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CYSTIC FIBROSIS

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Abstract

Cystic fibrosis is an autosomal recessive disease caused by mutations in the CFTR gene, which cause chloride channel abnormalities in mucus and sweat-producing cells. The respiratory system and the gastrointestinal tract are the first organs to be affected, but multiple organs are ultimately affected, resulting in life-threatening complications. Drug therapy, intensive physiotherapy, and dietary support are all needed for treatment. Previously, the emphasis was on symptom relief and avoiding complications, however protein rectifiers, which are believed to fix underlying structural and functional defects, have recently been studied. The corrector drugs provide some change. Gene therapy, cellular previously formed targeting, and newer medications for symptom relief are all promising approaches.

Introduction and pathophysiology

Cystic fibrosis (CF) is an autosomal recessive condition that affects many organs, with the lungs being the most heavily affected, resulting in death in 90 percent of cases(1). Cystic fibrosis trans-membrane conductance regulator mutation (henceforth CFTR) gene regulates the activity of other chloride and sodium channels at the cell surface epithelium by changing a protein (a regulated chloride channel)(2,3,4). There are about 70,000 cases worldwide, with about 1000 new cases being introduced each year. CF is most common in white people of north European origin, with 1 in 2000–3000 births suffering from the disease(5). and least in Asian-Americans having 1:30,000 newborns(6).

The CFTR protein allows chloride to move through mucus-producing cells, followed by water, and the mucus thins. Defective CFTR, on the other hand, causes dense, sticky mucus to block the pathways (7), resulting in severe lung infections, especially pseudomonas.

Huge neutrophil invasion produces elastase, which overwhelms lung antiproteases, causing tissue damage (8). Degranulating neutrophils often release a significant amount of nucleic acids and cytosol matrix proteins, which contribute to mucus hyperviscosity (9).

The mucous plugs in the GIT block the pancreatic canaliculi and gall bladder duct, blocking enzyme and bile flow into the duodenum, resulting in malabsorption and digestive problems. DIOS (Distal Intestinal Obstruction Syndrome) is a CF-specific condition that may occur in people with pancreatic insufficiency.

Ileo-cecal obstruction of inspissated intestinal contents characterizes this condition(10,11). Dehydration, arrhythmias, fatigue, exhaustion, heat stroke, and, in extreme cases, death result from a mineral deficiency in the blood caused by the loss of extra salt in sweat.

Epidimology

Changing diagnostic criteria and methods as well as improvements in clinical outcome have influenced the epidemiology of cystic fibrosis. Estimates of disease incidence are around 1 in 3,000 live births in persons of northern European descent(7)(8), with Ireland having the highest incidence at 1 in 1,400 live births(9). Incidence varies according to race and ethnicity; only 1 in 4,000 to 10,000 Latin Americans and 1 in 15,000 to 20,000 African Americans have cystic fibrosis, with even lower incidence rates in people of Asian background(8). These estimates are based on information from western countries epidemiological data are missing for large regions of the world, including the Middle East, Asia and Africa. Importantly, some small populations in eastern Europe have very high incidence rates, specifically Albania, where the incidence was noted to be 1 in 555 . This high incidence is also reflected in data noting very high incidence in Albanian immigrants to northern Italy(8).

Genetic

The CFTR gene is found on chromosome 7q31.2. More than 1900 mutations have been identified, the most common of which is the ‘F508del' (deletion of three bases coding for phenylalanine at the 508th position) (12). As shown in Table 1, there are six types of mutations.

Class I mutations cause a protein development defect that results in the complete absence of CFTR protein in 2–5% of cases worldwide, with the exception of Ashkenazi Jews, who have at least one copy in 60% of cases. Class II mutations cause abnormal protein processing, which leads to abnormal localization. It includes F508del, the most common mutation in the United States, accounting for 70% of disease-causing alleles. Around half of CF patients are homozygous for this allele, while the other half are heterozygous. Protein regulation defects caused by Class III mutations result in decreased activity. Other mutations, especially in the regulatory domain, are also included. The most common class III mutation is G551D. Protein conduction defects caused by Class IV mutations result in a change in ion flow frequency. R117H is the most common mutation. Class V mutations cause a decrease in the amount of functional CFTR protein (13,14,15,16,17), whereas class VI mutations increase protein turnover. Patients with mutations in Classes I–III have a more serious type of diarrhoea. However, gene modifiers such as TGF-beta1 and mannose-binding lectin have been shown to reduce the clinical importance of a particular set of mutations(18).

CLINICAL FEATURES

Cystic fibrosis is caused by dysfunction of the CFTR protein, a chloride channel of exocrine glands. The defect leads to diminished chloride secretion and, in turn, to increased sodium absorption through epithelial sodium channels and removal of water from secretions, which are therefore abnormally viscous . The consequences include obstruction, inflammation, infection (in the lungs and upper airways), and ensuing tissue reorganization and loss of function. The severity of the disease in the individual case partly depends on variable organ sensitivity and on the genetically determined residual function of the CFTR protein. 99% of the

affected male patients are infertile because of obstructive azoospermia, and 87% of patients have exocrine pancreatic insufficiency. Disease severity—particularly the degree of pulmonary involvement, which is a crucial determinant of morbidity and mortality—also depends on other disease-modifying genes and on the patient's socioeconomic setting

Exocrine pancreatic insufficiency (PI) is a character- istic type of organ involvement in cystic fibrosis. It is manifested by voluminous, fatty, shiny, malodorous, pulpy stools, abdominal symptoms, dystrophy, and deficiencies of fat-soluble vitamins (e.g., hemolytic anemia due to vitamin E deficiency) and trace elements (e.g., zinc dermatosis). The diagnosis can be estab- lished by a low fecal elastase measurement. Patients with primary pancreatic insufficiency are at elevated risk of chronic and/or recurrent pancreatitis)).

The course of chronic disease of the lungs and paranasal sinuses varies among patients with cystic fibrosis and can be hard to distinguish from frequent recurrent bouts of bronchitis and/or pneumonia, especially in preschool children. Children suffering from cough, sputum production, or wheezing of more than three months' duration, persistently abnormal radiological findings, persistently positive bacterial cultures of respiratory secretions, or clubbing of the fingers should undergo diagnostic testing for cystic fibrosis even if their neonatal screening test was negative. The same holds for children with bilateral chronic rhinosinusitis with frequent exacerbations (with or without nasal polyps).

Meconium ileus leads to a diagnosis of cystic fibro- sis in 20% of all affected children, sometimes prenatally. All neonates with meconium ileus, intestinal atresia, or volvulus should be tested for cystic fibrosis. Rarer clinical manifestations of cystic fibrosis include:

- hypochloremic alkalosis without vomiting in children (salt-wasting syndrome)
- chronic liver disease, especially focal biliary or multilobular cirrhosis;
- prolonged neonatal icterus;
- obstructive azoospermia.

As cystic fibrosis is inherited in an autosomal reces- sive pattern, the siblings of affected children have a 25% chance of being affected (e3) and should be tested for the disease whether or not they have symptoms.

Complication

Bronchiectasis, chronic infections leading to pneumonia, growths (nasal polyps), hemoptysis, pneumothorax, and ultimately respiratory failure are all respiratory system complications. Nutritional disorders, such as obesity and fat-soluble vitamins, and diabetes are examples of digestive system complications (Nearly 20 percent of people with cystic fibrosis develop diabetes by age 30). Progression of hepatic dysfunction, gallstones, intestinal obstruction, intussusception, small intestine bacterial overgrowth (SIBO), and distal intestinal obstruction syndrome (DIOS) are all possible symptoms.

Infertility, osteoporosis, electrolyte imbalances, and dehydration, which manifest as elevated heart rate, fatigue, exhaustion, and low blood pressure, are all possible complications.

Because of improved medical interventions and intensive treatment, the number of patients who survive beyond the age of 18 years has increased dramatically (from 29.2 percent in 1986 to 49.7 percent in 2013).

DIAGNOSIS

Determination of chloride concentration in sweat (sweat test) is the first procedure in the diagnostics of CF. Chloride level in sweat of over 60 mmol/L is considered pathological and below 40 mmol/L normal, while 40-60 mmol/L is border-line(4)(24) . The sweat test does not have a diagnostic value in neonates aged below the first seven days or of body weight less than 3000 gr, and neither in patients with oedema or eczema(24) . When analyzing sweat test findings it should be kept in mind that border- line or slightly increased chloride rates in sweat can be also found in other pathological conditions, such as untreated adrenal insufficiency, ectodermal dysplasia, glycogenosis type 1, hereditary nephrogenic diabetes insipidus, hypothyreosis, hyperparathyroidism,

mucopolysaccharidosis, fucosoidosis and severe malnutrition . Also, sweat test findings can be false in pyrexia, dehydration, high table salt consumption and during diuretic therapy.

Today DNA analysis represents a modern method in the diagnostics of CF. However, most laboratories can detect only most frequent mutations, so that genetic verification of rare variants of the disease are likely to go unnoticed

Others tests of diagnostic valued include a high level of immunoreactive serum trypsinogen, which is widely used within the framework of neonatal screening on CF, then a low level of pancreatic enzymes in the duodenal juice, high content of fat in stool, pathological pancreozymin-secretion test, low fecal elastase level, increased potential difference at the level of the nasal epithelium and other(24)(25)(26)

Treatment

The goals of treatment primarily include:

Respiratory system

Preventing and controlling lung infections—antibiotics are prescribed. These mainly consist of inhaled forms of azithromycin, tobramycin, aztreonam and levofloxacin. Other antibiotics recommended are ciprofloxacin, cephalexin, amoxicillin and doxycycline depending on the sensitivity patterns (19,20).

Control of airway inflammation—NSAIDs, inhaled and systemic steroids and cromolyn(21).

Reducing viscoelasticity and removing thick, sticky mucus from the lungs and dilating the airways—inhaled β agonists with humidified oxygen; a 3–6% hypertonic saline solution and dornase alfa are recommended(22,23,24). Additionally exercise and physiotherapy including positive expiratory pressure (PEP) device or a high frequency chest wall oscillation device (a percussion vest) is recommended(25).

GIT

Preventing or treating intestinal blockages—oral rehydration and osmotic laxatives (incomplete blockage) and hyperosmolar contrast enemas (complete DIOS). A balanced electrolyte intestinal lavage solution or enema containing (diatrizoate meglumine and diatrizoate sodium) depending on vomiting status(26) .To prevent recurrence, regular administration of oral polyethylene glycol 3350 may be given for 6 months to 1 year.

Pancreatic insufficiency—pancreatic enzyme replacement therapy (PERT) containing multiple combinations of proteases, lipases and amylases (27)

Nutrition and electrolyte

Providing appropriate nutrition and preventing dehydration—a high-calorie-fat diet, supplemental vitamins ADEK, and minerals including fluoride and zinc are recommended. Additionally sodium chloride supplementation is given tailored to patient's age and environmental conditions(28).

Medicinal drugs in use now and in the future

The existing and potential therapeutic goals are primarily aimed at correcting CFTR protein structural and functional abnormalities. In addition, certain agents for symptomatic relief are in the works.

CFTR modulators

A new group of drugs called CFTR modulators are available which are able to correct the basic defect in CF, i.e. CFTR protein itself though the exact mechanism is not fully elucidated.

1. Ivacaftor
2. Lumacaftor
3. Orkambi

Limitations that may exist

Despite the fact that the arrival of CFTR modulators has strengthened CF management, there are still some limitations, such as (a) ivacaftor's non-significant response in F508del mutation heterozygotes; (b) the need to continue other regular symptomatic treatment; (c) interactions with CYP3A inducers and inhibitors; and (d) side effects such as elevated transaminases, cataract, oropharyngeal discomfort; (e) negligible benefit in children under the age of 12; (f) need for higher doses up to 600 mg (in the case of lumacaftor); and (g) reciprocal interaction of lumacaftor and ivacaftor, resulting in increased ivacaftor metabolism and the need for a higher dose combination.

Furthermore, due to CFTR's multidomain structure and sequential folding, no single "corrector drug" can correct all of the misfolding in various domains, necessitating the use of a mixture of medications. Furthermore, there are sample size concerns in clinical trials, as complex requirements (primary and secondary endpoints) make selection more difficult in already restricted mutation specific populations.

Conclusion

While the management of CF patients has improved after the approval of CFTR modulators, it still falls short of expectations because CF requires not only protein rectifiers but also symptomatic medication and extensive physiotherapy, both of which involve concurrent therapies. Numerous genotypes also pose a problem. The majority of the ‘corrector' drugs in development are for older children.

In addition to their high prices, most of these medications have significant hepatic and other side effects. Furthermore, many of the drugs listed above are still in the early stages of development, with minimal evidence, and a positive result cannot be assured. There's still a need to discuss the disease's psychological and social consequences.

Future research

Aside from CFTR, new molecular targets and gene engineering techniques may be investigated. Modern biology approaches such as DNA nanotechnology, systems biology, metabolomics, disease modeling, and intracellular protein kinetics can aid in the discovery of new cystic fibrosis pathways and networks, as well as new therapeutic targets.

Furthermore, experimental physiotherapy approaches, new drugs for symptomatic relief, and complications prevention should not be overlooked.

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