Care of Adults with Cystinosis

A voyage of Discovery

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Overview

• Introduction
• Clinical aspects
• Organisation of Care for Adults with Cystinosis
  – The drivers for change
  – Transitional Care
• Cystinosis Rare Renal Disease working Group
• Cystinosis Registry
• Research for adults with cystinosis
• Future directions
Cystinosis

- Autosomal Recessive, incidence 1:150,000

- **Infantile Nephropathic form:**
  - Fanconi syndrome ~ 3-6 months
  - end stage renal disease (ESRD) ~ 10 years

- "**Late-onset**" (juvenile) form:
  - later onset (often during puberty)
  - mild tubulopathy, more proteinuria,
  - later progression to dialysis

- **Ophthalmalic form**
CTNS gene structure (17p13, 23 kb)

Most common mutation in European population: 57 kb deletion: CTNS gene, CARKL gene
(Town et al. 1998, Wamelink et al. 2008)
Pathophysiology of Cystinosis

Cystinosis in Adults

Game changers

• Kidney Transplantation
  ➢ Ongoing tissue accumulation

• Oral Cysteamine
  ➢ QDS-2g/day in adults

• Eye drops
  ➢ 0.55% 4-8x/day
When to Transplant: length of dialysis treatment before transplant

% event free survival

0 12 24 36 48 60 72 84 96 108 120

Months post-transplant

Pre-emptive
0–6 months
6–12 months
12–24 months
24+ months

No Recurrence of Cystinosis in Transplant Kidney
Good kidney survival
Renal Transplantation in Cystinosis

- Evidence of reduced T Cell immune responsiveness
- Patients who stop immunosuppression rarely reject
- PTLD?

Why better survival post transplant?

Extra-renal involvement

Eye
- photophobia
- keratopathy
- retinal blindness

Endocrine organs
- hypothyroidism
- diabetes mellitus
- male hypogonadism

Neuromuscular disease
- myopathy

Neurological complaints
- epilepsy
- mental deterioration
- cerebellar and pyramidal signs
- stroke-like episodes

Liver disease, exocrine pancreas deficiency

Gahl et al. 2002
Adult Survival in Cystinosis

Impact of Cysteamine

Cardiovascular Disease in Cystinosis
Coronary & Cerebral A calcification common

Ueda, M CJASN 2006:1: 555-562
End stage renal disease
Impact of Cysteamine

Diabetes/Hypothyroidism in Cystinosis
Impact of Cysteamine

Neuromuscular Problems
Reduced by Cysteamine

• Progressive muscle weakness and wasting starting in hands

• Progressive respiratory muscle weakness and recurrent aspiration
  – Breathlessness
  – Recurrent chest infections
  – Monitor lung function annually

Nesterova, Gahl. 2008; Paediatr Nephrol; 23: 863
Neuromuscular Disease in Cystinosis
Impact of Cyteamine

Swallowing

- Difficulty swallowing common in adults
- Oral/pharyngeal/oesophagus
- Dry mouth, slow eating, pain
- Affects nutrition
- Choking
- SALT assessment critical part of annual review-treatment
  - Altered texture diet
  - General advice
  - Artificial feeding-PEG

Central Nervous System
Reduced by Cysteamine

- Rare but more common in adults
- Forgetful, limb stiffness
- Very rarely dementia
- CT Scan
  - Atrophy
  - Calcification
- Rarely IIH
The Eye in Adult Cystinosis
(Oral cysteamine not effective)

- Corneal Cystine +
  - Photophobia
  - Blepharospasm
- Band Keratopathy
- Pigmentary retinopathy
- *Cystadrops (cysteamine gel formulation eye drops 0.55%)
  - Orphan Europe
  - Effective X1-4/day

Labbe ESPN 2011, Nesterova, Gahl. 2008; Paediatr Nephrol; 23: 863
Dental Disease in Cystinosis-Adults

Fully assessed 2010 for first time
• Abnormal enamel
• Delayed development
• Abnormal roots
• Cranio-facial development problems
Challenges
Contraception and Immunusuppression

Advise at discharge

- Safe, tolerated, effective, minimal interactions

Barrier methods

Progestogens
- Cerezette**
- Depot Progestogens

Contraception

Combined contraceptives

IUCD

– Mirena IUS*

Permanent

Impact of Pregnancy on Graft Survival
# Fetal outcome (Registry Data)

<table>
<thead>
<tr>
<th></th>
<th>NTPR (n=1418)</th>
<th>UKT PR (n=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Gestation (w)</td>
<td>36 weeks</td>
<td>36 weeks</td>
</tr>
<tr>
<td>Birth Wt (Kg)</td>
<td>2.4Kg</td>
<td>2.5Kg</td>
</tr>
<tr>
<td>Prematurity (&lt;37 weeks)</td>
<td>54%</td>
<td>55%</td>
</tr>
<tr>
<td>Low birth wt (&lt;2.5 Kg)</td>
<td>48%</td>
<td>54%</td>
</tr>
<tr>
<td>V low Birth wt (&lt;1.5Kg)</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>IUGR</td>
<td>20%</td>
<td>15%</td>
</tr>
</tbody>
</table>
Pre-conception Guidelines

• Contraception
• Pre-pregnancy Counselling
• Stable renal function, >1y post Tx
• Creatinine<175 (<125), <1g protein/24h
• BP< 140/90 on 2 or less drugs
• Prednisolone <15mg/day, azathioprine <2mg/Kg, CyA or Tacrolimus
• Stabilise patient pre-pregnancy-safe drugs

McKay AJT 2005;5:1592, Lessan-Pezeshki NDT 2002
Cystinosis-pregnancy

Special Issues
- Diabetes, thyroid
- Swallowing, reflux
- Respiratory function
- Cystagon

Cysteamine
- Fetotoxic at high dose in rats
- 3 human pregnancies reported-healthy baby
- Management of cysteamine in pregnancy
Young men with Cystinsois

- Despite early Cystagon
- Cystine deposition in testes
- Delayed puberty
- Low testosterone and inhibin B, raised gonadotrophins
- Testosterone replacement
- Azospermia but sperm on testicular biopsy
- Assisted conception?

Besouw et al. 2010: Fertil Steril; 96: 1880
Other less well recognised issues

- Reduced sweating, salivation, tears
- Hyperthermia
- Gingival problems
- Clotting abnormalities
Evolving Pattern

**Bone Marrow**
- Extensive cystine in marrow
- Low platelets, White cells
- Level of immune suppression?

**Liver Disease**
- Increasing recognised
- Non-Cirrhotic portal hypertension (NRH)
- Splenomegaly, ascites, varices-bleeding
Paediatric to Adult Transition

Key step for quality adult care
Transition & Transfer
Process vs. Event

Transfer of care

14y → 16y → 18y → 20y

Transition

Multiple Transitions
• School-college-Work
• Physical-puberty
• Independence
• Emotional etc
Transition vs Transfer of Medical Care

14y  16y  18y  20y

Transition

Transfer (individual)

Children's Hospital

Adult Services
Transition: Geography

Regional context (BCH)

≈50 miles by road  Population 5.5-6.0M
Why change what we are doing?

- South Asian, presented 3 months with FTT, Fanconi syndrome
- Diagnosis cystinosis (WBC cystine, genotype)
- Rickets, nutrition (PEG), growth hormone
- Rx cysteamine, variable compliance: smell, nausea
- Progressive CKD- Rx pre-emptive kidney transplant age 12
- Rx thyroxine,
- Age 16: Good transplant function, TSH 3, school (brother & sister)
- Transferred to UHB by letter
  - Seen in Tx clinic, variety SpRs, WBC Cystine levels ‘lost’, wrong bottle/time, 3 monthly follow up
  - WBC cystine levels-’incorrect sample’ >20 (target <1), TSH>99
  - Swallowing difficulties, recurrent chest infections
- Age 17, late acute rejection leading to return to dialysis
- Age 22, unemployed, depressed, parents give medicine
<table>
<thead>
<tr>
<th>Graft Survival (y)</th>
<th>Age Graft Loss (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.6</td>
<td>16</td>
</tr>
<tr>
<td>3.1</td>
<td>15</td>
</tr>
<tr>
<td>1.4</td>
<td>16</td>
</tr>
<tr>
<td>9.1</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>2.2</td>
<td>17</td>
</tr>
<tr>
<td>4.8</td>
<td>18</td>
</tr>
<tr>
<td>3.2</td>
<td>18</td>
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Poor planning of transition services for young people with cystinosis has significant clinical, psychological and health economic consequences. The impact is often greater than for other conditions.

Other Units?

- 20 young adults transferred to adult units-transplanted in Children’s renal unit
- 7 suffered unexplained Tx failure within 3 years

Most potentially avoidable

Watson 2000 & 2005

UHB/BCH experience ’95 to 2004
Survey of Transition

• 43 young adults transferred 2002-2006 (8 with cystinosis)
  – 30 transplant recipients, 13 on dialysis
• Questionnaires, mix of Tx and dialysis

Young Adults
  – I’m not same as those old people
  – I see someone different every time
  – Massive and busy-frightening
  – I wanted to go when I decided
  – I miss my mates
  – Adult unit more convenient

Carers
  • Loss of peer support
  • Different doctor each time
  • Doctor didn’t know about cystinosis
  • Scary letting go
Cystinosis Care Adults

- Rare genetic disorder identified in early childhood
- Cared for in Regional Paediatric Centres
- Adult NHS care patchy and poorly integrated
- Multi-speciality/professional team
- Patient (groups) knowledgeable
- Limited research base
- Adverse health outcomes and economic costs of poor care
Why is getting transition right so vital to young people with cystinosis?

• Normal transition ++
• Chronic kidney disease
  – CKD, dialysis or transplantation
• Cystinosis
  – Rare (education of adult clinicians)
  – Patient & carers live with disease for 2 decades
  – Non-renal multi-system issues
Renal allograft survival (days) before and after introduction of an integrated paediatric to adult transition and young adult clinical service

Harden P N et al. BMJ 2012;344:bmj.e3718
Key Issues

- Flexibility in transfer age
- Greater preparation for transfer at BCH
- Better introduction to adult services
- Development of adolescent clinic at UHB
- Overlap of services
- Key workers at both end to ensure tight communication
- Consistent staffing in adult services
- Prepare and support the carers
- Improved patient education
‘Transition tour’ of adult renal unit
Birmingham Model of Care
‘I know more than Doctor seeing me’,
Diagnosis: delayed >1y in half, 3 years in 20%
Support: Minimal information in half, patient society main source
Quarter patients have 4 clinics to attend
Only one third aware of treatment options
Most keen to be involved in research
UHB Rare Disease Service
Cystinosis

The Hub
UHB Rare Diseases Service
- One stop Clinic
- Diagnostics
- Multi-speciality
- Multi-professional
- Transition
- Patient support

UoB CRDPM (R&D Strategy)
Birmingham Children’s
- Transition

Intelligent IT Support
- Database for each disease
- Patient Access to health record
- Hub+Spoke access to Patient record
- Hub/spoke interaction (email/phone, video conf?)

Spoke (close to home)

Patient Support Groups
Pharma
Cystinosis Clinic at UHB

- Investigation protocolised
- Renal Metabolic CNS
- Sample timing, correct bottle and Lab transfer
- Annual review MDT: dietician, SALT, diabetes sister, links to Ophthalmology, Neurology support, cardiology
- Electronic database
- Results review
Rare Kidney Diseases Strategy

Rare Kidney Diseases:
An Integrated Strategy for Patients in the U.K.

The Renal Association and British Association for Paediatric Nephrology

April 2010

- Development of Disease Specific Working Groups
  - Diagnostic & Treatment
  - Patient information
  - Audit & Research
- Develop Care Pathways
  - Hub & Spoke
- Development of UK Registry (RadaR) under UKRR
Cystinosis-Rarerenal.org

Focus

- Best practice guidelines
- Champion condition
- Define model of Care
- Develop Comprehensive Cystinosis Registry (RadaR)
- Audit and research
Cystinosis Registry

- Cystinosis one of first disease pilots
- Extensive Registry already developed
- UK Renal Registry, RPV platform
  - Establish CEMARA link
Future Treatments?

- Cysteamine gel eye drops
- Cystadrops  Phase 3 Trials
Delayed Release Cysteamine in Young Adults
Can Concordance be improved?
Delayed Release Cysteamine in Young Adults

43 patients were enrolled in the study. 2 siblings withdrew at the end of the first RP103 period because of knee surgery of 1 of the siblings. 41 patients finished the study but 3 patients had their WBC cystine > 2 nmol/½ cystine/mg protein while under treatment with Cystagon® and were not included in the Per-Protocol Analysis.
DR Cysteamine in Young Adults
No reduction in GI side effects

• Oral cysteamine
  – X4/day
  – Compliance poor
  – Tolerability variable
  – GI side effects
  – Halitosis
  – Only 3/14 patients take X4/day in UHB cohort

| Table 3. Principal pharmacokinetic parameters for cysteamine after a single dose at steady state |
|---------------------------------------------------------------------------------|--------|--------|
| Cmax (mg/L)                                 | 2.73±1.36 | 3.70±1.72 |
| Tmax (min)                                  | 72±31     | 187±89  |
| AUC0−12h (min × mg/L)                       | 357±150   | 739±334 |
| t1/2 (min)                                  | 90±23     | 254±408 |
| CI/F (L/min)                                | 1.33±0.50 | 1.11±0.58 |
| Vd/F (L)                                    | 180±112   | 356±376 |
| AUCinf-D (min × mg/L)                       | 0.85±0.30 | 1.05±0.45 |

Langman C B et al. CJASN 2012;7:1112-1120
Comparison of cysteamine concentration and white blood cell cystine level over time.

Langman C B et al. CJASN 2012;7:1112-1120

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In vivo luciferase imaging and quantitative Ctns expression in Ctns−/− mice treated with WT BMCs as a function of time.

Syres K et al. Blood 2009;114:2542-2552
Mesenchymal Stem Cell microvesicle transfer of CTNSRed to intracellular compartment of CTNS(−/−) mutant fibroblasts.

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0042840
Summary

- Big challenges-real opportunities
- Ensure all adult patients with cystinosis have access to high quality care
  - Transition
  - Model of care
- Cystinosis DSWG
- RadaR-links with CEMARA
- Further integration of Research?
- Central Commissioning of care?
Questions