Brain Structure and Function in Nephropathic Cystinosis

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Cystinosis and the Brain

- Metabolic disorder (of cystine transport)
- Lysosomal storage disease (cystine accumulates in lysosomes)
  - Virtually all lysosomal storage diseases have adverse effects on brain function
  - Mechanism of neural dysfunction not clear
Brain involvement has been noted since the 1970s

- Structural changes on CT scan
- Structural changes on MRI
- Neuropathological changes at autopsy
- Neurological deficits on examination
- Neuromuscular problems (progressive weakness)
- Cognitive dysfunction (visual spatial and visual memory problems)
- Academic difficulties
- Late-onset cognitive decline
Neurological Complications of Cystinosis

- Neurological complications only recognized when kidney disease was able to be treated successfully with renal transplant.
- As children lived longer and healthier lives, other organ involvement (including brain and muscle) was identified.
Neurological Findings

- Fine motor/coordination difficulties
- Gross motor delays
- Low muscle tone
- Tremor
- Seizures
General Features

- Neurological abnormalities are diverse
- Some changes appear to be static and nonprogressive (e.g., cognitive differences)
- Others appear to improve over time (e.g., coordination problems)
- Still others worsen over time (e.g., myopathy, late cognitive decline)
Current Studies

- Children 3 years and older
  - Typically developing controls
  - Children with nephropathic cystinosis
- Longitudinal MRI scans of brain every 2 years
- Longitudinal neuropsychological testing every 2 years
Brain Development in Cystinosis

- Brain growth in young children with cystinosis shows differences from non-cystinotic children
  - Smaller brain volume
  - Gray and white matter volume differences
  - Seen in children at least as young as 3 years
“Normal” Control Brain 4 years old

Cystinosis 5 years old: cortical atrophy
4-yr old Control
<-----

5-yr old Cystinosis
Cortical Atrophy
<-----

5-yr old Cystinosis
Cortical and Central volume Loss
<-----

4-yr old Cystinosis
Central Volume Loss
<-----
Volumetric Analyses of Brain MRIs

- Quantitative volumetric analyses of brain MRI scans allows us to compare size of cystinosis and control brains as a whole and to look at regional differences in brain volumes.

- Diffusion tensor imaging allows us to look at the integrity of the white matter in the brain.
Decrease of gray matter volume in 25 patients with cystinosis compared to controls

Left inferior parietal lobule, BA 40, p < 0.0001, corrected
Decrease of gray matter volume in 25 patients with cystinosis compared to controls

Right inferior parietal lobule, BA 40, p < 0.001, corrected
Decrease of gray matter volume in 25 patients with cystinosis compared to controls

Right precentral gyrus, BA 4
p < 0.001, corrected
DTI Results

- White matter integrity is disrupted in parietal white matter bilaterally in the same areas as gray matter volume is diminished.
Coronal, sagittal, and transverse views of voxels with a significant decrease in fractional anisotropy in the left anterior parietal lobe and postcentral gyrus (global maximum with $P < .01$, corrected for entire cerebral volume; $-42 -26 48$ mm) in 7 children with cystinosis compared with controls. Results are superimposed on the white matter segment of a spatially normalized T1-weighted MRI.
Coronal and sagittal views of voxels with a significant decrease in fractional anisotropy in the right anterior parietal lobe and postcentral gyrus (P < .05, corrected for entire cerebral volume; 44 -14 34 mm) in 7 children with cystinosis compared with controls. Results are superimposed on the white matter segment of a spatially normalized T1-weighted MRI.
Summary of Brain Structural Differences in Young Children with Cystinosis

- Gray and white matter volume smaller
- Largest quantitative difference in right and left parietal lobes (areas thought to direct visual spatial functions)
What Causes Differences in Brain Development in Cystinosis?

Cause unknown; possibilities include:
- Early cystine accumulation (in utero) with damage to lysosomes
- Indirect effect of metabolic disturbances
- Direct effect of gene on some aspect of brain development
- Effect of medications

Longitudinal studies may help to determine which is the most likely cause.
Impact of Cystinosis on Cognitive Function

- Children and adults with cystinosis are more likely to demonstrate specific cognitive difficulties than non-cystinotic individuals
  - Visual spatial dysfunction
  - Visual memory dysfunction
  - Attentional problems
Cognitive Profiles in Cystinosis

- Normal intelligence
- Normal language
- Normal verbal learning
- Poor visuomotor skills
- Deficits in visuospatial processing
- Deficits in short-term visual memory
- Difficulty with visual learning
- Difficulty with tactile discrimination
- Normal reading skills
- Difficulty with math and spelling
Intact ability to recognize visually presented information

Deficit in visual spatial skills (e.g., map-reading)

Difficulty with visual memory (i.e., accurately remembering information presented visually)
The parietal lobes of the brain are thought to be most involved in visual spatial function.

Volume of gray matter in the parietal lobes correlates directly with visual spatial function in young cystinosis children.
Correlation between GM and SRSS in the right superior parietal lobule, BA 7

$r = 0.6$
$p < 0.001$
Correlation between GM and SRSS in the left inferior parietal lobule, BA 40

$r = 0.4$
$p < 0.03$
INTELLIGENCE AND VISUAL PERCEPTION

![Bar chart showing IQ and VFD scores for Cystinosis and Control groups.](chart.png)
10.1-year-old boy (control)

11.6-year-old boy (cystinosis)
12-year-old girl (control)

13.25-year-old girl (cystinosis)
Age 6 Years

Model

Control  Control  Cystinosis
Age 6 Years

Model

Control  Control  Cystinosis
Age 7 Years

Model

Control

Cystinosis
Age 7 Years

Model

Control

Cystinosis

Cystinosis
Age 8 Years
Model

Control

Cystinosis
Age 8 Years

Model

Control

Cystinosis
Age 9 Years

Model

Control

Cystinosis
Age 12 Years
Model

Control

Control

Cystinosis
What does it mean?

If the child has spatial problems, you may notice difficulties with:

- finding his/her way around,
- drawing or constructing,
- arithmetic, social studies.
How Visual Spatial Problems Affect Learning

Math is a very spatially-mediated skill to learn

\[
\begin{array}{c}
4592 \\
-1835 \\
2757
\end{array}
\quad
\begin{array}{c}
742 \\
\times 48 \\
5936 \\
2968 \\
35616
\end{array}
\]
Visuospatial Difficulties Impacting Arithmetic

<table>
<thead>
<tr>
<th>Not Carrying</th>
<th>Direction of Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>62.04</td>
</tr>
<tr>
<td>+ 6</td>
<td>- 5.31</td>
</tr>
<tr>
<td>71</td>
<td>63.33</td>
</tr>
</tbody>
</table>
Although visual spatial and visual memory functions may be impaired, language and auditory processing are intact; this information provides a basis with which to suggest potential remediations if the child is having academic difficulties related to visual spatial dysfunction.
Remediation Examples

- **MATH:** have the student verbalize or talk through the problem; list steps of a process on a study sheet, and allow the student to refer to the sheet; reinforce direction of proceeding with computations.

- **WRITTEN ASSIGNMENTS:** use large, lined paper and paper folding; allow student to quietly read aloud written work.
Verbal and Visual Learning in Cystinosis
VERBAL LEARNING AND MEMORY

![Graph showing verbal learning and memory comparison between control and Cystinosis groups.](image-url)
VISUAL LEARNING AND MEMORY

Graph 1:
- Y-axis: d'
- X-axis: Trial
- Control vs. Cystinosis

Graph 2:
- Y-axis: d'
- X-axis: Trial 5, 20 Min. Delay
- Control vs. Cystinosis
VISUAL AND VERBAL LEARNING IN CHILDREN AND ADULTS WITH CYSTINOSIS

![Graph showing T-Score Trials 1-5 for children and adults with cystinosis. The graph compares VLMT and CVLT performance between the two age groups.]
VISUAL LEARNING AND MEMORY
INCREASED EXPOSURE TIME

Trial

\[ d' \]

- Control
- Cystinosis

Trial 5 20 Min. Delay

\[ d' \]

- Control
- Cystinosis
*Increasing exposure time to visual stimuli improved performance
*Suggests that visual processing problem is due to deficit in visual processing speed
*Provides foundation for interventions focused on increasing processing time
Take home message...

- “Forewarned is forearmed”
- Young children with cystinosis entering formal school, may be at risk for difficulties in these areas
- Parents can take a proactive approach with schooling from the beginning to help ensure successes
Brain development is different in children with cystinosis.

Differences in brain development correlate with difficulties with visual spatial function.

Visual spatial difficulties may contribute to learning difficulties.

Awareness and intervention when appropriate can prevent later problems.
Intervention Studies

- Based on our data, an intervention study was designed and conducted (see poster)
- We could not determine whether the intervention might have helped because of lack of participation and lack of follow-through on the part of participants
- We are now proposing an intervention study that, if successful, can be incorporated into the classroom with no additional time commitment needed from already over-burdened families
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Thank you!!!