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A Review on Cystic Fibrosis: An Autosomal Disorder

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ABSTRACT

The gene that codes for the cystic fibrosis transmembrane conductance regulator (CFTR) is mutated in cystic fibrosis, an autosomal recessive disorder. The CFTR protein is subordinate to this gene. Male infertility, pancreatic exocrine insufficiency, chronic lung infection and inflammation, and other co-morbidities like diabetes or liver illness associated with cystic fibrosis are the characteristics of cystic fibrosis. Lung infections in children have been identified as a concern. A newborn screening is conducted within the first two to three days of a baby's life as part of the diagnosis process for cystic fibrosis. Sweat test: This common test looks for high amounts of chloride in your perspiration. Prenatal screening: this is done before or during pregnancy. Mucus thinners and bronchodilators are frequently utilized in conjunction with airway clearance procedures. The treatment options for CF include the use of CFTR modulators, antibiotics, and anti-inflammatory drugs. The alternative treatment options for cystic fibrosis (CF) include oxygen therapy, pulmonary rehabilitation, ventilator support, and extracorporeal membrane oxygenation (ECMO). In cases of severe lung disease, surgery can be necessary in advanced circumstances, such as lung transplants.

KEY WORDS: CF, CFTR, ECMO, Oxygen therapy, pre-natal screening

I. INTRODUCTION

Cystic fibrosis (CF) is a genetic Condition that affects a protein in the body. People who have cystic fibrosis have a faulty protein that affects the body cell's, its tissues, and the glands that make mucus and sweat. Cystic fibrosis is the most common life- shortening autosomal recessive disease. It is caused by mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene. The commonest mutation is the deletion of phenylalanine at codon 508 (phe508del, until recently known as ΔF508). This occurs in about 70% of patients with cystic fibrosis[1].

The structure of normal CFTR protein contains two groups of six membrane- spanning structural motifs, two intracellular nucleotide- binding folds (NBFs), and a highly charged 'R domain' containing multiple phosphorylation sites. Activation of the chloride channel requires phosphokinase A- mediated phosphorylation of the R domain and sustained ATP levels within the NBFs.A reduced volume of airway surface liquid causes failure of mucociliary clearance, the lungs' innate defence mechanism. The mucociliary dysfunction means that apatient with cystic fibrosis cannot effectively clear inhaled bacteria. For a bacteria load, a person with cystic fibrosis will have 10 times more inflammation than a person with Lower respiratory tract infection[2].

EPIDEMOLOGY

Researchers claim that the use of newborn screening has reduced the incidence of cystic fibrosis in numerous countries. it is roughly 1 in 4,500–6,000 live births among Caucasians, and is less common among Asians and African Americans. In India, however, the frequency ranges from 1 in 10,000 to 1 in 100,000 individuals. the better survival rate and higher diagnosis rate among patients with mild to moderate illness.[3].

ETIOLOGY

Cystic fibrosis is caused by mutations, or errors, in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, the outcome is either no CFTR protein produced at all or a defective CFTR protein that is unable to carry out its essential job in the cell. These mutations alter the function of the gene in five different categories.

Class 1 : PROTEIN PRODUCTION MUTATIONS

When the amino acids that make up proteins are arranged in a way that does not correctly code for the CFTR protein, mutations in

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protein production mutationoccur. A coding is in place to halt the protein's synthesis when it is supposed to. Production stops prematurely due to a mutation in the nonsense protein.

A splice mutation, which is another mutation affecting protein creation, contains extraneous coding that prevents the cell from appropriately interpreting the genetic code for protein. The signal that instructs the cell where the unnecessary letters in the instruction start and stop is altered by a splice mutation. No longer able to determine where to start and stop reading, the cell tries to read its RNA copy of the instructions.[4]

Class 2 : PROTEIN PROCESSING MUTATIONS

1,480 amino acids make up the CFTR protein. The CFTR protein takes on a stable three-dimensional shape when it is synthesised with all of the required amino acids. For chloride to be transported, it must have the proper form. The CFTR protein cannot develop its appropriate 3-D structure and function correctly when a mutation results in the deletion or addition of the wrong amino acid. It is thought that these mutations relate to protein processing.

F508del, the most prevalent CF mutation, is mostly thought to be a processing mutation. The CFTR protein loses one amino acid as a result. Trikafta®(elexacaftor/tezacaftor/ivacaftor) is a medication combination that functions by facilitating the CFTR protein with an F508del mutation to fold in a more conformal manner and then activates the proteins to allow more chloride to pass through.[5]

Class 3: GATING MUTATION

The CFTR protein has a gate and is formed like a tunnel or channel. When chloride must pass through the channel, the cell has the ability to open the gate. If not, the gate remains closed. Chloride cannot pass through because gating mutation locks the gate in the closed position.

The drug Kalydeco® (ivacaftor) helps people with gating mutations by forcing the gate on CFTR channel to stay open. This enables chloride to move through the channel and reduces the symptoms of CF.

Class 4: CONDUCTION MUTATION

Even though the CFTR protein forms the proper three-dimensional structure, it performs less well than it should due to a modification in one of its amino acids. Chloride must be able to pass through the protein channel of CFTR fast and smoothly in order for it to function as intended. Conduction mutations are a particular kind of mutation that alter the internal structure of a channel, making it more difficult for chloride to pass through. [6]

Class 5: INSUFFICIENT PROTEIN MUTATION

The reduced amount of normal CFTR Protein at the cell surface. This occurs for several reasons, A limited amount of CFTR Protein is produced, only a small number of protein at the cell surface works correctly or a normal protein at the cell surface degrades too quickly, leaving small number of proteins behind. Insufficient protein can be causes by several mutations, including missense and splice mutations.[7].

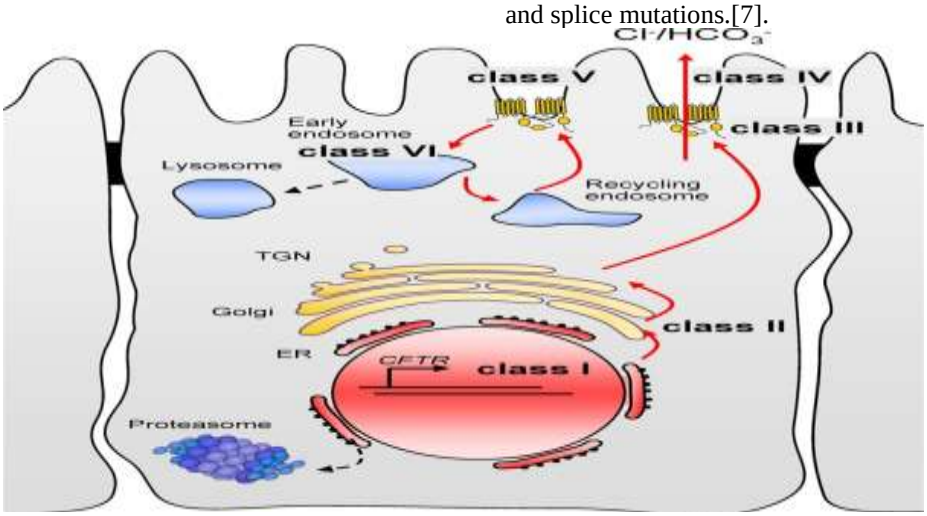

FIG.1. Classification of CF mutations based on cellular phenotype

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SIGNS AND SYMPTOMS

The signs and symptoms of Cystic fibrosis includes as follows:

Respiratory : The lungs' airways get clogged with the thick, sticky mucus that is linked with cystic fibrosis. Signs and symptoms that may accompany this include: a chronic cough that generates thick mucus (sputum); wheezing; intolerance to exercise; inflamed nasal passages or stuffy nose; and repeated lung infections.

Digestive : Thick mucus can obstruct the tubes that carry digesting enzymes from your pancreas to your small intestine. These digestive enzymes are necessary for your intestines to properly absorb the nutrients in the food you eat. The result is often: Poor growth and weight gain; malodorous, greasy stools; intestinal blockage, particularly in babies (meconium ileus); severe or prolonged constipation (rectal prolapse).

Classic cysticfibrosis: Children with classic CF have the following symptoms:failure to gain weight despite a good appetite and sufficient calories, lose or oily stools, Breathing difficulties. Common wheeze, recurrent pneumonia or bronchitis, Recurrent sinus infections.[9]

PATHOPHYSIOLOGY

The CF gene deficiency causes the CFTR protein to be missing or to function abnormally, which causes aberrant chloride conductance on the epithelial cell's apical membrane. Because airway surface liquid is necessary to maintain ciliary stability and functioning, this causes depletion of airway surface liquid in the lung, which in turn causes ciliary collapse and reduced mucociliary transport. This leads to a vicious cycle of infection, inflammation, and phlegm retention..[10]

DIAGNOSIS

It is important to diagnose cystic fibrosis as young as possible to start treatment early. New born screening make it possible to detect the disease early in life. The diagnose tests involved in the cystic fibrosis are:

1. **New born screening:** A newborn is screened for cystic fibrosis during the first two to three days of life. A lab tests a few droplets of blood from a heel prick on a specific card.
2. **Carrier screening to detect CFTR mutations:** One method to find carriers of mutants is through genetic testing. DNA from samples of your blood, saliva, or cheek cells is examined during genetic testing. It determines if you are a carrier of a CFTR gene mutation. Individuals who receive a CFTR gene mutation from one parent are known as carriers of the mutation, whereas those who have a mutation from both parents will be diagnosed with cystic fibrosis.
3. **Sweat test:**A sweat test looks for elevated chloride levels in perspiration. The common test used to diagnose cystic fibrosis is the sweat test. It can be used to confirm a positive diagnosis from a screening of your new-born.

Sweat test result of 60 or higher: diagnosis of cystic fibrosis
30-59: Uncertain diagnosis; more testing required
If under 30 : cystic fibrosis is improbable.

4. **Other tests:**

a) A chest radiograph can be used to diagnose atelectasis, bronchiectasis, hyperinflation, or abscesses.
b) The paranasal sinuses may show panopacification on sinus radiography.
c) When a new-borns has meconium ileus, abdominal radiography may be beneficial.

In order to assess and track the disease's course in cystic fibrosis, pulmonary function testing is a crucial tool. Pneumonia function testing most usually involves spirometry.

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Diagnosis Approach

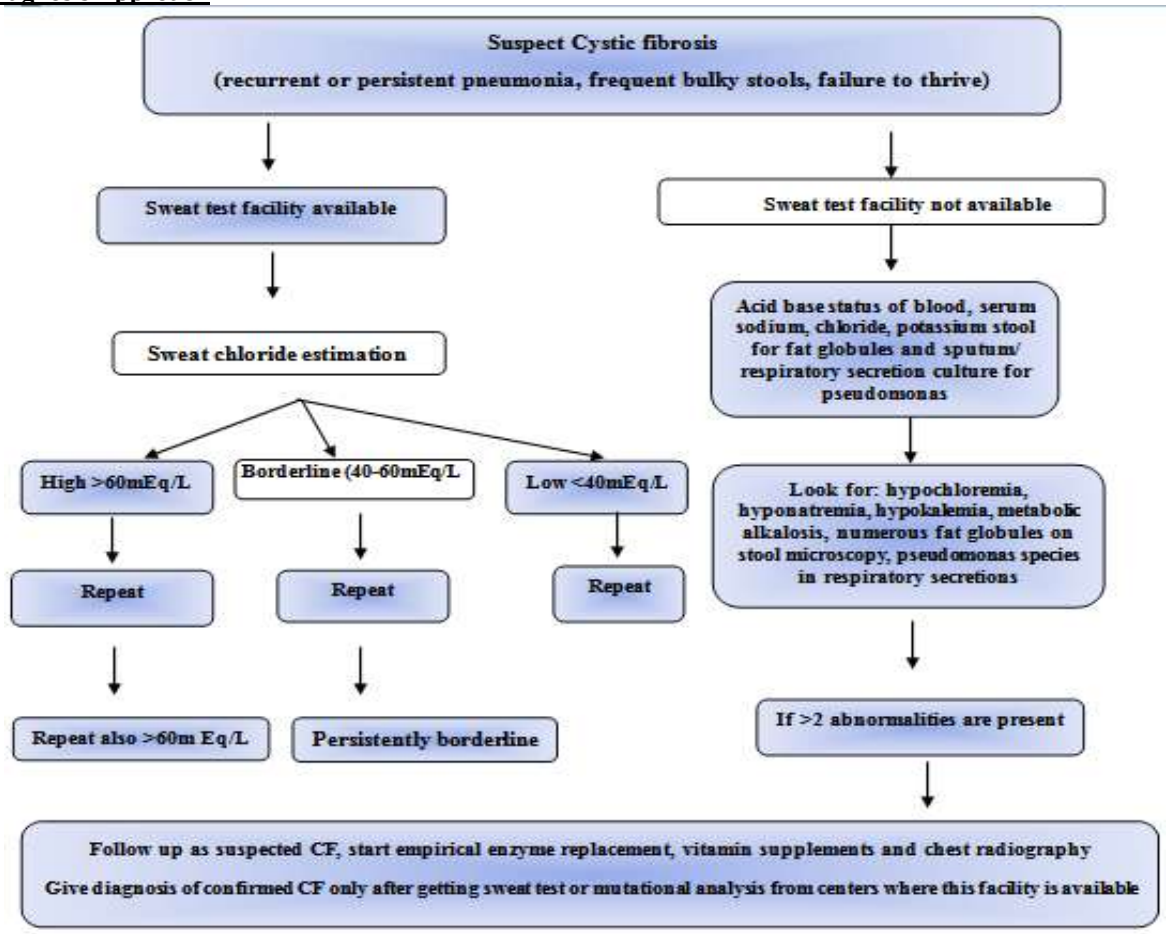

Fig.2. algorithm for diagnosis of Cystic fibrosis[11]

II. MANAGEMENT

Pharmacological treatment:

1. Common antibiotic therapy for CF Exacerbation:[12]

The antibiotics such as

→ AZTREONAM
200mg/kg/day , IV divided every 6-8 hrs.,

Side effects: Nasal congestion, Pharyngolaryngeal pain, Chest discomfort

→ CEFEPIME
150mg/kg/day IV divided every 8 hours,

Side effects: Difficulty breathing, Stomach cramps, Chills

→ CEFTAZIDIME
200mg/kg/day IV divided every 8 hours,

Side effects: Allergic reaction, Headache, Nausea and Vomiting

→ CIPROFLOXACIN
30mg/kg/day IV divided every 8-12 hours
40mg/kg/day PO divided every 12 hours

Side effects: Skin rashes, Chest pain, Changes in urination

→ IMIPENEM/ CILISTATIN
100mg/kg/day IV divided every 6 hours

Side effects: Swelling, redness, Thrush

→ MEROPENEM
120mg/kg/day IV divided every 8 hours

Side effects: Bluish lips or skin, fainting, lightheadness

→ PIPERACILLIN+ TAZOBACTUM
400mg/kg/day IV divided every 4-6 hours

Side effects: Bladder pain, Bloating, Changes in urination

→ TICARCILLIN+ CLAVULANATE
400mg/kg/day IV divided every 4-6 hours

Side effects: Epigastric discomfort, Hyper Sensitivity Reactions

→ TOBRAMYCIN$^{\uparrow\uparrow}$
7.5-15mg/kg/day IV divided every 8-24 Hours

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(more effective and less nephrotoxic)
Side effects: Dizziness, Allergic reactions, Bleeding gums

→ TRIMETHOPRIM/
20 mg/kg/day PO divided every 6-8 hours
SULFAMETHOXAZOLE
Side effects: Dizziness, Loss of appetite, Headache

→ VANCOMYCIN$^{\uparrow\uparrow}$
60mg/kg/day IV divided every 6-8 hours
Side effects: Peripheral edema, fatigue, flatulence, Urinary tract infection

2. Common drug therapy for CF:

Other pulmonary Therapy:

→ TOBRAMYCIN
300mginhaled twice daily administered in 28-day cycles
Side effects: Nephrotoxicity, Ototoxicity, dyspnea, Sinusitis

→ DORNASE ALPHA
2.5 mg inhaled daily
Side effects: chest pain, conjunctivitis, Pharyngitis

→ AZITHROMYCIN
25-40 kg: 250mg PO Mon, Wed, Fri
Side effects: Diarrhea, Nausea and Vomiting

→ 7% HYPERTONIC SALINE
4ml inhaled twice daily
Side effects: Cough, bronchospasm, hemoptysis

Gastrointestinal Therapy:

→ Fat-soluble vitamins
<1 year; 1ml PO daily
1-3 years: 1ml PO twice daily
4-10 years: 1Tablet/Capsule PO twice daily
>10 years: 1Tablet/Capsule PO twice daily

→ Pancreatic enzymes
1,000-2,500 lipase U/Kg/meal and one half dose with each snack

Others:

→ IVACAFTOR
>6y: 150mg orally
2-5 y: 50-75mg orally, every 12 hours
Side effects: Abdominal pain, diarrhea, elevated liver enzyme, headache

→ LUMACAFTOR/IVACAFTOR Age 12y and older: 2 tablets(200/125) twice daily with fat containing food.
Age 6-11y : 2 tablets(100/125) twice daily with fat containing food
Side effects: Nasal congestion, Amenorrhea, Abdominal pain, Diarrhea

→ IBUPROFEN
20-30mg/kg twice daily, maximum daily dose 3,200 mg/day
Side effects: Constipation, Abdominal pain, edema, neutropenia, prolonged bleeding time

Non-Pharmacological treatment:

Airway Clearence therapy:

Percussion and postural drainage → loosen and clears mucus

Positive expiratory pressure → opens airway

Active cycle of breathing technique → relaxes airway, clears mucus of lungs

Autogenic drainage → Moves mucus out of lungs

High- frequency chest wall oscillation machine →vibrates the chest, loosen and thin mucus

Physical activity → improves lung function.

III. CONCLUSION

Cystic fibrosis is an Autosomal Recessive Disorder caused by mutations of the gene encoding the cystic fibrosis transmembrane conductance regulator. The Sweat test, chest X ray and Lung function test are the most used Diagnostic parameters.Approximately 90% of individuals with cystic fibrosis who are 2 years of age or older may benefit from a combination of ivacaftor, tezacaftor, and elexacaftor. First-line pulmonary therapy include mucolytics, anti-inflammatories, and antibiotics.

Conflict of Interest: Nill

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