Review of UBDRS in JNCL: Reliability, Validity, and Endpoints

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Development of Outcome Measures

Identify and track biomarkers

Identify and track endophenotypes

Measure and follow clinical features
  • Quantifiable measurements
  • Clinical rating scale
The Unified Batten Disease Rating Scale (UBDRS)

Initial items for each subscale identified based on review of literature on clinical features of JNCL

Additional items added based on experience from movement disorder rating scales

Item elimination and modification based on initial reliability testing (Marshall et al., 2005)

Continued assessment of scale performance and reliability with modifications as guided by the data
The Unified Batten Disease Rating Scale (UBDRS)

Demographics / Diagnostics / Medical History / Medications

Physical Assessment

Seizure Assessment

Behavioral Assessment

Capability Assessment
  • Assuming Normal Vision
  • Given Actual Vision

Sequence of Symptom Onset

Global Impression of Symptom Severity
Subject Ascertainment

Establish registry of known cases (2001 - )

Travel to Annual Batten Disease Support and Research Association (BDSRA) family meeting (2002 - )

Establish Batten Disease Clinical Research Center at University of Rochester (2005 - )
  • Now a BDSRA Center of Excellence

All subjects genotyped at University of Rochester
<table>
<thead>
<tr>
<th>NUMBER OF EVALUATIONS</th>
<th>CLINICAL JNCL</th>
<th>CLN3 MUTATION</th>
<th>OTHER NCLs</th>
<th>UNDIAGNOSED</th>
<th>TOTAL SUBJECTS</th>
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<td><strong>TOTAL SUBJECTS</strong></td>
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<tr>
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<td>30</td>
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</tbody>
</table>
Clinical Features and Natural History of JNCL

Descriptive
- Age at onset
- Rate of Progression
  - Cross-sectional and longitudinal
  - Effect of CLN3 genotype
- Cognitive features

Hypothesis Testing
- Sex Differences

Use for retrospective evaluation of treatment

Baseline for clinical trials
## Average Age at Symptom Onset

<table>
<thead>
<tr>
<th></th>
<th>Vision Loss</th>
<th>Behavior Problems</th>
<th>Cognitive Problems</th>
<th>Seizures</th>
<th>Motor Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td>5.4 ± 1.5</td>
<td>7.0 ± 3.4</td>
<td>8.2 ± 4.0</td>
<td>9.8 ± 2.7</td>
<td>10.9 ± 4.4</td>
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<tr>
<td><strong>Females</strong></td>
<td>6.3 ± 1.4</td>
<td>9.5 ± 4.4</td>
<td>8.7 ± 2.9</td>
<td>9.4 ± 2.5</td>
<td>11.8 ± 3.6</td>
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<tr>
<td><strong>P</strong></td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.05</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
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</table>

Cialone et al, 2012
Inter-Rater Reliability

Physical

Behavior

Capability

RS = 0.83

RS = 0.68

RS = 0.86
Age as Surrogate for Progression

![Graph showing the relationship between age and disease duration with a correlation coefficient of r = 0.93.]

Disease Duration (years)

Age (years)
CLN3 Progression of Physical Impairment

A. Most recent scores for entire cohort

Physical impairment domain (severity) score vs. Age at testing (years)

B. CLN3 deletion homozygotes seen for:
- Single evaluation
- Multiple evaluations

Predicted values (95% CI)

C. CLN3 other genotypes seen for:
- Single evaluation
- Multiple evaluations

Predicted value (95% CI)

Kwon et al., 2011
Capability Scale

![Capability Scale graph with a scatter plot showing the relationship between Age (years) and Capability Score. The correlation coefficient R is -0.68.](image-url)
Convergent Validity: Physical and Capability Scales

The scatter plot shows a strong negative correlation between physical score and capability score, with a correlation coefficient of $R=-0.84$. This indicates that as the physical score increases, the capability score tends to decrease.
Discriminative Validity: Behavior Scale

![Graph showing discriminative validity between behavior and physical scores.](image)

- Number of participants (N): 80
- Correlation coefficient (R): -0.02
Physical Impairment vs. Cognitive Performance

Adams et al., 2007
Validation of UBDRS Cognitive CGI

Adams et al., 2007
DO GIRLS HAVE A MORE SEVERE DISEASE TRAJECTORY THAN BOYS?

Endpoints from UBDRS and Elsewhere
JNCL Girls Have a Shorter Disease Course

Later Disease Onset

Earlier Death

Cialone et al., 2012
JNCL Girls Have Earlier Loss of Independent Function

Cialone et al., 2012
Summary – Sex Differences

Girls have a shorter duration of disease and earlier loss of independence, resulting in lower quality of life

Why?
- Female sex is often thought to be neuroprotective
- Role of autoimmunity?
- Sociocultural factors: what are society’s expectations for girls?

Future Directions
- Look for other differences between girls and boys
- Better understanding of the molecular basis of the disease may lead to potential target for therapy
The Team

Neurologists
• Erika Augustine, MD
• Leon Dure, MD (UAB)
• Jennifer Kwon, MD, MPH
• Frederick Marshall, MD
• Jonathan Mink, MD, PhD
• Denia Ramirez, MD PhD

Neuropsychologist
• Heather Adams, PhD

Coordinators
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• Nicole Newhouse, RN
• Amy Vierhile, RN, PNP

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• Erika (Levy) Wexler (MD)
• Tiffani McDonough (MD)
• Jennifer Riehl (MD)
• Katherine Rose
• Sabrina Seehafer (PhD)
• Melissa Wang (MD)

Statisticians
• Michael McDermott, PhD
• Chris Beck, PhD

Molecular Geneticist
• Paul Rothberg, PhD

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