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«ANALYSIS OF CFTR GENE MUTATIONS IN CHILDREN WITH CYSTIC FIBROSIS AND THEIR CLINICAL CORRELATION WITH ENDOCRINE PATHOLOGY" (LITERATURE REVIEW)

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Abstract:
Cystic fibrosis is a genetic disorder caused by mutations in the CFTR gene. This autosomal recessive disorder is diagnosed in many regions by newborn screening, while in other regions, diagnosis is based on a cluster of recognized multiorgan clinical manifestations, elevated sweat chloride concentrations, or CFTR mutations. Cystic fibrosis is often associated with a shortened life expectancy, and the most common cause of death is end-stage lung disease.

Keywords: CFTR gene; Cystic fibrosis; Fibrosis cystica; General CFTR; gene therapy

ETIOLOGY

Cystic fibrosis is caused by a genetic mutation in the gene on chromosome 7 encoding the protein CFTR. This protein functions as a transmembrane chloride channel activated by cAMP. In the clinical course of the disease, both copies of the gene are mutated. More than 2,000 different mutations in the CFTR gene have been identified that can cause cystic fibrosis. These mutations are divided into the following 5 classes:

- Class I: Impaired protein synthesis
- Class II: Impaired protein processing
- Class III: Impaired regulation
- Class IV: Impaired chloride conductance
- Class V: Accelerated channel turnover

EPIDEMIOLOGY

Researchers now know that cystic fibrosis is an autosomal recessive disorder of exocrine gland function that most commonly affects individuals of Northern European descent, with an incidence of 1 in 3,500, and African Americans, with an incidence of 1 in 15,000. However, for unknown reasons, the prevalence is significantly lower in Asia (1 in 30,000). The most common mutation is [delta]F508 in exon 11, found in 70% of white patients with cystic fibrosis in the United States and in two-thirds of all cases worldwide. This mutation is a class II mutation of abnormal folding of CFTR, resulting in premature breakdown in the Golgi apparatus. The [delta]F508 mutation typically leads to exocrine pancreatic insufficiency and a higher risk of meconium ileus.

PATHOPHYSIOLOGY - Worldwide, approximately 89,000 people live with cystic fibrosis. The pathophysiological changes in cystic fibrosis are primarily caused by the loss of CFTR function and its important role as an anion channel in the apical epithelium. Loss of CFTR function alters hydration and pH in exocrine ducts, leading to obstruction and dilation of exocrine glands in many organs. Decreased CFTR function in sweat glands leads to increased salt loss and elevated chloride concentrations in sweat. Mucinous obstruction of pancreatic acini and ducts, as well as glandular obstruction of the vas deferens and submucosal glands of the respiratory tract, lead to organ destruction and fibrosis. The endobronchial airway space in people with cystic fibrosis is typically initially infected with bacterial pathogens such as Staphylococcus aureus and Haemophilus influenzae, followed by Pseudomonas aeruginosa. These infections are associated with a neutrophilic inflammatory response and persistent mucopurulent plugging, leading to bronchiectasis.

With the advent of CFTR modulator therapy, the pathogenesis of clinical disease is changing, and early intervention can partially prevent the development of

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multiorgan pathology. In utero administration of the CFTR modulator ivacaftor to ferret fetuses with a glycine substitution at residue 551 for an aspartic acid variant (p.Gly551Asp; legacyG551D) reduced meconium ileus and improved exocrine pancreatic function, growth, and survival.

CLINICAL PICTURE

Because pathogenic variants of the CFTR gene lead to different protein dysfunctions, the clinical presentation and rate of disease progression vary. More than 80% of people with cystic fibrosis and two severe gene variants have sequelae of exocrine pancreatic insufficiency, including protein and fat malnutrition, steatorrhea, and growth retardation. Both upper and lower respiratory tract disease begins in infancy with cough, rapid breathing, or wheezing or crackles on chest auscultation. As patients become infected with pathogens such as S. aureus and then P. aeruginosa, they frequently experience acute pulmonary exacerbations characterized by cough, sputum production, and shortness of breath, requiring more frequent airway clearance and often hospitalization.

Chronic endobronchial infections and inflammation lead to decreased lung function, characterized by decreased forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) measured by spirometry. Most patients with cystic fibrosis develop an obstructive pattern on spirometry. Recurrent pulmonary infections cause bronchiectasis, a major cause of morbidity and mortality. Additionally, patients with advanced cystic fibrosis may develop pulmonary hypertension, which is associated with decreased survival.49 Adults in the United States are reported to have an increased risk of comorbidities,1 including cystic fibrosis-related diabetes (29.2%),50 liver disease with cirrhosis (4.1%),51 and osteoporosis (7.5%).52 People with cystic fibrosis who have at least one copy of a CFTR variant with residual function often have a later onset of lung disease but have disease progression comparable to people with minimally functional variants.

Of the 563 infants diagnosed through newborn screening in the United States in 2021, 88.3% were asymptomatic at diagnosis. Among the 216 diagnosed after 6 months of age, the most common symptoms were acute or persistent respiratory distress (50.2%), such as cough or wheezing, nasal polyps or sinus disease (15.5%), congenital bilateral absence of the vas deferens or infertility (9%), steatorrhea or bowel abnormalities (7.7%), failure to thrive (6.9%), and clubbing of the fingers (2.6%). Diagnostic criteria for cystic fibrosis include one or more organ-specific findings and elevated sweat chloride levels or genetic confirmation of two disease-causing variants of the CFTR gene.

Most newborn screening methods involve measuring immunoreactive trypsinogen (IRT) in a drop of blood followed by DNA testing for CFTR variants. However, the thresholds defining elevated IRT and selecting CFTR variants may vary across states in the United States, affecting the prevalence of positive screening results. The sweat chloride test is the primary diagnostic test for cystic fibrosis, with high sensitivity (99%) and specificity (93%) and established guidelines for technical quality and accuracy at specialized cystic fibrosis centers. An elevated chloride concentration in sweat (60 mEq/L) is consistent with the diagnosis. Intermediate sweat chloride levels (30–59 mEq/L) warrant further biochemical, genetic testing, or nasal potential difference measurements, as well as long-term follow-up in specialized centers, as some patients may subsequently be diagnosed with definite cystic fibrosis, the incidence of which ranges from 6% to 48% based on prospective and retrospective case series and registry studies.

TREATMENT

Long-term therapy

Patients with cystic fibrosis are recommended to have at least quarterly visits with a specialized multidisciplinary team, including physicians, nurses, social workers, and dietitians, to monitor disease progression and manage multiorgan manifestations. For children aged 12 years and older, annual screening for psychosocial health problems is recommended. Monitoring of comorbidities includes an annual oral glucose tolerance test (10 years) for cystic fibrosis-related diabetes, dual-energy X-ray absorptiometry every 2–5 years (>8 years) to determine bone density, and colonoscopy every 5 years (40 years) for colorectal cancer.

Lung transplant

Despite significant advances in cystic fibrosis treatment, the disease continues to progress, and without surgical intervention, the lungs will eventually fail prematurely. Lung transplantation is the treatment of choice for end-stage lung failure. The timing of transplantation depends on many factors.

The International Society of Heart and Lung Transplantation has published a list of conditions to use when considering referral for transplantation and takes into account a 5-year predicted survival <50%, an FEV1 that has declined to 30% of predicted values, a rapid decline in FEV1 despite optimal therapy, a 6-minute walk distance of less than 400 meters, the development of pulmonary hypertension in the absence of a

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hypoxemic exacerbation, clinical deterioration characterized by an increasing frequency of exacerbations including acute respiratory failure requiring noninvasive ventilation, a pattern of poor clinical recovery after successive exacerbations, worsening nutritional status despite supplementation, and pneumothorax or life-threatening hemoptysis despite bronchial artery embolization.

Almost all lung transplants for cystic fibrosis require replacement of both lungs, as the patient's own affected lung serves as a source of infected secretions, which can pose a threat to the transplanted lung and cause respiratory failure. It should be noted that transplantation is not a cure for cystic fibrosis, but it does prolong life and provide significant symptomatic relief.

Diet and exercise

Patients with cystic fibrosis are advised to consume a high-fat diet and take fat-soluble vitamins to compensate for malabsorption. Furthermore, patients with cystic fibrosis are advised to consume a high-calorie diet to maintain a healthy weight and combat chronic inflammation and frequent infections. According to the Cystic Fibrosis Foundation, women should consume 2,500 to 3,000 calories per day, and men should consume 3,000 to 3,700 calories per day.

Those living in hot climates or participating in activities that induce sweating are advised to increase their sodium intake. Oral nutrition is preferred; if intake does not meet metabolic needs, as determined by a continuing decline in body mass index, enteral (tube) nutrition should be considered. This is typically administered through a gastric or small intestinal tube. Numerous controlled trials of enteral nutrition in patients with cystic fibrosis have shown benefits in the form of improved or neutral lung function after disease exacerbations, which directly correlates with body mass index. However, it is noted that no randomized trials of enteral nutrition in patients with cystic fibrosis have been conducted to date. Parenteral nutrition should be considered only if oral or enteral nutrition does not meet metabolic needs. Parenteral nutrition has been associated with an increased risk of sepsis and should be used sparingly. Regular exercise is recommended for patients with cystic fibrosis to maintain and support lung function.

CFTR MODULATOR THERAPY

CFTR modulator therapy works through two mechanisms to enhance CFTR function. Potentiators, such as ivacaftor, increase the probability that the protein channel is open, allowing chloride or bicarbonate to pass more easily across the cell membrane. Correctors, such as lumacaftor, tezacaftor, and elexacaftor, increase the number of channels on the cell surface, promoting proper protein folding, which enables transport to the cell surface (Figure 2). Severe variants, such as F508del, require both potentiators and correctors to improve channel number and function. Four modulators are currently approved by drug regulatory agencies in the US and Europe, and eligibility for each treatment depends on the specific CFTR genetic variants present. Ivacaftor is available as monotherapy, and lumacaftor-ivacaftor, tezacaftor-ivacaftor, and elexacaftortezacaftor-ivacaftor are available as combination therapy.

CONCLUSIONS

Cystic fibrosis affects approximately 89,000 people worldwide and is associated with a spectrum of diseases related to exocrine dysfunction, including chronic respiratory bacterial infections and reduced life expectancy. First-line pulmonary therapy consists of mucolytics, anti-inflammatory agents, and antibiotics, and approximately 90% of people with cystic fibrosis aged 2 years and older benefit from the combination of ivacaftor, tezacaftor, and elexacaftor.

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