A Proposed Staging System for CLN3 Disease (Juvenile Batten disease)

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Introduction

The Neuronal Ceroid Lipofuscinoses (NCLs) comprise more than 10 different rare, inherited, fatal lysosomal diseases of childhood. Juvenile Batten Disease, due to mutations in CLN3, is characterized by progressive vision loss, epilepsy, dementia, behavioral difficulties, and motor impairment.

The Unified Batten Disease Rating Scale (UBDRS) is a disease-specific rating scale that was developed to assess disease severity in 4 domains: physical, behavior, seizures, and functional capability.

Objectives

To develop a staging system for CLN3 disease based on clinically meaningful endpoints that can facilitate stratification by disease severity for use in future clinical trials.

Methods

- Data from individuals with genetically confirmed CLN3 disease were extracted from the University of Rochester natural history database.
- Data from 100 unique individual subjects consisting of a total of 290 evaluations were used for development and testing.
- The initial system tested (System 1) consisted of 5 stages. Stages were proposed based on discrete endpoints.

<table>
<thead>
<tr>
<th>Stages</th>
<th>System 1</th>
<th>System 2</th>
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<tbody>
<tr>
<td>Stage 0</td>
<td>Genetic Diagnosis (Asymptomatic)</td>
<td>Genetic Diagnosis (Asymptomatic)</td>
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<tr>
<td>Stage 1</td>
<td>Loss of vision</td>
<td>Loss of vision</td>
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<tr>
<td>Stage 2</td>
<td>First seizure</td>
<td>First seizure</td>
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<tr>
<td>Stage 3</td>
<td>Loss of independence in ADLs</td>
<td>Loss of independent gait</td>
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<tr>
<td>Stage 4</td>
<td>Loss of independent gait</td>
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</tbody>
</table>

Stage 2 (First Seizure) and Stage 3 (Loss of Independence in ADLs) overlapped substantially. We eliminated Stage 3 because the First Seizure was a more discrete end-point.

Discussion

- The proposed staging system is based on clinically meaningful end-points and has excellent construct validity.
- In this proposed staging system, individuals with CLN3 disease progress through each stage of the disease as a function of age.
- Elimination of the "Loss of Independence in ADLs stage from System 1 resulted in more discrete stages with little overlap.
- A valid staging system has high potential for use in stratification for clinical trials and for development of stage-specific outcome measures.

Acknowledgements

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