MR Imaging Assessment of Inborn Errors of Metabolism

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Potential Uses of MR Imaging

- Establish diagnosis
- Assess brain structural changes
- Explain clinical findings
- Measure disease progression
- Evaluate effects of therapy
Types of MR Imaging

- Conventional clinical imaging
- Functional, e.g., brain activation studies
- Hemodynamic, e.g., perfusion imaging
- Metabolic, e.g., MR spectroscopy
- Microstructural, e.g. diffusion imaging
Target Disease and Technique

- Krabbe disease as a paradigm
- Brief review of MR spectroscopy
- Diffusion tensor imaging
MR Spectroscopy

- Depicts concentrations of various metabolites as peaks on a spectrum
- Diagnosis of inborn metabolic errors
- Many spectra are non-specific
- Means for assessing disease progression when diagnosis is known
Normal MR Spectrum
MR Spectroscopy: Krabbe

Decreased axons

Cell Turnover (demyelination)

Marker of (reactive) astrocytes

P Brockmann et al. Neurology 2003; 60:819-825
Diffusion Imaging
Diffusion Tensor MR Imaging

- Microscopic water motion within brain tends to occur predominantly along the long axis of white matter tracts
- Diffusion tensor imaging depicts that tendency
Anisotropy

- Compact white matter tracts have a very strong tendency for diffusion of water along the long axis of tracts

- That tendency is termed anisotropy

- Expressed by a metric termed fractional anisotropy (FA)
Diffusion Tensor Imaging

- FA values reflect integrity of (1) myelin sheaths and (2) axons
- FA values decrease following demyelination and/or axonal loss
Anisotropy

Lim KO, et al. Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. *Arch Gen Psychiatry* 1999; 56:367-374.
Diffusion Tensor

Anisotropic diffusion

Eigenvalues

Melhem ER, Mori S, Mukundan G, Kraut MA, Pomper MG, van Zijl PCM. Diffusion tensor MR imaging of the brain and white matter tractography.

*AJR* 2002; 178; 3-16
Diffusion Tensor Imaging

- Less compact white matter tracts have a less strong tendency for water motion to be directed along the long axis of tracts.

- Tensor diffusion imaging provides a method for measuring integrity of white matter tracts.
Age-related FA Increases

Corpus Callosum (Splenium)  First year of life
Age-related FA Increases

DTI - Mean FA of Normals (all ages)

GCCA – Genu of corpus callosum; SCCA – Splenium of CC

INA – Internal capsule; OR_A – Optic Radiations; FWMA – Frontal White Matter tracts
White Matter Tractography
DTI in Leukodystrophies

• In leukodystrophies, white matter is predominantly affected

• Hypothesis: DTI is a more sensitive measure of white matter involvement than conventional MR imaging in leukodystrophies
**Krabbe Disease**

- Diffusion tensor imaging appears to be:
  - Sensitive for WM changes
  - Likely more sensitive than T2-weighted images early in disease course
  - Findings may correlate with treatment effect
Potential Uses of MR Imaging

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Patients

- Nine infants with Krabbe's disease underwent a total of 16 MR studies during the first year of life
- Tests of mental development, gross motor skills, and fine motor skills (score range: 0-100) within 1 month of imaging

Patients

- One infant had 4 scans, 3 infants had 2 scans and 6 infants had 1 scan
- 3 weeks (n=2), 5 weeks (n=2), 5 months (n=1), 6 months (n=2), 7 months (n=1), and 9 months (n=1)
- No normal controls
MR Scans

- Scored using the Loes scale based on signal abnormality and atrophy; 0 to 32
- 2 neuroradiologists, by consensus
- Goal was not to assess therapeutic benefit of transplantation
- Compare clinical evaluations with MR findings as reflected by Loes scores
Loes Scoring System

- Developed for adrenoleukodystrophy
- Divides the entire brain into 9 regions
- 9 regions are divided into 23 sub-regions
- Each sub-region is given a score of 0, 1 or 0.5 based on signal intensity
- Signal score can range from 0 to 23
Loes Scoring System

• Assesses atrophy in 4 brain regions and 2 sub-regions (score of 0-1)

• Whole-brain atrophy rating (score of 0-3)

• Score for entire MR scan can range from 0 (best) to 32 (worst)
Neurobehavioral Tests

- Mental development test
- Gross motor skills test
- Fine motor skills test
Neurobehavioral Tests

- Mental development - Capute scale
- Gross motor skills - Mullen and/or Peabody Developmental Motor Scales
- Fine motor skills - Mullen scale
- Scores expressed as age-equivalents
Comparison 1

Total brain score (0-32)

- Mental development age equivalent
- Gross motor skills age equivalent
- Fine motor skills age equivalent
Comparison 2

Gross motor skills age equivalent

Pyramidal system (0-3)

Fine motor skills age equivalent
Comparison 3

Note the very narrow range of possible scores (0-1)

- Gross motor skills age equivalent
- Fine motor skills age equivalent
Statistical Tests

• Mixed models to adjust for multiple observations per infant

• Calculated standardized coefficients, which are equivalent to correlations; $p < .05$
MR Imaging Scores

- Mean score for entire brain: $7.79 \pm 6.20$ (range: 0-22.5)

- Mean score for pyramidal system: $1.18 \pm 1.10$ (range: 0-3.00)

- Mean score for internal capsule: $0.47 \pm 0.48$ (range: 0-1.00)
## Developmental Scores

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean (±) SD (range)</th>
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<tbody>
<tr>
<td>Mental Development Quotient</td>
<td>65 ±31 (9-100)</td>
</tr>
<tr>
<td>Gross Motor Age Equivalent Quotient</td>
<td>48±39 (6-105)</td>
</tr>
<tr>
<td>Fine Motor Age Equivalent Quotient</td>
<td>57 ±35 (12-105)</td>
</tr>
</tbody>
</table>
Comparison 1

Mental development index
-0.78 (p=0.003)

Gross motor age equivalent
-0.74 (p=0.003)

Fine motor age equivalent
-0.80 (p<0.001)
Comparison 2

Pyramidal system

Gross motor skills test
-0.58 (p=0.028)

Fine motor skills test
-0.73 (p=0.003)
Comparison 3

Internal capsule

- Gross motor skills test
  -0.35 (p=0.24)

- Fine motor skills test
  -0.38 (p=0.22)
Limitations

• No normal controls
• We did not test scoring reproducibility
• We did not test the Loes scoring system against another MR scoring system
• We don’t know how to account for clinical-imaging discrepancies
Tractography Analysis

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Control subject:
Frontal WM      .300
Occipital WM    .363

Untreated Krabbe patient:
Frontal WM      .182
Occipital WM    .170

Assessing Therapy

• Measuring effects of stem cell transplantation for treatment of Krabbe disease

• Age of transplantation appears to be significant for prognosis
Serial Imaging of Infant Transplanted at 3 weeks of Age

18 months post-TX

29 months post-TX
Krabbe: Early vs Late Treatment

Frontal WM: normalized FA values

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Treated vs Untreated Krabbe Patients

Tractography Analysis

**Unknowns**

- Can we predict development of clinical symptoms?
- Can we determine which regions of the CNS are most affected?
- Can we measure treatment response?
Summary

• MR imaging provides a number of methods for identifying regions of brain affected by inborn errors

• MR imaging clearly is a potential means for tracking therapy

• Some challenges: identifying asymptomatic patients who may ultimately be candidates for therapy
Diffusion Tensor

Eigenvalues

- $\lambda_1$ Axial diffusivity
- Axonal damage
- $\lambda_{2,3}$ Radial diffusivity
- Myelin damage

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Summary

• CNS disease will be measured using conventional MR images
• Diffusion tensor imaging will provide an additional, exploratory means to evaluate white matter injury