Original Research Paper

Volume - 13 | Issue - 08 | August - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Pharmaceutical Science

CYSTIC FIBROSIS – AN OVERVIEW

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ABSTRACT Cystic fibrosis is an autosomal recessive disease caused by mutations of the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR). Here we summarize, at the basic descriptive level, clinical and genetic characteristics of cystic fibrosis gene mutations, while emphasizing differences between CF mutations found in Chinese pediatric CF patients compared to those found in Caucasian CF patients. In addition, we describe animal models used to study human cystic fibrosis disease and highlight unique features of each model that mimic specific human CF-associated signs and symptoms. At the clinical level, we summarize CF clinical manifestations and diagnostic, treatment, and prognostic methods to provide clinicians with information toward reducing CF misdiagnosis and missed diagnosis rates.

KEYWORDS : Animal Model, Cftr, Chinese, Clinical Feature, Cystic Fibrosis

1.INTRODUCTION

Cystic fibrosis (CF) is a genetic (inherited) disease that causes sticky, thick mucus to build up in organs, including your lungs and pancreas.

If you don't have CF, the mucus that lines organs and body cavities, such as your lungs and nose, is slippery and watery. If you do have CF, thick mucus clogs the airways and makes it difficult to breathe.[1]

Mucus also blocks the ducts in the pancreas, causing problems with digesting food. Babies and children who have CF might not be able to absorb enough nutrients from food. CF, which is chronic (long-lasting) and progressive (getting worse over time), also affects your liver, sinus, intestines and sex organs.

There's also a form of disease called “atypical cystic fibrosis.” It's different from classic CF because it's a milder form and may only affect one organ. The other “atypical” thing about it is that it usually comes on much later in life. “Typical” or classic CF generally shows up in the first few years of a child's life.[1]

Among white children in the U.S., the rate of CF cases is 1 in 2,500 to 3,500 new-borns. CF affects about 1 in 17,000 Black new-borns and 1 in 31,000 new-borns of Asian descent.

2. Symptoms Of Cystic Fibrosis

Children who have classic CF have the following symptoms:

- Failure to thrive (inability to gain weight despite having a good appetite and taking in enough calories).
- Loose or oily stools.
- Trouble breathing.
- Recurrent wheezing.
- Frequent lung infections (recurrent pneumonia or bronchitis).
- Recurrent sinus infections.
- A nagging cough.
- Slow growth.

3. Causes Of Cystic Fibrosis

Cystic fibrosis is caused by a change, or mutation, in a gene called CFTR (cystic fibrosis transmembrane conductance regulator).[2] This gene controls the flow of salt and fluids in and out of your cells. If the CFTR gene doesn't work the way it should, a sticky mucus builds up in your body. Cystic fibrosis is genetic. People who have CF inherit two faulty genes, one from each parent. CF is said to be recessive because you need to have two gene variants to have the condition itself. (An older name for gene variant is gene mutation.)

Your parents don't have to have cystic fibrosis for you to have CF. In fact, many families don't have a family history of CF. If your family doesn't have a history of cystic fibrosis, the person with the gene variant is called the carrier. About 1 in 31 people in the U.S. is a carrier who is free of CF symptoms.

Precautions of cystic fibrosis

People with atypical cystic fibrosis may be adults by the time they're diagnosed with atypical CF. Respiratory signs and symptoms may include:

- Chronic sinusitis.
- Breathing problems, possibly diagnosed as asthma or chronic obstructive pulmonary disease (COPD).
- Nasal polyps.
- Frequent bouts of pneumonia.[3]

Targeting Gene Defect

Gene Replacement Therapy

CFTR gene was discovered in 1989, since then gene replacement therapy is being actively researched as a onetime treatment in CF patients; i.e., replacing the mutated gene with a functional copy. But this approach has not yielded any promising results. One major barrier is the lack of efficient vectors that can deliver functional CFTR gene without having immunological consequences.[4]

Gene editing

Gene editing approaches are also being tried, by using nucleases to enzymatically correct the mutated genes in the naïve cell. One of the most promising tools in today's scenario is the CRISPR/Cas9 technology (Figure 1), which used RNA-protein complex composed of Cas9 enzyme, which binds to a guide RNA, to identify the target DNA sequence. Repair of CFTR locus in human intestinal cells has been tried, which was successful in restoring CFTR function. While this technology also faces risk of off-target insertion, it shows great promise.[5]

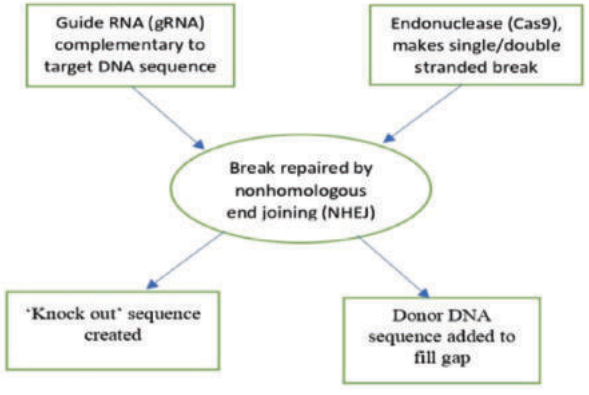


Figure 1: Gene editing approach using CRISPR/Cas9 technology. Since, gene therapy has limited options in the current treatment of CF, it becomes important to understand the basic CFTR defects and identify novel molecular markers.

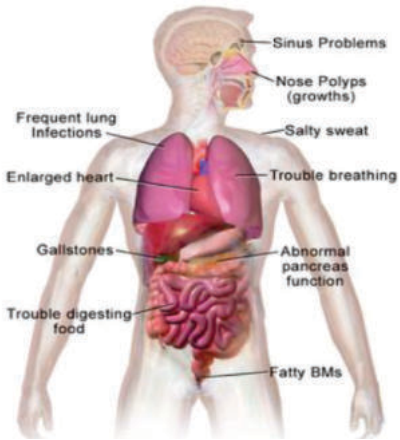
4. Cystic Fibrosis Diagnosis

In most cases, CF is diagnosed during childhood. Doctors diagnose CF with a thorough evaluation and by using different tests. These include;

Newborn screening:
Your healthcare provider takes a few drops of blood from a heel prick, usually while your newborn is in the hospital, and places the drops on a special card called a Guthrie card. The screening looks for a list of conditions, including CF. Every U.S. state requires the testing of newborns at birth and a few weeks later.

Sweat test:
The sweat test measures the amount of chloride in the body's sweat, which is higher in people who have CF. In the test, your healthcare provider spreads a chemical called pilocarpine on your skin, then applies a small amount of electric stimulation to encourage the sweat glands to produce sweat. Your provider then collects the sweat in a plastic coil or on a piece of filter paper or gauze. People of any age can have a sweat test. It's not painful and does not use a needle. This is the most conclusive test for CF.

Genetic tests:
Blood samples are tested for the genes that cause CF.



Health problems associated with cystic fibrosis.[7]

Chest X-rays
Your healthcare provider will order X-rays of the chest are used to support or confirm CF, but a chest X-ray isn't the only test needed to confirm a diagnosis. Other tests must be done.

Sinus X-rays:
As with chest X-rays, sinus X-rays can confirm CF in people who show certain symptoms. Other forms of testing are used along with sinus X-rays.

Lung function tests:
The most common lung function test uses a device called a spirometer. You breathe in completely, then push the inhaled breath into the mouthpiece of the spirometer.

Sputum culture:
Your healthcare provider takes a sample of your sputum (spit) and tests it for bacteria. Certain bacteria, such as Pseudomonas, are most commonly found in people who have CF.

Nasal potential difference (NPD):
This test uses a voltmeter and electrodes placed in two places in your nose and one place outside of your nose to measure the electricity generated by the transfer of ions in solution across the nasal tissue. The test uses three different types of solutions.

Intestinal current measurement (ICM):
You'll have to have a biopsy of rectal tissue for this test. The tissue is made to secrete chloride, which is then measured.

In people who have atypical cystic fibrosis, the sweat test may be normal in terms of the levels of chloride.[8] Some people with atypical CF may have been born before testing became routine. Your provider may order NPD and ICM tests when the diagnosis is questionable.

5. Treatment
You'll probably have a healthcare team that includes a specialist in cystic fibrosis and many other types of caregivers. There is no cure for cystic fibrosis, but your team will help you manage the disease. The major focus of management is keeping your airways clear. Your provider will also prescribe medicine when needed.

Keeping airways clear
You can help to keep your airways clear if you have cystic fibrosis in a number of ways:
- You can learn special ways of coughing and breathing.
- You can use devices that fit into your mouth or therapy vests that rely on vibrations to loosen mucus.
- You can learn something called chest physical therapy, also known as postural drainage and percussion to loosen mucus. With this method, you move into certain positions so that your lungs can drain. Another person claps their hand on your chest and/or your back to help loosen the mucus. You might combine this with coughing.

Medications for cystic fibrosis
Your provider may prescribe these medicines, which won't cure CF, but which will help you in certain situations. They include:
- Antibiotics to treat lung infections or prevent them.
- Inhaled bronchodilators to make breathing easier by opening and relaxing your airways.
- Inhaled medicine to make mucus thinner and easier to get rid of.
- Anti-inflammatory drugs, including steroids and non-steroidal anti-inflammatories.
- Medications to treat the cause of cystic fibrosis in people with certain gene variants.
- Pancreatic enzymes to aid in digestion.
- Stool softeners to help with constipation.

Medications-
1. TRIKAFTA
2. LEEXARFTOR
3. IVACAFTOR
4. TEZACAFTAR

Surgeries for cystic fibrosis
You may need surgery for cystic fibrosis or one of its complications. These might include:
- Surgery on your nose or sinuses.
- Bowel surgery to remove blockages.
- Transplant surgery, including a double lung transplant or a liver transplant.

High-calorie, high-fat diet needed for cystic fibrosis (CF)
People with cystic fibrosis have nutritional needs that aren't the same as the needs of people without CF. People with CF may need 1.5 to 2 times the number of calories as people without CF. You need the extra calories if you have CF because you use more energy than other people to breathe, fight lung infections and maintain your strength [9].

You also need more calories and fat because cystic fibrosis stops the digestive enzymes made by your pancreas from working completely. This means nutrients and fats from foods aren't fully absorbed by your intestines.

Although the enzyme capsules that are taken before all meals and snacks helps digest fats, proteins and starches, a certain amount of nutrients and fats don't get absorbed. If your body doesn't absorb enough fats, then fat-soluble vitamins aren't being fully absorbed either, and these vitamins are needed to protect the lungs.

It's also important to stress that people with cystic fibrosis should keep a higher-than-normal weight starting in early childhood. Researchers have shown that young people with CF who maintain a higher weight grow faster and taller up to puberty and again grow taller when they hit their growth spurt at puberty.

Young people with CF who started life at a lower weight did not grow as many inches, started puberty at a later age and never got that same puberty growth spurt. Reaching your full genetic potential — getting as tall as possible with lungs as large as possible — is another reason why higher-than-normal weight in young people with CF is so important.

Another common misbelief is that salt (sodium) is unhealthy for all people. This isn't true for children and adults with CF. People with CF lose a lot of salt in their sweat. Although there's not a set standard,

healthcare providers generally tell people with CF to eat salty foods. This is true especially during hot, humid weather and exercise. If you have CF, you can probably add salt to meals and snacks as desired. Ask your provider or a registered dietician about the amount of salt you need each day.

Complications of cystic fibrosis

The complications of CF include the following:

- Adults who have CF can have problems with breathing, digestion and their reproductive organs.
- The thick mucus present in people who have CF can hold bacteria, which can lead to more infections.
- People who have CF have a higher risk of developing diabetes or the bone-thinning conditions like osteopenia and osteoporosis.
- Men who have CF are not able to father children without the aid of alternative reproductive technology. Women who have CF can have a decrease in fertility (the ability to have children) and complications in pregnancy.

I take care of myself if I have cystic fibrosis

An adult with cystic fibrosis has different needs than a child with CF. If you're a parent of a child with CF or if you're an adult with CF, you can do a lot to promote a healthy life. This includes developing and following recommendations from a treatment plan developed with your healthcare team.[10][11]

Follow suggestions from your providers about eating enough, eating well and exercising wisely. Ask your provider if pulmonary rehabilitation would be a good idea for you.

Take care to prevent infections by distancing yourself from people who are ill. Practice good hand washing techniques. Get the vaccines that your providers say are needed.

Follow any recommended schedule of appointments with your provider and other members of your healthcare team. If you need help with social or emotional issues, reach out to your team and examine your options. Decide if you'd like to be part of a clinical trial. Ask your provider to point you in the right direction to be a participant.

CONCLUSION

Cystic fibrosis is a complex, multifactorial genetic disorder, affecting thousands of children and adults worldwide. Accordingly, its management is also multi-dimensional, keeping into account the disease course and its symptomatic management on a daily basis. Although with the advent of disease specific CFTR modulators the management of CF patients has improved, no single corrector drug is potent enough to fix the multi domain structure and function of CFTR protein on its own. A combination of drugs having varied mechanisms of action, along with intensive physiotherapy is needed to curtail the disease progression and clinical symptoms.

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