Cystic Fibrosis

a) Diagnostic Dilemmas

b) The New Problems

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So what exactly is CF?

- A genetic diagnosis
- An electrolyte diagnosis
- An electrical diagnosis
- A symptomatic diagnosis
• It depends
• Management is not dependent on diagnosis
Consensus Statement - Diagnosis

- Clinical phenotype, or CF in a sibling, or positive newborn screening test

  Plus

- Abnormal CFTR: elevated sweat [Cl⁻], nasal PD abnormal, or positive genotype

*J Pediatr 1998; 132: 589-595*
CF Diagnosis - Lessons From USA

- Virtually all can be diagnosed by a sweat test - (98% of 19,992)

- False positive diagnoses are not unknown - 45 reversed in 1996

- Late diagnoses are too common - 10% not diagnosed until adult life

Source: CFF patient registry, 1996 annual data report, Bethesda, Maryland, 1997
Diagnosis of Grey Case CF

• You do not need 2 genes for a diagnosis
• You do not need a positive sweat test for a diagnosis.
• AND
• The child who is very well
  ❖ But, has positive tests for CF!
The Child With Equivocal Sweat Electrolytes

2,349 sweat tests

30<[Cl\textsuperscript{-}]<60, n=98

N=68, <18 years

N=43, traced, gene sequenced

N=10, 2 CFTR mutations
The Child With Equivocal Sweat Electrolytes: Conclusions

- 23% children with intermediate sweat electrolytes had two CF genes
- 4/9 had a normal nasal potential (amiloride, isoprenaline/low chloride)
- Beware the ‘not abnormal’ sweat test

_BluJournal_ 2002; 165: 757-761
False Positive Sweat Test

- Eczema
- Untreated adrenal insufficiency
- Type 1 glycogen storage disease
- Nephrogenic DI
- Malnutrition
- Panhypopituitarism
- Artifact - sweat test incorrectly performed
- Aids
- Fucoscdiosis
- Hypothyroidism
- Ectodermal dysplasia
- Mucopolysacharidosis
The Concept of ‘Pre-CF’

Child completely well

Plus

• Abnormal sweat test: *chemical pre-CF*
• Abnormal genotype: *genetic pre-CF*
• Abnormal PD: *electrical pre-CF*
CF with no CFTR Mutations

- 34 CF centres, 74 patients, 148 chromosomes
- 73 alleles discovered

- 39 DNA sequencing
- 34 mutation screens

- N=29 2 mutations
- N=14 1 mutation
- N=30 0 mutations
T for Two? 5T-7T-9T

- 9T – No problems
- 5T – Reduced CFTR, hinterland of disease-causing mutation
- 7T – yes and no, with reservations!
CFTR function

- <1%: Classical severe CF PI
- 5%: CF PS
- 10%: CBAVD
- 50%: Pancreatitis, ABPA, chronic sinusitis, diffuse panbronchiolitis
- 100%: Normal health

Adapted from Griesenbach et al, Thorax 1999
1-Diagnosis of CF: 2011

- Is and remains a *clinical* one primarily – *compatible phenotype*

- Laboratory tests confirmative only

- The more negative tests, and the more atypical the phenotype – consider alternative diagnoses, and test for them
2-Diagnosis of CF: 2011

• Whatever the diagnosis, treat what you find, and look for trouble

• 314/409 on USCFF Registry with normal, equivocal or missing sweat test were diagnosed on clinical grounds alone.

• The clinician is alive and well!
National standard protocol for newborn screening for cystic fibrosis

Appendix 1

Day 5 blood spot samples: IRT

IRT < 99.5th centile

Report: CF not suspected

IRT > 99.5th centile

DNA analysis – 4 mutations

Two CF mutations

DNA analysis – 29 or 31 panel

Refer with presumptive diagnosis of CF

IRT on 2nd blood spot

One CF mutation

IRT > 99.9 centile

Yes

IRT on 2nd blood spot

Av. > Cut-off 2

‘High likelihood’ Clinical referral

Av. < Cut-off 2

‘Low likelihood’ Advice, counselling

No

Av. > Cut-off 2

Report: CF not suspected

Av. < Cut-off 2

‘High likelihood’ Clinical referral

Note: 0.25 CF infants will not be identified through screening (IRT inaccurate in meconium ileus)

No mutation detected

41
CF. The next big things

• CF Related Diabetes
  • Non tuberculous mycobacteria especially M. Abcessus.
  • Aspergillus and allergic bronchopulmonary aspergillosis (ABPA)
  • Osteoporosis and use of water soluble Vitamin K
Diagnosis of CFRD

- An AFTERNOON, UNSTARVED oral glucose tolerance test.
CF. The next big things

- CF Related Diabetes
- Non tuberculous mycobacteria especially M. Abcessus.
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NTM
NTM Treatment

- 3 weeks IV amikacin, meropenem and cefoxitin plus oral clarithromycin
- Then 2 years of oral clarithromycin and ciprofloxacin and nebulised amikacin and meropenem
Aspergillus and ABPA

- Tortuous
- Use Itraconazole 200mg TWO times a day give with coca cola.
- Pulsed iv methyl prednisolone 10mg/kg twice day for 3 days is better than oral prednisolone, better result, fewer side effects
And finally....... 

- What is the role of the doctor in an Multidisciplinary team?

- Or........

- How to make an average person lookreally good?!
PATIENT

ME!

THERAPIST
ME    PARENT
• Surround yourself with really good people

• To become unnecessary!