A review of Cystic Fibrosis

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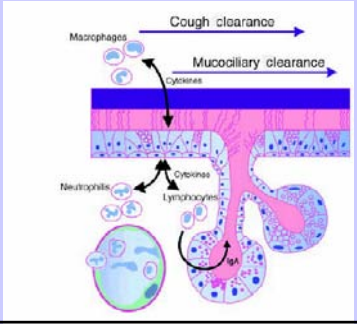
Cystic Fibrosis

- One of the most common lethal inherited AR disorders in the Caucasian population worldwide
- Recessive disease associated with loss of function mutations in the CF transmembrane conductance regulator (CFTR) gene

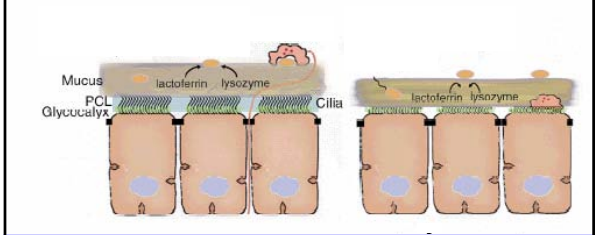
Innate immune system in CF

- Abnormalities in the fluid lining the airway surface (Quinton, *Nature* 1983)
- Compromised host defenses
- Smith et al. provided the first link between a defect in CFTR and a breach in pulmonary host defense (*Cell* 1996)

Innate defense mechanisms



Abnormal ASL in CF



Mutations of the CFTR gene

- 70% of patients carry at least one copy of the most common mutation -ΔF508-
- Over 800 unique mutations have been described
- http://www.genet.sickkids.on.ca/cftr/
- Based on the molecular outcome, genotypes can be assigned to 5 classes

Mutations of the CFTR gene

- Most of the reported mutations in CFTR are point mutations involving a few nucleotides:
  - Missense (40%)
  - Frameshift (22%)
  - Nonsense (or termination) (18%)
  - Splice-site (18%)
  - Others (promoter, in-frame deletions)

Clinical Presentation

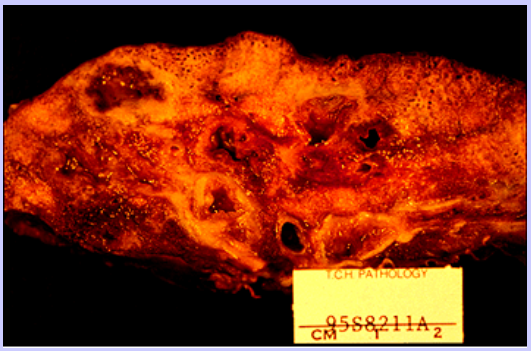
- Frequency of one in 2000 to 3000 live births
- Persistent pulmonary infections
- Pancreatic insufficiency
- Elevated sweat chloride levels
- Many patients with mild or atypical symptoms (*forme fruste*)

CFTR mutation and its clinical manifestations

- Affecting all the exocrine tissues
- Deranged chloride transport leading to thick, viscous secretions and affecting the following organ systems:
  - Respiratory tract
  - Pancreas
  - Liver
  - Intestinal tract
  - Reproductive tract
  - Sweat glands

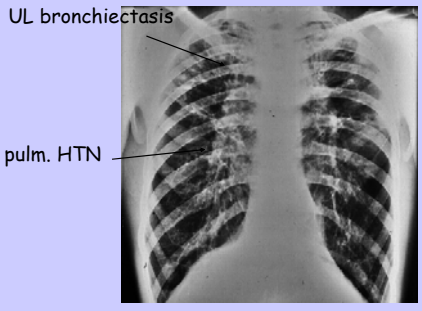
Respiratory tract

- Persistent, productive cough & purulent sputum
- Bacterial colonization with MDR organisms (*S. Aureus, H. Influenza, P. Aeruginosa, B.Cepacia*)
- Chronic bronchitis with or without bronchiectasis (RUL), hyperinflation and obstructive airway disease
- Cystic bullous disease, recurrent pneumothorax
- Acute exacerbations (weight loss)



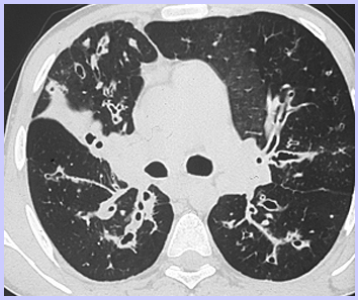
Purulent secretions in dilated airways

Chest x-ray



Hyperexpansion

CTscan of the Chest



Marked, diffuse bronchiectasis

Sinus disease

- Majority of patients
- Panopacification of paranasal sinuses in 90 to 100% of patients older than 8 months
- Chronic rhinosinusitis (*forme fruste*, heterozygote or carrier of a CFTR mutation)

Pancreatic disease

- Pancreatic insufficiency (PI) is present from birth in most patients
- Insufficient secretion of enzymes leading to malabsorption of fat and protein
- Steatorrhea and malnutrition, FTT
- Fat-soluble vitamins deficiencies (AEDK)
- Idiopathic chronic pancreatitis associated with CFTR mutations

Diabetes and CF

- PS vs PI
- Patients with exocrine deficiency have decreased insulin secretion, but normal glucose tolerance due to the unusual combination of increased hepatic glucose production and increased peripheral glucose utilization
- Initially able to counteract the effects of insulin deficiency but patients eventually develop DM

Meconium Ileus

- MI is the presenting problem in 10 to 20% of newborns with CF
- Virtually pathognomonic of CF
- Small bowel obstruction occurs in older children and adult, termed MI equivalent or distal ileal obstruction syndrome (DIOS)
- DIOS occurs in up to 15% of adults patients, associated with severe, advanced lung disease
- Surgical intervention is frequently required to relieve the obstruction and may lead to recurrent problems with adhesions

Liver & Biliary disease

- Focal biliary cirrhosis, due to inspissated bile duct
- Symptomatic portal hypertension in 2-5% of patients with CF
- Asymptomatic liver disease is common
- Cholelithiases in up to 12% of patients, due to excessive loss of bile acids in the stool (production of lithogenic bile)
- Prophylactic cholecystectomy in some centers pre-lung transplant

Fertility and CF

- 98% of male infertile despite adequate spermatogenesis
- Congenital bilateral absence of the vas deferens, a disease spectrum of CF
- Critical role of CFTR in the organogenesis of the Wolffian structure
- 20% Female infertility
  - Secondary amenorrhea (induced by malnutrition)
  - Abnormally tenacious cervical mucus
  - Good outcome if FEV_1 > 50-60%

Musculoskeletal disorders

- Osteoporosis
  - Direct link between the CFTR mutation and the pathogenesis of bone loss but mxn still speculative
- Hypertrophic osteoarthropathy
  - Abnormal proliferation of the skin and osseous tissue at the distal part of the extremities
  - x-ray evidence of periosteal new bone formation
  - Clubbing, part of the same disease spectrum but much more common
- CF-associated arthropathy (arthritis, nodular lesions and purpura) in 2-9% of patients

Diagnosis of CF

- More than 40% with respiratory symptoms
- FTT 29%
- Steatorrhea 24%
- Meconium ileus 19%
- Less than 10% on the basis of newborn screening
- 7% > 18 y.o (infertility, GI disease, DM)

Sweat Chloride test

- Gold standard for the diagnosis of CF
- Collection of sweat with pilocarpine iontophoresis
- Chloride value of > 60mEq/L distinguishes most patients with CF
- False positive
  - Hypothyroidism, hypoPTH, adrenal insufficiency, pseudohypoaldosteronism
- Gene studies for CFTR mutations

Treatments

- Largely symptomatic
  - Antibiotics (inhaled, PO, IV)
  - Bronchodilators
  - Chest physiotherapy
    - Clapping, flutter valve
    - Postural drainage
  - DNAse (decrease the viscosity of sputum, conflicting results)
  - Anti-inflammatory agents (NSAIDs)
  - Referral for organ transplants (lung (DLT), liver)

Attention!

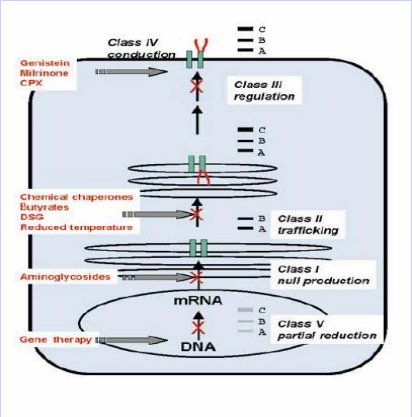
- Altered pharmacokinetics in CF patients
  - Volume of distribution of hydrophilic drugs (aminoglycosides, penicillins, cephalosporins) are increased because of malnutrition and decreased adipose tissue
  - Increased hepatic clearance of sulfa drugs because of accelerated acetylation
  - Increased renal clearance of trimethoprim (unknown mxn)
  - Renal clearance of aminoglycosides is considerably accelerated for unclear reasons, requiring a starting dose of about triple those normally recommended

Lung transplant

- Timing of referral: FEV_1 < 30% predicted
- Better outcome with patients without *Burkholderia Cepacia* infection, chronic steroid use and malnutrition
- Left with the non-pulmonary symptoms (& trx!!)
- PI and abnormal bowel motility make cyclosporine absorption and dosing difficult
- Pre-existing pleural disease from recurrent pneumothorax and chronic suppurative lung disease increases the risk of pleural haemorrhage and difficulty removing the native lung

Gene therapy in CF

- Gene therapy for the treatment of CF is a "natural"
- Well-characterized gene product
- The level of CFTR expression in affected cells generally appears to be low
- Heterozygotes appear to be phenotypically perfectly normal



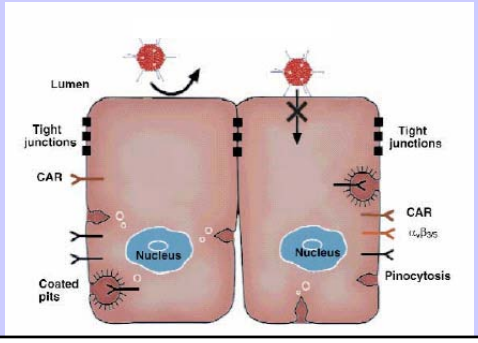
Gene therapy in CF (Cont'd)

- Dysfunctional epithelial lining cells in the organ most affected by CF (the lungs) are available for direct vector delivery via topical administration
- Little evidence to suggest that an effective gene-transfer is eminent

Gene therapy: Why not?

- The inability to produce such a therapy reflects in part:
  - The learning curve with respect to vector technology
  - The failure to appreciate the capacity of the airway epithelial cells to defend themselves against the penetration of gene-therapy vector

Airway epithelia



Conclusion

- The diagnosis of inherited disorders is increasingly more complex
- No longer sufficient to make a clinical diagnosis
- We must determine the precise sequence abnormalities in order to select the appropriate therapeutic approach

Conclusion

- Current treatment target the symptoms of CF
- Progress must now be made in repairing the nucleotide abnormality or assisting a defective protein
- Because a single mutation can affect both protein function and location, combination therapy is likely to be needed