Overview of Cystinosis in Adults

1st National Cystinosis Meeting
Birmingham
October 1st 2013

Dr Stephen Waldek
Independent Medical Consultant
Manchester
stephenwaldek@yahoo.co.uk
Nephropathic Cystinosis

- Defect in cystinosin
- Integral membrane protein
- Putative transporter for Cysteine out of the lysosome
- 367 AA and 7 trans-membrane domains
- Gene on chromosome 17p13 with 12 exons.
- Good correlation between severity and genotype.
Most children survive well into adulthood—5th decade
Later onset milder phenotypes exist
  ▪ Different, purely glomerular pathology
The seeds of complications are sown in childhood but the effects are often not a problem till adolescence or early adulthood.
Cystinosis is a Truly Multi-System Disease and thus it requires a truly multi-disciplinary approach to management.

The Metabolic team (or renal team) need to act as assessors and coordinators.
The Kidney in Adults with Cystinosis

- Dialysis and Transplant management
  - If managed well patient and graft survival no different from most other renal diseases
  - Host cells can infiltrate graft and get some crystal deposits
- Not all patients have reached end stage by the time they transfer to adult services
  - Manage CKD as well as fluid, electrolyte, and Ca^{++} homeostasis.
Non-End Stage Renal Failure

- Patients can be stabilised well into adult life
- Close attention to fluid balance
  - Regular fluids
  - Compensate for heavy losses
  - $\text{Na}^+$ and $\text{K}^+$ supplements if needed together with a source of $\text{HCO}_3^-$
  - Phosphate replacement and occasionally $\text{Mg}^{++}$ need to be given
  - Vitamin D is essential and nearly always needed ($\text{I alpha or 1, 25 (OH)}_2$)
  - Carnitine deficiency
Thyroid disease (Hypothyroidism)

- Almost invariable at some point in the course of the disease
- Easy to treat
- Easy to miss!
  - Regular checks needed.
- Dose of replacement therapy usually increases with age.
- Can it be influenced by better metabolic disease control?
Secondary Diabetes

• 20-30% of patients, but time of onset variable
  ◦ Might be influenced by good metabolic control

• Managed as per early onset type 2.
  ◦ Diet
  ◦ Metformin and other oral drugs do work BUT insulin often needed

• Diabetic complications do occur but not as often as one might predict

Vantyghem M-C et al Orphannet J Rare Dis 2012; 7:11
Nutritional Problems

- Pancreatic exocrine deficit
  - Responds to replacement therapy and good early metabolic control

- Swallowing dysfunction
  - Does respond to Rx
    - Sonies BC et al. 2005 Medicine (Baltimore) 2005;84:137-46

- Slow eating
  - Cause is “central”
  - Associated with disinterest in food
Ovarian failure

- Very common and distressing
  - Develops in most girls despite good biochemical control
  - Hormone replacement therapy important
    - Protect bones.
    - May help growth
- No increased risk of secondary malignancy.
- [Testicular failure also occurs]
Pregnancy

- There have been case reports of successful pregnancy

- Uterus is unaffected.

- Expert advice needed BUT
  - Discuss at an early stage.
Bone disease
Bone Disease

- Multifactorial
  - Direct renal effects
    - Renal failure
    - Urinary loss of $\text{Ca}^+$ with acidosis
  - Vitamin D deficiency
  - Effects of drugs
  - Sex hormone deficiency
  - Direct effects of crystal deposits
  - Secondary to muscle disease
The Eye

Corneal and Conjunctival deposits

Retinopathy is common but is often forgotten

Kaiser-Knupfer MI et al Arch Ophth 1886;104:706-11

Regular **ophthalmological** review is **mandatory**.
Myopathy (vaculopathy) is increasingly a problem in long survivors. Probably occurring later in life due to better control of disease. May be aggravated by anti-rejection drugs and/or bone problems.
Mild cognitive impairment can occur with enlarged ventricles and mild atrophy.

Rare in adults, but if present can make management and rehabilitation difficult.

Educational/occupational achievements may be limited but evidence lacking.

Benign intra-cranial hypertension
Cardiac and Respiratory Involvement

Significant cardiomyopathy due to crystal deposits causing fibrosis predominantly

Reduced exercise tolerance due to pulmonary disease

These are rare in adults if childhood treatment has been effective. However, must be looked for in adults

Anikster Y et al Chest 2001; 119:394-401
Specific Therapy----Free Aminothiol **Cysteamine**

- Membrane permeable and enters lysosome
- Di-sulfide bonded with cysteine
- Subsequent complex is removed via a different transmembrane transporter.
Using Cysteamine

- **Eye preparations**
  - Every 3-4 hours best.
  - Difficult to be compliant.

- **Systemic**
  - Total daily dose 60-90 mgs/Kgm
  - 6 hourly
  - Compliance a problem.
    - Frequency
    - Side effects
    - Taste
Side effects

- **Uncommon**
  - Rash and fever as part of “allergy”
  - Decreased appetite with nausea
    - Unfortunate
  - Diarrhoea

- **Rarer and more serious**
  - Headaches
  - Seizures
  - Extreme drowsiness
  - Bad dreams and hallucinations
A note on Compliance

- Usually good at first
- Reduces towards adolescence
- Improves after 18 years
  OR
- After significant “event”
How effective is Cysteamine?

- If compliance is good!
  - Slowing and/or preventing most complications
  - Reduces leucocyte cysteine levels by 95%
    - Target (90%)
  - Death rate significantly reduced but NOT normalized (yet)

Gahl et al Ann of Int Med 2007; 147:4)242--250
• 86 adults (mean age 26.7yrs)  75 received Cycteamine  
• Mean age of starting Rx 9.9yrs mean duration 17.4yrs  
• 78 had ESRD (mean age 11.1yrs)  
• 62 had hypothyroidism (mean age 131.4yrs)  
• 48 had diabetes (mean age 17.1yrs)  
• Best results f Rx started before aged 5  
• Life expectancy much improved

Brodin-Sartorius A et al Kidney Int 2012 (2):179-89
Other therapy

- Long acting cysteamine
  - Given every 12 hours
  - Also as drops

- Potential for Stem Cell Transplant
  - Works in a mouse model
    - Syres et al 2009 114 (12): 2542-2552
Psyco-scocial Issues—1

- Major problem in adults
  - Little studied.
- Education and Employment
  - Therapy commitments
  - Education underachievement
  - Tiredness and lethargy
- Rigors of therapy and Social life
- Acquiring social skills
  - Disease related
  - “Wrapped in Wool” syndrome
Psyco-social Issues—2

- **Short stature**
  - Growth hormone may work

- **Fair skin and blonde thin hair**
  - Due to lack of melanin synthesis
    - Chiavenini C et al. 2012 May FASEB J
  - Limits light exposure (thus holidays and other activities)

- **Sexual/reproduction issues**
  - Affects relationships

- **Depression**
  - Responds to Counselling
Conclusion

- Cystinosis is a multi-organ disease and thus---
- Needs a CO-ORDINATED Multi-agency approach
- Renal replacement therapy saves lives BUT
- Allows other complications to develop
  - These need to be—
    - Detected
    - Treated
    - Monitored
THANK YOU

My thanks also to all those colleagues who referred patients into the service and those who helped mange them.