Functional Performance in Patients with Late-Onset Tay-Sachs and Sandhoff Diseases

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Background

Late-Onset GM2 Gangliosidosis

- Tay-Sachs and Sandhoff diseases
- Deficiency of hexosaminidase leads to accumulation of GM2, primarily in the CNS
- Age of onset in childhood to adulthood
- Slowly progressive over years to decades
- Features include ataxia, dystonia, weakness
- Result in poor balance/falls, impaired walking/speech/hand dexterity/cognitive processing, and psychiatric illness

GM2 Gangliosidosis Is Caused by Deficiency of β-Hexosaminidase A (Tay-Sachs) or A+B (Sandhoff)

Residual Hexosaminidase Activity Determines Disease Severity and Age of Onset

Late-Onset Tay-Sachs Disease Clinical Course

Methods

- An observational, cross-sectional study of patients with late-onset Tay-Sachs or Sandhoff disease who attended the 2015 annual NTSSAD family conference
- Patients were recruited by NTSSAD for participation in the study
- Study approved by a central institutional review board and written informed consent obtained from patients and caregivers
- Assessments:
  - Severity Scale – Physician Global Impression (PGI), Brief Ataxia Rating Scale (BARS)
  - Mobility (Transfer and Walk) – Timed Get Up and Go Test (TUGS)
  - Hand Dexterity – 9-Hole Pegboard Test (9HPT)
  - Tinnitus – Archimedes Spiral (ASMD)
  - Speech – Rainbow Passage (RP)
  - Executive Function – Trail Making Tests A and B (TMT A & B)
  - Quality of Life, Health Status – SF-12, EQ-5D (SF12, EQ50)
- Analysis:
  - Descriptive statistics and Spearman’s rank correlations

Patient Demographic and Disease Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Mean ± SD, or %</th>
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<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>67 ± 16</td>
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<tr>
<td>Education (years), mean ± SD</td>
<td>9 ± 4</td>
</tr>
<tr>
<td>Marital status</td>
<td>70% married, 25% single, 5% unknown</td>
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<tr>
<td>Disability status</td>
<td>6% total, 6% no disability</td>
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<tr>
<td>Employment (or retired)</td>
<td>42% employed</td>
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<tr>
<td>Median (min, max)</td>
<td>3.0 (1.0–5.0) 2.6 (1.0–6.0)</td>
</tr>
<tr>
<td>% Abnormal</td>
<td>100% (12/12) 50% (6/12)</td>
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GM1-Galactosialidosis

- Includes Sandhoff disease who attended the 2015 annual NTSAD family conference

Physician Global Impression Scale (PGI 0–5)

0: Normal
1: Mild
2: Moderate
3: Moderate/severe
4: Severe

Brief Ataxia Rating Scale (BARS 0–40)

- Gait
  - Normal
  - Marked impairment of gait, but able to walk with feet in tandem position
  - Walking without support, but limb coordination abnormal and irregular
  - Walking without support, but with considerable staggering, difficulty in half turn
  - Walking without support, inability to walk for 5 meter distance
  - Walking possible only with one cane
  - Walking possible only with two canes or a walker
  - Walking possible with one accompanying person
  - Walking impossible with one accompanying person (≥2 persons assist, wheelchair)

- Finger-to-Nose Test
  - Approximation of opposition and alignment of arm and hand, wrist and fingers correct
  - Slowing of movement of arm and hand with decomposition of the movement
  - Segregated movement in 3 phases and/or moderate impairment in reaching phase
  - Segregated movement in more than 3 phases or more than moderate impairment in reaching phase
  - Dysarthria: growing the patient from reaching score

- Finger Intrusions
  - Prominent and irregular

- Phonation
  - Prominent and irregular

- Dysarthria
  - Marked impairment

- Medical history

- Questionnaire

- Results

- Trail Making Test Part A, but not Part B, Correlated with BARS Score

- Trail Making Test Part A:
  - Mean ± SD: -2.3 ± 3.3
  - Median: -1.96
  - Range: 0.5 to -10.23
- Trail Making Test Part B:
  - Mean ± SD: -3.3 ± 3.0
  - Median: 3.0
  - Range: 0.01 to 8.22
- % Abnormal: 100% (12/12) 50% (6/12)

- Timed Get Up and Go Test (and Go Test) Correlated with BARS Score

- Spontaneous Speech vs. Recited Speech
  - Mean ± SD: 3.6 ± 1.3
  - Median: 3.1
  - Range: 0.36 to 4.00
  - % Abnormal: 50% (6/12) 50% (6/12)

- Archimedes Spiral Correlated Highly with BARS Score

- Archimedes Spiral, % Tracing
  - Mean ± SD: 72.7 ± 17.6
  - Median: 57.7
  - Range: 15.9–83.6
  - % Abnormal*: 67% (7/10)

- Conclusions

- Late-onset GM2 gangliosidosis patients have a high disease burden confirmed by physical performance measures, caretake and device use, and focus group discussions.
  - Study confirmed functional impairments in mobility, transfers, speech, manual dexterity, and executive function.
  - BARS score correlated with disease severity and functional performance testing, suggesting that these assessments may be useful outcome measures for monitoring patients.
  - Follow-up testing will be useful for determining sensitivity to change.

References

4. Public domain image from Wikipedia.
5. Sanofi Genzyme-sponsored study of late-onset Tay-Sachs and Sandhoff disease, Genzyme-sponsored study of late-onset Tay-Sachs and Sandhoff disease, Genzyme-sponsored study of late-onset Tay-Sachs and Sandhoff disease.