Cystic Fibrosis

Advances and Asian Perspective

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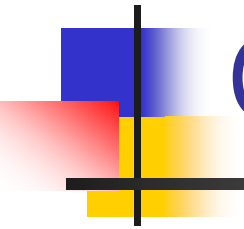
Cystic Fibrosis

- An Overview
- Asian Perspective
- Advances

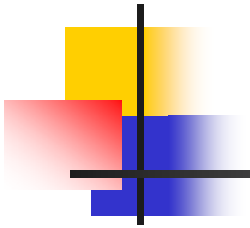


Cystic Fibrosis

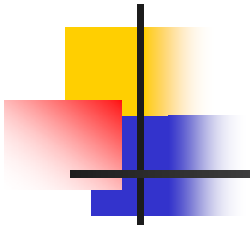
An Overview

Epidemiology and Pathogenesis

- Most common severe AR disorder in Caucasians
- Carrier rate of 1:25/Incidence of 1:2500
- Mutation affecting gene on long arm of chromosome 7
- CFTR - Cystic fibrosis transmembrane conductance regulator – a chloride channel- essential for salt and water movement across membranes.



- ΔF508 most common mutation-67% UK
- Numerous others in the same region
- Increased sweat sodium chloride
- Increased potential difference across respiratory epithelium detected in the nose
- Increased viscosity of secretions/ciliary dysfunction/chronic infection and bronchiectasis



- Disorders in the gut epithelium/ pancreas/liver (malabsorption/DM/cirrhosis)
- Infertility in most men
- Lung fn normal at birth but deteriorates.
- Staph and Pseudomonas predominate

Why is it so common?

- Carrier advantage in E coli diarrhea and cholera.

Management Principles

- Lung Disease
  - Maintaining function
  - Monitoring bacteriology
  - Transplant when appropriate
- Nutrition
  - Nutritional support/ weight/enzymes
- GI
  - Portal HT/Biliary cirrhosis

Management

- Endocrine
  - CFRD
  - Osteporosis
- Fertility advice
- Psychosocial well being

CF Pulmonary Sepsis

- Causes much mortality/morbidity
- Chronic colonization at an early age with bronchiectasis by 5 years
- FEV_1 best marker of deterioration/ improves with antibiotics
- To assess decline/ exacerbation/ antibiotic response.

Organisms

- Colonization changes over time.
- Goals
  - Prevent
  - Eradicate
  - Control
- H influenzae/ S aureus/ P aeruginosa(non mucoid/ mucoid)
- Burkholderia cepacia/MRSA/NTM

Antibiotics

- Higher doses and durations
- Clinical response guided by cultures
- Macrolides
- At home IV antibiotics/ usual course 2 wks

Other pulmonary interventions

- Physiotherapy
- DNAse
- Oxygen and NIV
- Steroids: ABPA/ exacerbations/ terminally
- Immunization: influenza/ pneumococcal

Transplant

- Life expectancy less than 2 years
- FEV_1 less than 30%
- Hypoxia and hypercapnia
- Young female patients deteriorate faster
- Infection/ acute rejection
- Bronchiolitis obliterans 40%
- 1 year survival 58%

Other pulmonary problems

- Pneumothorax
- ABPA
- Non-tuberculous mycobacteria
- CF asthma
- Haemoptysis

- Prognosis improving with better control of bronchial sepsis
- Median survival is about 40 years for those born in the nineties

- Gene therapy

Asian Perspective

- Are North Indians Caucasian?
- 1:2500 White Americans
- 1:15000 Black Americans
- 1:31000 Asian Americans
- Unknown in Indians
- Low index of suspicion and therefore late diagnosis

Cystic fibrosis in North Indian Children
Singh M et al; Indian J Pediatr 2002; 69(7):627-629

Bhakoo 1968	Chandigarh	1
Mehta 1969	Chandigarh	13
Reddy 1970	Andhra	2
Prasad 1990	New Delhi	2
Devanayagam 1990	Madras	68
Sarkar 1992	Calcutta	1
Kabra 1996	New Delhi	15
Singh 1998	Chandigarh	12

Cystic Fibrosis PGI (1995-1997)

- **Clinical Characteristics**
- Total patients 17
- Mean age at presentation (Year): 4.78+3.42
- Mean duration of symptoms(year) 4.05+ 2.1
- **Jammu and Kashmir , Panjab, UP, Rajasthan, HP**
- Mean sweat Chloride concentration (meq/l)81.8 + 25.
- Abnormal CXR (Peribronchial thickening, cystic changes) 15/17
- Abnormal CTchest, atelectasis, bronchiectasis (10) Patchy
- Malabsorption work up 4/6
- Genetic mutations DF 508 3/10 cases
- Clinical diagnosis 14/17 cases
- Autopsy 3/17
- Pulmonary disease alone 7/17
- Pulm + GI 9/17
- Pseudomonas colonization of the respiratory tract 12/17

Asian perspective

- DF 508 19-44% vs 70%
- UK CF Database
- 5274 children 88 from ISC ie 3.75%
- 63 Pakistani/12 Indian/7 Bangla/6 others
- Greater severity in Indians?

When is CF a possibility?

- Meconium ileus at birth
- Persistent pneumonia
- Malabsorption and failure to thrive (appetite+)
- Both together
- Salt losing syndromes
- Obstructive azoospermia

Confirmation

- Sweat chloride (> 60 mEq/L)
- Nasal potential difference measurements
- Mutation analysis
- No panel exists

Suppportive lab tests

- Low Na+/ low Cl-/metabolic alkalosis
- Airway colonization
- Pancreatic function tests(Stool elastase-1)
- Obstructive azoospermia
- CXR
- Sinus radiology

CF is rare but....

- Early diagnosis is beneficial
- Negative Mutation analysis does not rule out the condition
- Clinical evaluation/sweat test/ancillary tests

- 15/381 were South Asian
- (20/248 709 873 US population)
- Higher than all previous estimates
- ? Inadequate awareness and diagnosis only in severe cases

The prevalence and clinical characteristics of cystic fibrosis in South Asian Canadian immigrants
M Mei-Zahav et al
Arch Dis Child 2005;90:675-679

What is already known..

- CF is rare in populations not of European Caucasian origin
- More severe disease has been reported in South Asian CF patients
- Δ508 is less prevalent in South Asians

What this study adds...

- Prevalence and clinical course of CF in children of South Asian origin is similar to that in the general Toronto population
- Previous reports reflect inadequate awareness of CF in this ethnic group
- Δ508 is confirmed to be lower in this group(41% vs 66%)

- Failure to thrive is a manifestation of CF
- Kwarshiorkor and marasmus are often treated without CF being considered a D/D
- Consider CF in severe PEM!!

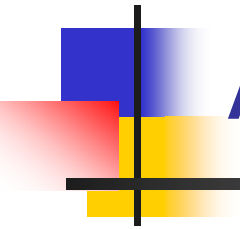
Cystic fibrosis presenting as kwashiorkor in a Sri Lankan infant
M Mei-Zahav et al
Arch Dis Child 2003;88:724-725

Cystic fibrosis in Asian Indians
Powers et al
Arch Pediatr Adolesc Med;150,May 1996

- 2 Asians referred with CF to a Chicago hospital in 1993
- Survey of 116 US centers to estimate incidence
- 1:40 750 (20/815 000)
- Possibility of underdiagnosis on ethnicity alone.

Cystic fibrosis in Asians
IM Bowler et al
Arch Dis Child 1993;68:120-2

- Clinical course in 9 Pakistani immigrants
- Grew Pseudomonas earlier
- Worse PFTs
- Higher IgG levels
- Lower wt for age/wt for ht
- ΔF508 4/9 vs 17/18
- More severe clinical course



Advances

HRCT: A Potential Outcome Measure

- HRCT & volumetric CT detect CF changes earlier than global PFT.
- Scoring used to define severity, progression, evaluation of treatment.
- Composite CT/PFT scores
- Quantitative airway and air trapping measurements

Therapeutic Trials

- Protein Rescue & Ion Transport Therapies
- Anti-inflammatory Therapies
- Anti-infection Therapies
- Nutritional/GI Therapies
- Mucus Clearance and Regulation Therapies
- Observational Studies

Protein Rescue & Ion Transport Therapies

- **TDN: Safety and Effectiveness of Curcumin in Adults with CF**
- TDN: Oral PTC124 for Nonsense Mutation-Mediated CF
- TDN: Inhaled INS37217 (denufosol) to Correct Salt Transport in CF

Anti-inflammatory Therapies

- Effect of Simvastatin on CF Airway Inflammation
- Effects of N-acetylcysteine Supplementation
- Safety and Tolerability of Oral Glutathione in CF
- Pilot Studies of Three Anti-Inflammatory Drugs (HCQ/MTX/Pioglitazone)

Anti-infection Therapies

- **Pilot: Comparing IV and Inhaled Antibiotics for Pseudomonas in Early CF (IV Ceftazidime + Tobramycin vs inhaled tobramycin for 2/4 wks)**

- Antibiotic Susceptibility Testing Using the Standard vs. the Biofilm Method

Phase II

- **Azithromycin in Individuals with CF and *B. cepacia***
- **Extremely resistant and produces intense inflammation**
- **Azithromycin has shown some promise when used long term**

Macrolides in CF

- 3 recent trials of azithromycin
- Improved FEV1 between 3.6-6.2%
- Decreased antibiotic use and exacerbations; wt gain
- Well tolerated
- Comparable with TOBI/DNAse

Mechanism of action

- Anti-microbial
- Anti-inflammatory
- Interaction with CFTR: better for homozygotes
- ? Change in sputum rheology
- Additive to other therapies

Phase III

- TDN: Treating Early *P. aeruginosa* Airway Infection in Young Patients with CF (EPIC Clinical Trial)
- TDN: Study of Risk Factors for Acquisition of *P. aeruginosa* and Early Anti-Pseudomonal Treatment (EPIC Observational Study)
- **TDN: Two Trials of Aztreonam Inhalation in Individuals With CF and *P. aeruginosa* Lung Infections**
- **TDN: Follow-up Study of Long-term Azithromycin**
- **Tobramycin Inhalation Powder in CF Patients With *P. aeruginosa***

Phase II

- Trial of Safety and Effectiveness of Inhaled Glutathione

Mucus Clearance and Regulatory Therapies

- **Aerosolized Surfactant and Hypertonic Saline for CF Lung Disease**
- **Lomucin (Talniflumate) to Reduce Mucus Overproduction**
- **Targeted Studies of Hypertonic Saline for CF Lung Disease**
- **Hypertonic Saline for Infants and Young Children With CF**

Advances in Gene therapy

- No other treatment options
- Easier for monogenic disorders
- 29 trials since 1993
- Initial hopes for progress belied
- Ease of non-invasive access to lungs
- Delivery to relevant cells difficult

Clinical Trials

- Adenoviruses used earlier
- Do not transfect airway epithelial cells
- Repeat admin not possible
- Adeno associated virus better
  - Safety profile
  - Broad tissue tropism
  - Long duration of expression
  - Superior escape from immune surveillance

Moss RB et al:Repeated adeno-associated virus serotype 2 aerosol mediated CFTR gene transfer to the lungs of patients with CF.Chest 2004,125:509-521

- Small improvements in function
- Reduction in IL-8
- Seen after first dose only
- Mild disease: difficult to detect improvement
- Severe disease: poor transduction because of increased inflammation and sputum barrier.

Konstan M et al: Single dose escalation study to evaluate safety of nasal administration of CFTR001 gene transfer vector to subjects with CF. Mol Ther 2004,7:S386

- Smaller nonviral gene transfer agents
- Less than 25nm
- Nasal adm in 12 patients
- 7/12 showed correction in Cl transport(15d)
- No placebo group
- Spillover from treated nostril to control nostril

Viral vectors

- Adenovirus mediated gene transfer poor in the absence of epithelial damage.
- No receptor on apical surface of airway cells
- Use of sodium caprate to open tight junctions to expose receptors on basolateral surfaces increased 25x
- Risk of systemic invasion by bacteria??

- Immune response after first administration.
- Reduced in vectors depleted of all viral genes
- Sendai virus most efficient: cannot be repeated!
- Lentivirus pseudotyped with Ebola are efficient but need repetition.

Non viral vectors

- Improving efficiency of these a major focus
- Adding sugars to polyplexes as airway cells express lectins which bind and internalise glycoconjugates
- Airway epithelial cell promoters to avoid CFTR expression in other cells eg FOXJ1
- Physical delivery methods eg electroporation, magnetism, USG, vibration to enhance transfecton.

Animal models

- Many CF knockout mouse models generated; gut disease more than lung disease.

- New models in ferrets, sheep,and pigs

End point assays

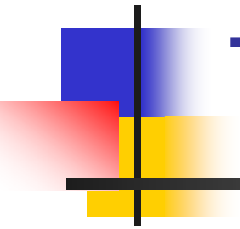
- Reduction in decline in lung fn.
- Reduction in episodes of infection
- Large numbers required to study these end points
- Surrogate end points needed eg bacterial burden, inflammatory markers, imaging

Gene therapy: current status

- Gene transfer to airway cells is inefficient
- Lung designed to keep foreign particles out
- New viral and non viral agents
- Physical delivery methods
- Surrogate end points

Conclusion

- CF may be more common in our country than previously thought.
- Needs to be actively excluded in conditions as diverse as marasmus to bronchiectasis and infertility



Thank you