitor the disease state and progression. Examples of these are chest radiography, sinus radiography, abdominal radiology, and spirometry, or a pulmonary function test.[2]

It is critical to identify the class of the CFTR mutation that is responsible for cystic fibrosis in each patient since there are mutation-specific therapies available for different classes.[33]

DIFFERENTIAL DIAGNOSES

- Acute sinusitis
- Aspergillosis
- Asthma
- Bronchiectasis
- Bronchiolitis
- Celiac disease (sprue)
- Ciliary dyskinesia
- Nutritional considerations in failure to thrive
- Short stature.[35]

PROGNOSIS

Modern therapeutic possibilities allow for the prevention of complications resulting from cystic fibrosis, thus improving the prognosis of the disease each year. Most children diagnosed with cystic fibrosis are able to live healthily until adulthood. They are able to go to school, and young adults are able to go to work. The lung disease that comes with cystic fibrosis will worsen until patients are in their thirties, which would be when lung transplantation is required. After lung transplantation, it is expected that patients can live for a median value of 8.5 years longer.[2] The average life expectancy for cystic fibrosis patients is 37 years, and death is most often the result of lung complications.[36]

TREATMENT

Conventionally, the treatment for cystic fibrosis has focused on addressing the symptoms of the disease. General treatments for lung disease comprise chest physical therapy, mucus clearance, and antibiotic therapy for infection control.[37] More recent treatments, however, consist of techniques that aim to fix the fundamental physiological abnormalities that arise with mutations of the CFTR gene. Other interventions compensate for pancreatic insufficiency and can slow down the decline of the respiratory system.[38] Most importantly, lung transplantation is an essential treatment for cystic fibrosis as well.[39] It must be noted, nevertheless, that transplantation is not the ultimate cure, although it does prolong life and offers significant symptomatic relief.[2]

For mucus clearance, numerous therapies have been developed. The high-frequency chest wall oscillation technique involves putting on a vest that is attached to a machine that mechanically performs chest physical therapy for the patient by vibrating at a high frequency.[40] The vibration loosens up and thins the mucus, separating it from the walls of the airways. Using positive expiratory pressure masks is also known to be helpful. There are also techniques such as the active cycle breathing technique and autogenic drainage, which loosen the mucus and mobilize it up the airways, allowing for easier clearance by coughing.[38] Aerobic exercise is another tip for clearing the airways as well. These mucus clearance techniques are usually prescribed based on the condition of each individual, and there is no proof as to which one works best.[41]

The excess mucus build-up in the lungs comes from not only airway secretions but also from the DNA of the neutrophil extracellular traps. Therefore, recombinant human DNase, such as dornase alfa, is also established as a treatment that can decrease sputum viscosity. Another effective mechanism is to increase hydration of airway secretions using inhaled agents such as a 7% hypertonic saline. Doing so will help stimulate movement of vascular water into the thick airway secretions, aiding cilia in mobilizing the sputum and promoting coughing for clearance.[38] Mucolytics, anti-inflammatory drugs, kinesitherapy, and other forms of respiratory rehabilitation may also be given to patients to alleviate respiratory complaints concerning pulmonary ventilation.[5]

As for infection control, there are a variety of antibiotic regimens that are commonly used although antibiotic

resistance has become an escalating problem. Nebulized antibiotics that are routinely administered work well in the lower trachea and the upper airways, but not so much in the deeper airways as the concentration is not high enough. To deliver the antibiotics straight to the deep respiratory tract through the pulmonary circulation, the drugs should be taken intravenously or orally. Both methods may also be used concurrently to target bacteria that live throughout the whole lung, such as *P. aeruginosa*. Even so, the bacteria may still form biofilms to resist the drugs, resulting in chronic infection. There is still an ongoing study to confirm whether the antibiotic-resistant bacterial strains are sensitive to acidified nitrite or HNO_2 when administered at a pH of 6.5, which is the pH of the lungs of a cystic fibrosis patient.[38]

In addition to the general treatments, there are also other new therapeutics that target the genetic defects.[42] One of the methods is to repair either the DNA or RNA of the mutant that codes for the defective CFTR protein. Afterward, viral vectors are utilized to insert the corrected copies of the CFTR gene into the epithelial cells of the airways.[38] However, there could be adverse effects from the immune responses following gene transmission; thus, as technology continues to advance, this therapeutic mode serves as a very important area for further investigation.[43]

Apart from the gene transfer method, there are other successful ones that act directly on the mutant CFTR protein. Orkambi, or the combination of lumacaftor and ivacaftor, for instance, aims to correct the most common ΔF508 mutation.[42,44] While lumacaftor corrects the misprocessing of the mutation and increases the presence of the CFTR protein at the cell surface, ivacaftor activates the CFTR channel, allowing it to open for movement of chloride and bicarbonate.[45] This drug combination is suitable for approximately 40% of patients with cystic fibrosis and particularly shows improvement in those who are homozygous for the ΔF508 mutation.[46] Whereas ivacaftor is an FDA-approved potentiator – meaning that it has been approved by the U.S. Food and Drug Administration – that can benefit cystic fibrosis patients on its own, however, lumacaftor alone does not bring significant effects.[38] In addition, a third drug sold under the brand name TRIKAFTA, which is a combination of elexacaftor, tezacaftor, and ivacaftor,[47] has only recently been approved by the FDA as being able to fix the ΔF508 defect not only in individuals who are homozygous for the mutation but also in patients who have only one copy of the mutation.[48] Both of these CFTR modulators can be life-transforming since they are able to prevent large-scale complications, especially if the treatment begins early in childhood.[49]

Other therapies in development regarding basic gene defects include read-through agents or molecules that interact with the ribosome to prevent the premature stop codon in Class 1 CFTR mutations from being read during translation. Several others are those known as CFTR amplifiers and stabilizers, oligonucleotide-based drugs,[50] and activators of other chloride channels.[42]

Since cystic fibrosis has a serious impact on the nutrition status of the patients diagnosed with the disease, nutrition management is required as well. To compensate for pancreatic exocrine insufficiency, a high-fat, high-protein, high-calorie diet together with adequate pancreatic enzymes substitution, and vitamin and mineral replacement are vitally needed.[51] To meet metabolic demands, enteral feeding should be considered as well.[52]

CONCLUSION

In most cases, cystic fibrosis is seen as a relatively rare yet lethal disease that is influenced by various factors and that disturbs multiple systems of the human body. Nevertheless, the amount of information that is continuously discovered thanks to today's technology has greatly contributed to the advancements made in the diagnosis, healthcare, and treatment of cystic fibrosis over the past years. What's more, the life perspectives of cystic fibrosis patients have significantly improved as well.

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