Cystic fibrosis – therapeutic challenge in cystic fibrosis children

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Abstract

Cystic fibrosis (CF) is the most common autosomal recessive disease with fatal outcome in Caucasians with a frequency of 1 in 2500 live births. It is caused by mutations in a single gene on the long arm of chromosome 7 encoding a protein called the cystic fibrosis transmembrane regulator (CFTR). The defect in CFTR leads to pathological changes in all organs with mucus-secreting glands, e.g. airways, pancreas, gut, biliary tract, vas deferens and sweat glands. Despite impressive advances in understanding the molecular basis of the disease, life expectancy is still limited in CF and chronic infection of the lung resulting in fibrosis and bronchiectasis followed by respiratory insufficiency is still the main factor in morbidity and the leading cause of death. Poor nutritional status is one of the major problems in the vicious cycle of chronic inflammation and lung destruction and its impact on outcome in lung function has been demonstrated. The possible role of growth hormone treatment in this context will be discussed.

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Genetics

Cystic fibrosis (CF) is the most common autosomal recessive disease with fatal outcome in Caucasians with a frequency of 1 in 2500 live births. It is caused by mutations in a single gene on the long arm of chromosome 7 encoding a protein called the cystic fibrosis transmembrane regulator (CFTR). Since the detection of the gene in 1989 more than 1000 mutations have been identified and these can be grouped into five classes (Table 1) (1–3). Class 1–3 mutations are associated with pancreatic insufficiency and are considered to be the more severe mutations, class 4 and 5 mutations are characterised by pancreatic sufficiency and higher age at diagnosis because of the later onset of typical symptoms. However, attempts to link the CFTR mutation to individual outcomes or severity of lung disease have failed. In addition to environmental factors, modifying genes regulating innate host defence are currently being investigated (4).

Pathophysiology

The defect in CFTR leads to pathological changes in all organs with mucus-secreting glands, e.g. airways, pancreas, gut, biliary tract, vas deferens and sweat glands. CFTR functions as a chloride channel at the cell surface, and results in defective ion transport when it is missing or not functioning (5, 6). The result is a water- and volume-depleted, thickened mucus, which leads to secondary problems in all affected organs.

The main symptoms are caused by an impaired mucociliary clearance in the airways leading to chronic bacterial colonisation and airway inflammation, and finally lung destruction. The obstruction of the pancreatic duct followed by pancreatic fibrosis leads to pancreatic insufficiency with malabsorption and maldigestion. Initially Langerhans cells are not involved, so the prevalence of diabetes mellitus is low in the first decade. With increasing age of patients, impaired glucose tolerance is becoming a relevant clinical problem, affecting more than half of the adult patients with about 25% being insulin dependent (7). CFTR is also expressed in the bile ducts, leading to chronic inflammation and periportal fibrosis in about one-third of patients with only very few resulting in liver cirrhosis (2–5%) (8). Obliteration of the vas deferens is the cause of infertility in 98% of the male patients. Female fertility seems to be nearly normal, although cervical mucus can be dehydrated and sperm activation can be impaired by the lack of HCO₃ (9). Recently some other possible functions of CFTR have been discussed. There are studies supporting the hypothesis that CFTR malfunctioning also influences HCO₃ transport. There is some evidence that CFTR might function as a pseudomonas receptor at the apical membrane of bronchial epithelium cells which internalise and kill pathogens. Thus, if the CFTR is not functioning, the bacteria in the airway lumen are free to multiply. The possible role of CFTR in lipid metabolism and the elevated resting energy expenditure is not fully understood (10, 11).

Table 1 Classes of CFTR mutations.

Class 1	No synthesis
Class 2	Defective intracellular processing
Class 3	Defective regulation
Class 4	Reduced conductance
Class 5	Partly defective production or processing

Clinical manifestation

Despite impressive advances in understanding the molecular basis of the disease, life expectancy is still limited in CF although it has improved dramatically in the last decades (Fig. 1). Chronic infection of the lung resulting in fibrosis and bronchiectasis followed by respiratory insufficiency is still the main factor of morbidity and the leading cause of death. Main symptoms in infancy are gastrointestinal and secondary to the pancreatic insufficiency. These children present with failure to thrive despite good appetite, they show abdominal distension and have massive fatty stools. The earliest manifestation of CF is the meconium ileus which occurs in 10–15% of CF patients. It can occur from the eighteenth week of gestation and results in bowel dilatation with thickened intestinal walls, intestinal atresia, perforation and peritonitis. These features are usually detected by prenatal ultrasound. In other patients, pancreatic insufficiency develops in the first months of life, so they might present with recurrent bronchitis or pneumonia before malabsorption is diagnosed. The diagnosis is made with a sweat test, a chloride concentration of > 60 mmol/l being diagnostic for CF. Yet, there are about 5% false-negative results, mainly in pancreatic-sufficient patients with milder mutations. Genotyping for the most common mutations (which are regionally different) confirms the diagnosis and should always be done if there are suspicious symptoms and borderline sweat tests. The typical clinical features of CF are listed in Table 2.

Table 2 Clinical symptoms of cystic fibrosis.

Organs	Symptoms
Airways	Chronic sinusitis, nasal polyps, chronic bronchitis and airway obstruction, pneumonia, bronchiectasis and lung fibrosis, emphysema, pneumothorax, haemoptysis, respiratory insufficiency, pulmonary hypertension and cor pulmonale
Gastrointestinal tract	Pancreatic insufficiency, chronic pancreatitis, malnutrition, distal intestinal obstruction (subileus, volvulus, mucocoele), cholestasis (periportal fibrosis, cirrhosis, portal hypertension, cholecystolithiasis, cholecystitis, cholangitis), diabetes mellitus, gastroesophageal reflux, chronic gastritis
Other organs	Salt wasting with metabolic alkalosis (pseudo-Bartter's syndrome), obstructive azoospermia, osteoporosis, nephrolithiasis, autoimmune diseases (chronic polyarthritis, amyloidosis, IgA-nephritis, etc.)

Nutritional status

In this context I will focus on the topic of malnutrition because this is one of the major problems in the vicious cycle of chronic inflammation and lung destruction leading to early death. Several studies show a good correlation between nutritional status and outcome in lung function (12–15). The reasons for malnourishment are various: on the one hand we have an elevated resting energy expenditure, which is rising further with chronic inflammation and impaired lung function. Even with optimal supplementation of pancreatic enzymes, 100% fat digestion is never established. These increased energy requirements are on the other hand accompanied by decreased energy intakes because of anorexia due to chronic infection, abdominal pain, frequent vomiting because of coughing and

Figure 1 Median age and proportion of adult patients from the German CF registry 2001.

Figure 2 Vicious cycle of energy imbalance and chronic inflammation.

psychological eating disorders. Figure 2 shows how malnutrition and chronic inflammation interact to contribute to the decline of lung function. The nutritional status of CF children has improved a lot in recent years with a diet high in fat and energy, and very aggressive nutritional management when children show signs of growth retardation according to their percentiles (see Table 3). Despite improved nutritional management, there is still a significant proportion of patients, especially adolescents and adults who are below 90% weight for height or who have a body mass index below 19 (Fig. 3) (16). Lately some studies have presented detailed data on resting energy expenditure (REE) which was shown to be markedly elevated in children and adolescents with CF compared with healthy controls; the difference being greater in females than in males. Pancreatic insufficiency was the strongest predictor for elevated REE. The greater energy expenditure in females may explain their difficulties in maintaining their weight and may contribute to their shorter life expectancy (17).

The musculo-skeletal system

Exercise capacity is reduced in patients with CF and correlates with lung function as well as with lean body mass (18). This together with chronic inflammation

Figure 3 Proportion of patients with malnutrition according to age (weight for height <90% in children; BMI <19 for adults).

leads to significant problems in bone mineralisation (19). Pathologic fractures are becoming a well-recognised clinical problem in adult patients. Sufficient supplementation with calcium and vitamin D is obligatory, regular exercise is now recommended for every patient.

Conclusion

Although chronic lung infection is still the predominant feature in CF the influence of nutritional status and exercise capacity on long-term outcome is evident. In this context, treatment with growth hormone is tempting, especially after the publication of good results in other severe conditions with catabolic status, e.g. patients with cancer or HIV infection, or after poly-trauma and burns. To date in CF we only have results from small studies with diverse results concerning the effects on growth and lung function. Larger prospective

Table 3 Graduated scheme for nutritional management in CF.

1. Regular control of nutritional status from diagnosis onwards
2. Falling below the percentile is followed by intense nutritional guidance, supply of nutrients with high energy
3. Enhancement of caloric intake by administration of high-energy supplements
4. Additional tube feeding overnight (mainly via percutaneous endoscopic gastrostomy tube (PEG))
5. Continuous gastrostomy feeding over 24 h

studies are needed (and are already underway) to evaluate the benefits and potential risks of such a treatment. Since CF is a multiorgan disease the therapeutic approach is a multidisciplinary one. Consequent anti-infectious and anti-inflammatory treatment as well as a comprehensive nutritional management are the major contributors to a better outcome. In addition, regular exercise and physiotherapy, and expert management of diabetes and other organ complications are necessary.

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