Neurological manifestations in Cystinosis

Nick Davies
Birmingham Muscle and Nerve Centre
Queen Elizabeth Hospital
Birmingham
Neurological manifestations in Cystinosis

- before cysteamine was available
- despite cysteamine therapy
- potential complications of cysteamine itself or other drugs used in this disorder
Complications before cysteamine was available

• before 1960 every person born with cystinosis died in infancy or < age 10

• before cysteamine, renal transplant improved survival to 2\textsuperscript{nd}/3\textsuperscript{rd} decade

• visual disturbance, corneal and retinal
• muscle weakness
• CNS problems
Complications before cysteamine was available

A study in 1993 of 36 patients (11 on cysteamine)

22% blind or severe visual impairment
86% hypothyroid
30% distal myopathy
58% dysphagia
22% cerebral calcification

Gahl JAMA 1993
Fig. 2 Late complications of cystinosis: a) vacuoles in the muscle cells, b) cystine crystals in the hand muscles, c) hepatic nodular hyperplasia, d) bone marrow cystine crystals, e) adult patient with trunk muscle wasting, f) hand muscle atrophy, g) barium swallowing study: Pooling in valleculae and pyriform sinuses, h) cerebral calcifications.
Figure 1. Oral Motor Index as a Function of Age in Patients with Nephropathic Cystinosis.

The oral motor index is plotted as a function of age at the time of examination in 43 patients. Circles represent patients who had not undergone renal transplantation, and squares those who had. The higher the oral motor index, the greater the oral motor dysfunction. The horizontal lines indicate mean values, and the vertical bars the standard error for the age groups 0 to 10, 11 to 20, and 21 to 31 years.
Complications before cysteamine was available

1982 – 19y hemiparesis and dysarthria, 50% had encephalopathy
1987 – confusion, memory loss and cerebral atrophy
1988 – severe vacuolar myopathy in a 20y progressed from hands to difficulty sitting up
  cystine crystals confirmed on biopsy
1989 – mental retardation, epilepsy, tremor pyramidal syndrome
Neurological complications despite cysteamine
Cysteamine available since 1976 but FDA approval 1994

A 38y female was followed in one study
Age 6 – presented with renal problems
Age 13 – dialysis
Age 14 – renal transplant
Age 23 – poor concentration/coordination
Age 29 – sleepy, MRI head – atrophy
CYSTEAMINE started
Age 32 – distal myopathy, encephalopathy improved
A. Short stature and generalized muscle wasting are evident in a 39-year-old man with cystinosis. B. Marked atrophy of the interosseous muscles of the hands is seen in the same patient. C. Electron microscopy of a postmortem specimen revealed shard-like crystals in the cornea of a 22-year-old patient.
Nijmegen group studied 10 adults (19-36y)
7 on cysteamine, 3 not

Table 1. Clinical characteristics of adult cystinosis patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>Height (cm)</th>
<th>Age at start of dialysis</th>
<th>Age at renal transplants</th>
<th>Most recent creatinine value (μmol/l)</th>
<th>Professional status</th>
<th>Visual acuity</th>
<th>Thyroid function</th>
<th>Glycaemia</th>
<th>Neurological and muscle dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>F</td>
<td>161</td>
<td>18</td>
<td>–</td>
<td>600</td>
<td>health care studies</td>
<td>decreased</td>
<td>normal</td>
<td>normal</td>
<td>no</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>F</td>
<td>160.1</td>
<td>10</td>
<td>12/14</td>
<td>160</td>
<td>shop assistant</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>sw/dys</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>M</td>
<td>158.5</td>
<td>12</td>
<td>14</td>
<td>100</td>
<td>low professional studies secretary</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>no</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>F</td>
<td>150</td>
<td>11</td>
<td>12</td>
<td>79</td>
<td>does not work</td>
<td>*</td>
<td>decreased</td>
<td>normal</td>
<td>no</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>M</td>
<td>150</td>
<td>7</td>
<td>7/9/19</td>
<td>58</td>
<td>does not work</td>
<td>decreased</td>
<td>decreased</td>
<td>normal</td>
<td>epilepsy</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>M</td>
<td>168.8</td>
<td>17</td>
<td>19</td>
<td>655</td>
<td>does not work</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>no</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>M</td>
<td>163</td>
<td>13</td>
<td>16</td>
<td>800</td>
<td>driver</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>no</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>M</td>
<td>175.0</td>
<td>not started</td>
<td>–</td>
<td>571</td>
<td>mechanic</td>
<td>*</td>
<td>normal</td>
<td>normal</td>
<td>no</td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>F</td>
<td>154.7</td>
<td>11</td>
<td>22</td>
<td>96</td>
<td>nurse</td>
<td>decreased</td>
<td>*</td>
<td>normal</td>
<td>no</td>
</tr>
<tr>
<td>10</td>
<td>36</td>
<td>M</td>
<td>166</td>
<td>22</td>
<td>19/25</td>
<td>120</td>
<td>does not work</td>
<td>decreased</td>
<td>decreased</td>
<td>normal</td>
<td>sw/dys, dyspnoea</td>
</tr>
</tbody>
</table>

sw/dys. swallow dysfunction; *not controlled/unknown; **IDDM, insulin-dependent diabetes mellitus.
<table>
<thead>
<tr>
<th>Neurological complication</th>
<th>Bethesda study 1993 N=36</th>
<th>Nijmegen study 2002 N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual loss/blindness</td>
<td>22%**</td>
<td>40%</td>
</tr>
<tr>
<td>CNS disorder</td>
<td>22%</td>
<td>10%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>58%</td>
<td>20%*</td>
</tr>
</tbody>
</table>
Nijmegen study conclusions

To reduce complications

• improving compliance with therapy was pivotal

• a reliable/consistent way of measuring cystine was essential

• multidisciplinary approach is necessary
Neurological complications despite cysteamine

Bethesda study 2007 (Ann Intern Med)

100 patients (18-45y)
From 1985-2006
92% transplanted
39 had long term cysteamine

Myopathy decreased if on cysteamine >20yrs

Respiratory muscle weakness (FVC) better if on cysteamine >10y (86% v 54%)
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, n/n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received a transplant</td>
<td>92/100 (92)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>75/100 (75)</td>
</tr>
<tr>
<td>Hypogonadism (in men)</td>
<td>39/53 (74)</td>
</tr>
<tr>
<td>Pulmonary dysfunction†</td>
<td>53/77 (69)</td>
</tr>
<tr>
<td>Swallowing abnormality</td>
<td>58/97 (60)</td>
</tr>
<tr>
<td>Myopathy</td>
<td>50/100 (50)</td>
</tr>
<tr>
<td>Hypercholesterolemia‡</td>
<td>31/94 (33)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>32/100 (32)</td>
</tr>
<tr>
<td>Vascular calcifications</td>
<td>16/52 (31)</td>
</tr>
<tr>
<td>Diabetes mellitus requiring insulin therapy</td>
<td>24/100 (24)</td>
</tr>
<tr>
<td>Cerebral calcifications</td>
<td>21/95 (22)</td>
</tr>
<tr>
<td>Deceased</td>
<td>33/100 (33)</td>
</tr>
</tbody>
</table>

* Not all patients were evaluated for every characteristic.
† Mean values for FVC, FEV₁, total lung capacity, and diffusing capacity for carbon monoxide were less than 80% of predicted values.
‡ Total serum cholesterol level >5.2 mmol/L (>200 mg/dL).
One hundred adults with cystinosis received cysteamine for a certain period of time and then did not receive cysteamine for a defined period of time, and each patient had or did not have a specific complication at the time of admission. Duration of cysteamine therapy was grouped in 10-year increments. The frequencies of diabetes, myopathy, pulmonary dysfunction, and death increased with time off cysteamine therapy and decreased with time on cysteamine therapy.
Neurological complications despite cysteamine

Cognitive dysfunction

Mild learning difficulty
Visuospatial problems

No clear benefit from Cysteamine
• cystine accumulation
• microvascular disease
• B-B barrier breakdown

Journal Medical Case Reports 2008
Muller M
Neurological complications despite cysteamine

Atherosclerosis/Stroke
Case reports only plus vessel calcification
Small, non-invasive study of 13 patients showed no difference with controls (J Inherit Metab Dis 2011)

Benign intracranial hypertension (BIH)

- Headaches worse first thing in the morning
- Occasional shutting down of vision
Neurological complications of cysteamine and other drugs used in cystinosis

**Cysteamine**

- Ataxia
- Encephalopathy
- Seizures
- Lupus-like, APS
- Copper deficiency
- ?Inflammatory myelopathy
Neurological complications of cysteamine and other drugs used in cystinosis

Immunosuppressive agents

• steroids

• tacrolimus

• cyclosporin
Neurological complications of cysteamine and other drugs used in cystinosis

Other drugs

**Statins** – muscle damage secondary to vitamin D deficiency +/- coenzyme Q10

**PPI/metformin** – B12 deficiency
Some neurological complications of cystinosis do not respond to cyteamine

e.g. the distal myopathy, WHY?

Other mechanisms at work

• autophagy

• increased oxidative stress/mitochondrial dysfunction
Neurological complications of cystinosis

Conclusions

• Cysteamine has dramatically reduced mortality and morbidity in cystinosis

• It clearly delays the onset of renal dysfunction, encephalopathy and dysphagia

• Myopathy and cognitive disorders and possibly cerebrovascular disease do not respond so well to treatment
Neurological complications of cystinosis

• Disease mechanisms other than cystine accumulation need to be considered including oxidative stress and secondary mitochondrial dysfunction

• In addition to Vitamin D supplementation, copper, carnitine and antioxidant therapies should be considered

• A multi-disciplinary approach should be adopted with particular attention given to neuromuscular respiratory disorders and risk of aspiration