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REVIEW

Cystic fibrosis in neonates and infants

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Abstract Cystic fibrosis (CF) is a common autosomal recessive disorder, characterized by chronic bronchopulmonary infection, pancreatic insufficiency, and subsequently, other multisystem complications. Most children are diagnosed before school age. Here we review the pathophysiology of the condition, the age-related presentations of CF up until school age, and the appropriate use of diagnostic tests. A specialist centre should supervise treatment. There are exciting new advances in monitoring techniques in the preschool years, including CT scanning, bronchoscopy and gas mixing indices. Recent advances in the knowledge of the molecular biology of CF hold out the hope of specific therapies which can reverse the underlying defect causing death from CF lung disease.

Contents

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1. Introduction

Cystic fibrosis (CF) is the commonest inherited disease of white races. It is inherited as an autosomal recessive disorder, and leads to chronic bronchopulmonary infection, pancreatic insufficiency, and eventually, other multisystem complications including macronodular cirrhosis, diabetes, and osteopaenia. The fundamental defect is absent or reduced function of a protein, cystic fibrosis transmembrane regulator (CFTR), encoded on the long arm of chromosome 7. The prevalence varies between 1 in 2000 (Ireland) and 1 in around 500,000 (Japan) [1,2]. The disease can be found in virtually every ethnic group. Presentation may be at any stage from antenatally to extreme old age, and the complexities of management extend throughout most organ systems. This review focuses solely on the aspects of the disease that are relevant to the newborn and infants. The prognosis has improved dramatically; median survival for babies born in the 1990s or later is predicted to be forty years [3]. The reader is referred to standard references elsewhere for information on other aspects of CF [2].

2. Pathophysiology of cystic fibrosis

2.1. Molecular biology

CFTR undergoes complex processing between translation and the appearance of the mature functional protein at the apical cell membrane. Five classes of CFTR mutations have been described [4], which carry prognostic significance (Table 1) [5]. Furthermore, there is interest in class specific, molecular therapy for CF, for example using aminoglycosides to bypass a premature stop codon [6], and Sodium Phenylbutyrate to transport the commonest CFTR mutation in white races, ΔF_{508}, a class 2 mutation, to the apical cell membrane [7]. The severe mutations, usually associated with pancreatic insufficiency, are Classes 1—3. Compound heterozygotes for a mild and severe mutation generally have a mild clinical phenotype. Although there is reasonable correlation between pancreatic status and genotype, the relationship between severity of lung disease and genotype is much less clear.

2.2. Pathophysiology

CFTR has many functions (Table 2) [8] of which the best studied is the role as a chloride channel. The precise mechanisms whereby CFTR dysfunction produces CF lung disease is unclear. A number of hypotheses have been advanced, and currently the 'low volume' hypothesis is favoured. The evidence has been summarized elsewhere [9], but briefly, it is thought that hyperabsorption of sodium and water, secondary to over-activity of the sodium channel ENaC, leads to reduction in the height of the extracellular fluid layer, impairment of ciliary function, and failure of clearance of micro-organisms leading to chronic infection. In support of this hypothesis is a recent paper in which a very realistic model of CF lung disease was produced in

Table 1 Classes of CFTR mutation

Mutation class	Nature of defect	Example of genotype
Class 1	No synthesis	Nonsense, G542X Frame shift, 394delTT
Class 2	Block in processing	ΔF_{508}
Class 3	Block in regulation	G551D
Class 4	Altered conductance	R117H
Class 5	Reduced synthesis	A455E Alternative splicing, 3849+10 kbC→T