Section on Human Biochemical Genetics
MGB, NHGRI, NIH
Adult Medical Issues in Cystinosis

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<table>
<thead>
<tr>
<th>Age</th>
<th>Clinical Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>None</td>
</tr>
<tr>
<td>Infancy</td>
<td>Renal tubular Fanconi syndrome</td>
</tr>
<tr>
<td></td>
<td>Growth retardation</td>
</tr>
<tr>
<td>Age 10</td>
<td>Renal failure</td>
</tr>
<tr>
<td></td>
<td>Photophobic</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
</tbody>
</table>
Renal Allografts in Cystinosis

- Patients do well.
- Disease does not recur in graft.
- Cystine accumulation continues in other organs, causing post-transplant complications.
## CYSTINOSIS NATURAL HISTORY

### Post-Transplant Complications

- Diabetes mellitus
- Corneal and retinal damage
- Myopathy
- Swallowing difficulty
- Vascular and cerebral calcification
- Liver damage
- Pseudotumor cerebri
- Male hypogonadism
- Decreased lung function
- Death
Band keratopathy in a 14-year old girl
22-year old with cystinosis, myopathy, and swallowing difficulty. Died of aspiration.

Cystinosis patient with atrophy of tongue muscles.
Vacuolar Myopathy of Cystinosis

Variation in fiber size, type I fiber atrophy, ring fibers

Intracellular Vacuoles
Transmission EM of cystine crystals within lysosomes of perimesial cell

Scanning EM of cystine crystals within cellular lysosomes of muscle
Swallowing Difficulty

Pooling in valleculae and pyriform sinuses

Rare double bolus
Coronary Artery Calcification

Coronary angiogram of 25-year old man
Chest CT of 25-year old man with cystinosis
Cerebral atrophy in a 24-year old man

Cerebral calcifications in an adult with cystinosis

Pseudotumor cerebri; increased intracranial pressure
Liver Disease

17 mo: Diagnosis; no cysteamine
9 y: Renal failure
9-16 y: Peritoneal dialysis, peritonitis
17 y: Cadaveric renal allograft
17-19 y: Liver disease
  – Hematemesis; hepatosplenomegaly, ascites, gastroesophageal varices
  – Portal hypertension; sclerotherapy, banding
  – Anemia, hyperammononemia, 100 u of blood
19 y: Died of bacterial peritonitis
Gastric varix

Duodenal varix
Mild portal fibrosis

Increased reticulin staining with nodularity; Nodular Regenerative Hyperplasia
# 100 Nephropathic Cystinosis Adults (NIH, 1986-2006)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count/Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>26.2 ± 0.6 (18-45)</td>
<td></td>
</tr>
<tr>
<td>Transplanted</td>
<td>92/100</td>
<td>92%</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>75/100</td>
<td>75%</td>
</tr>
<tr>
<td>Male hypogonadism</td>
<td>39/53</td>
<td>74%</td>
</tr>
<tr>
<td>Poor lung function</td>
<td>53/77</td>
<td>69%</td>
</tr>
<tr>
<td>Impaired swallowing</td>
<td>58/97</td>
<td>60%</td>
</tr>
</tbody>
</table>
### 100 Nephropathic Cystinosis Adults (NIH, 1986-2006)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count/Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myopathy</td>
<td>50/100</td>
<td>50%</td>
</tr>
<tr>
<td>Cholesterol &gt;200 mg/dL</td>
<td>31/94</td>
<td>33%</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>32/100</td>
<td>32%</td>
</tr>
<tr>
<td>Calcified coronaries</td>
<td>16/52</td>
<td>31%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>24/100</td>
<td>24%</td>
</tr>
<tr>
<td>Calcified basal ganglia</td>
<td>21/95</td>
<td>22%</td>
</tr>
<tr>
<td>DEATH</td>
<td>33/100</td>
<td>33%</td>
</tr>
</tbody>
</table>

(Mean age 28.5 ± 1.1 y)
## Adult Cystinosis Patients (NIH, 1986-2006)

### Causes of Death (N=33)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis [bowel perf. (3); peritonitis]</td>
<td>9</td>
</tr>
<tr>
<td>Unknown; sudden death</td>
<td>8</td>
</tr>
<tr>
<td>Uremia [refused dialysis (3)]</td>
<td>5</td>
</tr>
<tr>
<td>Pneumonia/Aspiration</td>
<td>5</td>
</tr>
<tr>
<td>Liver disease</td>
<td>3</td>
</tr>
<tr>
<td>CNS deterioration</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
</tr>
</tbody>
</table>
HS-CH$_2$-CH$_2$-NH$_2$

CYSTEAMINE
## NIH Intent-to-treat Analysis for Oral Cysteamine (1960-1992)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Predicted age at which creat clearance is zero (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cysteamine</td>
<td>9.5</td>
</tr>
<tr>
<td>Partial cysteamine</td>
<td>20.0</td>
</tr>
<tr>
<td>Excellent cysteamine</td>
<td>74.3</td>
</tr>
</tbody>
</table>
Renal Failure in Cystinosis

% not in renal failure

Cysteamine

Control

Age -years

(modified from Proc EDTA (1982) 19:582-9)
No Cysteamine

Cysteamine

Muscle Cystine

Age (years)
Cysteamine Effect: Cystinosis Liver

Untreated 10 year old  Cysteamine-treated 9 year old
- Approved August 15, 1994
- Approved for pre-transplant patients only
- Cost remains reasonable: ~$3000-$5000/year in U.S.
Pre-transplant, oral cysteamine therapy:

- Preserves renal function
- Allows for a normal growth rate
- Preserves thyroid function
- Depletes muscle & liver of cystine
Most cystinosis patients begun on cysteamine therapy early (1-2 years of age) still require a renal transplant in their late teens or early twenties.
# Post-Transplant Cystinosis

<table>
<thead>
<tr>
<th>Complication</th>
<th>Cysteamine helps?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swallowing difficulty</td>
<td>Yes</td>
</tr>
<tr>
<td>Vascular calcifications</td>
<td>Yes</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Yes</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes</td>
</tr>
<tr>
<td>Myopathy</td>
<td>Yes</td>
</tr>
<tr>
<td>Pulmonary dysfunction</td>
<td>Yes</td>
</tr>
<tr>
<td>Death</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Yes</td>
</tr>
<tr>
<td>Liver damage</td>
<td>?</td>
</tr>
<tr>
<td>Pseudotumor cerebri</td>
<td>?</td>
</tr>
<tr>
<td>Male hypogonadism</td>
<td>?</td>
</tr>
</tbody>
</table>
101 Cystinosis Patients

Swallowing Severity Score vs. Years With Cysteamine
41 Post-Transplant Cystinosis Patients had Chest CT Scans:

- 28 Normal (mean age 22 y)
- 13 Coronary Artery Calcification (mean age 36 y)
% OF PATIENTS WITH MYOPATHY

**Years OFF Cysteamine**

- 0-10: n=24
- 11-20: n=28
- 21-30: n=38
- 31-40: n=10

**% Distribution**

- 0%: 2
- 10%: 5
- 20%: 22
- 30%: 73
- 40%: 0
- 50%: 0
- 60%: 0
- 70%: 0
- 80%: 0
- 90%: 0

**Years ON Cysteamine**

- 0-10: n=5
- 11-20: n=0
- 21-30: n=0
- 31-40: n=0

**% Distribution**

- 0%: 1
- 10%: 0
- 20%: 0
- 30%: 0
- 40%: 0
- 50%: 0
- 60%: 0
- 70%: 0
- 80%: 0
- 90%: 0
% OF PATIENTS WITH PULMONARY DYSFUNCTION

Years OFF Cysteamine

- 0-10: n=21
- 11-20: n=18
- 21-30: n=28
- 31-40: n=10

Years ON Cysteamine

- 0-10: n=53
- 11-20: n=20
- 21-30: n=4
- 31-40: n=0
# 100 Adult Cystinosis Patients

<table>
<thead>
<tr>
<th>Cysteamine</th>
<th>N</th>
<th>Age (y)</th>
<th>On (y)</th>
<th>Off (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8 y</td>
<td>61</td>
<td>27.0</td>
<td>2.0</td>
<td>25.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(+0.3)</td>
<td>(+0.8)</td>
</tr>
<tr>
<td>&gt; 8 y</td>
<td>39</td>
<td>25.8</td>
<td>15.1</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(+0.9)</td>
<td>(+1.6)</td>
</tr>
</tbody>
</table>
100 Adult Cystinosis Patients

<table>
<thead>
<tr>
<th>Cysteamine</th>
<th>N</th>
<th>%</th>
<th>Age (y)</th>
<th>Deceased</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8 y</td>
<td>61</td>
<td>100</td>
<td>11.0 (+0.4)</td>
<td>30 (49%)</td>
</tr>
<tr>
<td>&gt; 8 y</td>
<td>39</td>
<td>79</td>
<td>14.8 (+0.8)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td>&lt;&lt; 0.001</td>
<td>&lt;&lt;0.001</td>
</tr>
</tbody>
</table>
## 100 Adult Cystinosis Patients

<table>
<thead>
<tr>
<th>Cysteamine</th>
<th>N</th>
<th>Cholesterol (mg/dL)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8 y</td>
<td>61</td>
<td>195</td>
<td>143.6</td>
<td>45.3</td>
</tr>
<tr>
<td>&gt; 8 y</td>
<td>39</td>
<td>170</td>
<td>154.7</td>
<td>53.2</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>&lt; 0.02</td>
<td>&lt;&lt;0.001</td>
<td>&lt;&lt;0.001</td>
</tr>
</tbody>
</table>
100 Adult Cystinosis Patients

<table>
<thead>
<tr>
<th>Cysteamine</th>
<th>N</th>
<th># Complications*/Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 8 y</td>
<td>61</td>
<td>4.0 ± 0.3</td>
</tr>
<tr>
<td>&gt; 8 y</td>
<td>39</td>
<td>2.2 ± 0.3</td>
</tr>
</tbody>
</table>

*p < 0.001

*Myopathy, diabetes, pulmonary dysfunction, retinopathy, coronary artery calcification, cerebral calcification, swallowing difficulty, hypothyroidism.
Effect of Oral Cysteamine on the Late Complications of Nephropathic Cystinosis:

IT HELPS!
Cystinosis - Outcomes

Born in:

- 1955 - Death in infancy/childhood
- 1965 - Death or transplant, complications
- 1975 - Death or transplant, complications
- 1985 - Delay until age 15-25 in transplant
  - Expect no late complications

Early diagnosis is critical!
Nephrogenic Fibrosing Dermopathy
Nephrogenic Fibrosing Dermopathy

- Entity first reported in 1997
- 15 patients on chronic dialysis developed scleroderma-like disease
- Most rapidly progressive and debilitating -- no apparent benefit to range of anti-inflammatory and immunosuppressive drugs
- Cause unknown:
  - ? Dialysate or dialyzer toxin
  - ? Erythropoietin
  - ? Occult infection
  - ? Autoimmunity
Pathology findings indicated that it is a systemic fibrosing disorder – renamed: “nephrogenic systemic fibrosis”

- **Fibrosis**
  - Skeletal muscle
  - Myocardium
  - Lung and pulmonary vasculature
  - Diaphragm
Nephrogenic Systemic Fibrosis

- Registry established at Yale
- 215 definitive cases (spectrum of disease?)
- Not all cases on dialysis but all had renal insufficiency
- **Eureka moment!!** Spring 2006, Austrian and Danish clinicians noted most cases had MRI procedures within previous month – **Gadolinium proposed as likely culprit**
June 2006 (25 cases); updated December 2006

- FDA has received reports of 90 patients with moderate to end-stage kidney disease who developed NSF/NFD after they had an MRI or MRA with a gadolinium-based contrast agent.
- Patients with moderate to end-stage kidney disease who receive an MRI or MRA with a gadolinium-based contrast agent may get NSF/NFD which is debilitating and may cause death.
FOR IMMEDIATE RELEASE
May 23, 2007
FDA Requests Boxed Warning for Contrast Agents Used to Improve MRI Images
Risk Mitigation Strategy

- Eliminate higher-risk Gadolinium cmpds: those with low-affinity of Gad for chelate
- Consider alternative imaging techniques in patients with eGFR <30 ml/min
- Avoid multi-dose Gad if eGFR 30-60
- Improve ascertainment of compromised renal function
Cystinosis Past: The Natural History

AR; 1 in 200,000 births

Lysosomal storage disease due to impaired transport of cystine out of lysosomes (Crystals in many tissues)

Damage to many organs (Especially kidney)
Transmission EM of conjunctival cell
(Dr. T. Kuwabara)

Scanning EM of liver Kupfer cell
(Dr. Kamal Ishak)
Cystinosis: Future

- New cystine-depleting agents, studied in mouse models
- Better delivery to the GI tract
- Better transplant methods & meds
- Approval of Cystagon for post-transplant patients
- Approval of cysteamine eyedrops
- Newborn screening!
Frequency of retinopathy increases with time OFF cysteamine treatment.
Frequency of retinopathy decreases with time ON cysteamine treatment.