Cystic fibrosis: A rare disease


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Abstract
Cystic fibrosis (CF) is a hereditary autosomal recessive disease predominantly affecting Caucasian children and young adults. It arises from mutations in the CFTR (Cystic fibrosis transmembrane Conductance regulator) gene, leading to thick, sticky mucus accumulation and subsequent organ damage, primarily in the lungs and digestive system. Diagnostic methods include neonatal screening, sweat chloride tests, and genetic testing. Management focuses on clearing airways, preventing infections, and maintaining nutrition. Emerging treatments target CFTR gene mutations, including gene therapy and genome editing. This review summarizes CF's background, prevalence, etiology, complications, diagnosis, treatments, and future research directions.

Keywords: Cystic fibrosis, CFTR gene, Pulmonary complications, Genetic testing, Therapeutic interventions

1. Introduction
Cystic fibrosis (CF) is a complex and chronic genetic disorder characterized by a malfunction in the CFTR gene, located on chromosome 7, which encodes the CF transmembrane conductance regulator protein. This protein plays a crucial role in regulating ion transport across epithelial cell membranes in various organs. In CF, the dysfunction of CFTR leads to altered ion transport, particularly affecting the respiratory and digestive systems, as well as the sweat glands and reproductive system in most cases. The disease typically manifests early in life, during infancy, and presents with a wide range of symptoms. The classic phenotype includes progressive obstructive pulmonary disease, exocrine pancreatic insufficiency, and elevated sweat chloride and sodium levels, observed in the majority of patients. Despite advances in treatment and management, CF remains a chronic and progressive illness, often with a reduced lifespan. On average, individuals with CF have a lifespan of approximately 30 years. While CF-like symptoms have been recognized for over two centuries, the term "cystic fibrosis" was formally coined in 1938 to describe the disease's characteristic pancreatic involvement. Today, ongoing research continues to improve our understanding of CF and develop new therapies to enhance the quality of life and longevity for those affected by this condition (1-6).

2. Epidemiology
Cystic fibrosis (CF) presents a complex picture of prevalence, affecting primarily Caucasians but also occurring in other racial and ethnic groups, albeit less frequently. In the United States, approximately 30,000 Americans, along with 3,000 Canadians and 20,000 Europeans, grapple with CF, while an alarming 12 million individuals in the U.S. unknowingly carry an abnormal CF

gene.Globally, prevalence rates vary, from 1 in 1,400 in Ireland to 1 in 3,500 in the U.S., with lower rates observed in regions like Asia and Africa (7). In Latin America, CF affects 1 in 1,600 to 14,000 live new-borns, with a detection rate of pathogenic variants around 41.6% (8). Mortality in childhood primarily stems from respiratory infections and malnutrition due to pancreatic insufficiency, particularly in resource-limited countries like Mexico and Latin America, though advancements in therapies have extended survival to an average of 18 years. In developed nations such as Canada, the U.S., and the U.K., where advanced treatments are accessible, life expectancy exceeds 40 years, with long survivors living beyond 47 years, underscoring the impact of improved therapies on enhancing CF patient lifespan (9,10).

3. Genetic inheritance

Cystic fibrosis (CF) is a monogenic autosomal recessive genetic disorder, indicating that offspring resulting from a union between a mother who is a carrier of the CF gene and a non-carrier father have a 50% probability of inheriting the carrier status and a 50% probability of remaining unaffected. Similarly, in cases where both parents carry the CF gene, their offspring have a 25% likelihood of being unaffected, a 50% likelihood of inheriting the carrier status akin to their parents, and a 25% likelihood of manifesting CF symptoms. This genetic inheritance pattern underscores the necessity for comprehensive genetic counselling and testing to ascertain CF risk within familial contexts (11).

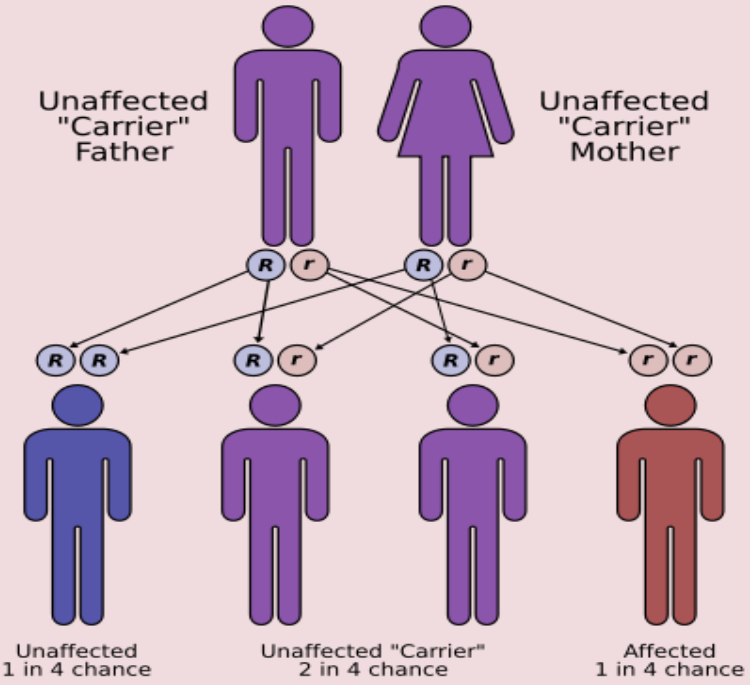

Figure 1. Autosomal recessive cystic fibrosis (12)

(Source: Disabled World. (2022, April 13)

4. Symptoms

- Salty-tasting skin on kissing
- Persistent coughing, at times with phlegm
- Frequent lung infections including pneumonia or bronchitis
- Wheezing or shortness of breath
- Poor growth or weight gain in spite of a good appetite (13,14)

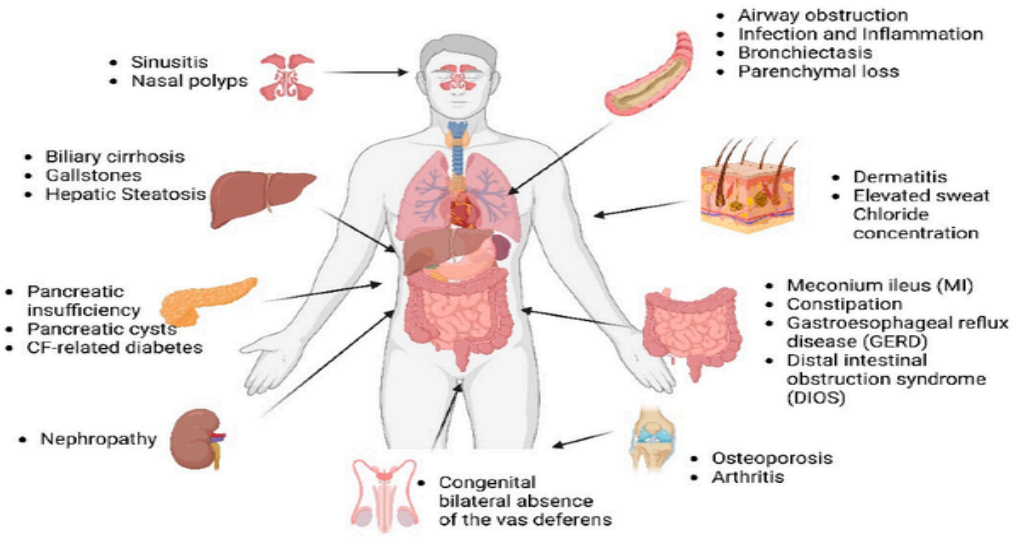

Figure 2. Symptoms of cystic fibrosis (15)

(Source: Ramananda Y, Naren AP, Arora K. Functional Consequences of CFTR Interactions in Cystic Fibrosis. Int. J. Mol. Sci. 2024;25:3384)

5. Diagnostic methods

Diagnosing cystic fibrosis (CF) involves several tests to identify its characteristic features.

5.1 **Sweat electrolyte level measurement**: Elevated chloride levels (>60 mmol/L) indicate CF.
5.2 **Salty skin test**: Infants with CF may exhibit salty skin when kissed, serving as a notable sign of the disease.
5.3 **Newborn screening**: Utilizes the Guthrie blood spot test followed by genetic testing for CFTR gene mutations, commonly conducted in the UK.
5.4 **Blood tests**: Assess immunoreactive trypsinogen levels, aiding in CF diagnosis.
5.5 **Chest X-rays**: Show lung inflammation, fibrosis, and scarring indicative of CF-related airway obstruction and lung infections.
5.6 **Sinus X-rays**: Reveal signs of sinusitis, another common manifestation of CF.
5.7 **Lung function tests:** Evaluate respiratory function, assisting in CF diagnosis and monitoring.
5.8 **Sputum cultures:** Identify pathogens responsible for lung infections in CF patients.
5.9 **Genetic testing:** Crucial for detecting CFTR gene mutations, with PCR and DNA sequencing being common methods.
5.10 **Comprehensive tests:** Such as the Ambry Test, employing temporal temperature gradient electrophoresis analysis and DNA sequencing, may be necessary due to the extensive mutation spectrum of the CFTR gene.
5.11 **Combined approach**: Utilizing clinical, radiographic, and genetic tests is vital for accurate CF diagnosis and management. (16-18)

6. Management and treatment

Cystic fibrosis (CF) management primarily focuses on symptom control, complication prevention, and improving patients' quality of life, as there is presently no cure for the condition. To combat lung infections, a variety of antibiotics are prescribed depending on the severity, with options including azithromycin, tobramycin, aztreonam, levofloxacin, ciprofloxacin, cephalexin, amoxicillin, and doxycycline. These antibiotics are administered orally or through inhaled forms to target respiratory inflammation and prevent infections (19,20). Bronchodilators, such as beta-agonists, are also utilized to dilate airways and reduce the viscosity of mucus in the lungs, aiding in its clearance. Inhaled Dornase Alfa, or pulmozyme, is another treatment option that breaks down excess DNA in pulmonary secretions, lowering the risk of respiratory tract infections (21,22).

For gastrointestinal issues commonly associated with CF, treatment includes oral rehydration therapy to combat dehydration, osmotic laxatives to soften stools, and hyperosmolar contrast enemas for distal intestinal obstruction syndrome (DIOS). Pancreatic enzyme replacement therapy (PERT) is crucial for overcoming pancreatic insufficiency, allowing for better absorption of nutrients. PERT supplements contain enzymes to aid in the digestion of proteins, carbohydrates, and fats, preventing malabsorption and malnutrition. Additionally, CF patients require a specialized diet rich in calories, vitamins (A, D, E, K), minerals, and sodium chloride supplementation, tailored to their individual needs and environmental conditions.

Supportive therapies play a significant role in managing CF symptoms and improving overall well-being. These include airway clearance techniques using bronchodilators, mucolytic agents, and various devices, as well as the use of steroid inhalers to reduce inflammation. Recombinant human DNase I (rhDNase I) inhalation is also utilized to assist in mucus clearance. Moreover, recent breakthroughs in CF research have led to the development of CFTR modulators, drugs that target the specific gene defect underlying CF. While the long-term benefits of these medications are still being studied, and initial clinical trials have shown promise in slowing disease progression in the lungs, potentially enhancing the quality of life for CF patients (23-25).

7. Conclusion

Cystic fibrosis (CF) is a complex genetic disorder caused by mutations in the CFTR gene, leading to defective ion transport across epithelial cell membranes and affecting the respiratory and digestive systems. Diagnosis involves sweat tests, genetic screening, and various imaging and lab tests to confirm CFTR mutations and characteristic symptoms. Although there is no cure for CF, treatment advances have greatly improved life expectancy and quality of life. Management focuses on symptom control and complication prevention through antibiotics, bronchodilators, mucolytics, enzyme replacement therapies, and specialized diets. Supportive therapies, including airway clearance techniques and CFTR modulators, further enhance patient outcomes. These therapeutic advancements have increased survival rates and improved the quality of life for CF patients, especially in developed countries. Ongoing research continues to offer hope for further improvements in managing and treating cystic fibrosis.

8. Future considerations

Advancements in cystic fibrosis (CF) treatment focus on addressing the disease's root causes rather than solely managing symptoms. By targeting early abnormalities in CF's pathophysiology, there's hope to improve outcomes and reduce treatment burdens. Therapeutic approaches like messenger RNA therapy, DNA/gene therapy, and gene editing aim to correct structural and functional CFTR protein abnormalities. While CFTR modulators offer relief, limitations such as variable efficacy and cost considerations persist. Screening initiatives for parents and prenatal molecular screening may help reduce CF's population burden. The ultimate goal is to develop interventions effectively halting or slowing disease progression, offering hope for enhanced quality of life for CF patients.

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