Natural history of cognitive development in neuronopathic Mucopolysaccharidosis type II (MPSII, Hunter syndrome): Contribution of genotype to developmental course.

Joohyun Seo¹, Motomichi Kosuga², Yasuyuki Fukuhara², Elsa Shapiro³, Torayuki Okuyama¹
¹ Clinical Laboratory Medicine, National Center for Child Health and Development, Tokyo, Japan
² Division of Medical Genetics, National Center for Child Health and Development, Tokyo, Japan
³ Department of Pediatrics, University of Minnesota Twin Cities, United States

Summary

Neuronopathic Mucopolysaccharidosis (MPS II) can be divided into two groups based on the genetic mutation. Group MS is characterized by missense mutations and is presumed to have slight residual enzyme activity, and Group NT is considered to have null type mutations, such as deletions, recombination with pseudogene, and nonsense mutations.

The patients as a whole demonstrated cognitive growth until about 36~42 months of age, followed by a plateau in development, and decline starts at about 48~60 month of age. While the decline was slow for the entire group, the patients in Group NT show a more rapid decline than do those in Group MS.

Introduction

- MPS II is an X-linked disorder defined by a deficiency of iduronidate-2-sulfatase resulting in accumulation of dermatan sulfate and heparan sulfate. Two forms have been described both the neuronopathic form and the non-neuronopathic form are characterized by significant somatic disease affecting almost all bodily systems.
- The natural history of cognitive growth in the progressive neuronopathic form of MPS II is poorly defined due to the lack of data for children under four years of age and associations between mutation analysis and cognitive assessments.
- As new treatments designed to treat the central nervous system problems in brain are being developed and tested in clinical trials, the need for cognitive natural history of MPS II as a comparator is crucial.
- The ability to predict the developmental course of the patient is necessary to assess treatment outcomes.

Methods

- Subject: 13 Japanese neuronopathic patients with neuronopathic MPS II treated by intravenous enzyme replacement therapy
- Diagnosis: Enzyme activity of iduronate-2-sulfatase in leukocytes
  Concentration of urinary glycosaminoglycans
  Genetic test
- Developmental test: Kyoto Scale of Psychological Development 2001 (KSPD)
- Analysis: Linear mixed-effects model
  Random intercept, group (MS and NT)
  Age-in-month (linear, quadratic, cubic)
  Interaction of group and age-in-months

2) The KSPD is a standardized developmental assessment tool, developed and widely used in Japan for all age groups. The KSPD was shown to be significantly correlated with Bayley Scales of Infant Development III, Stanford Binet Intelligence Scale (Japanese ver. Tanaka-Binet).
Results (1)

- MPS II can be divided into two groups based on the genetic mutation.
- Group MS is characterized by missense mutations and is presumed to have slight residual enzyme activity, and Group NT is considered to have null type mutations, such as deletions, recombination with pseudogene, and nonsense mutations.

### Table 1. Age and cognitive ability assessment in Group MS and Group NT

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Mutation</th>
<th>CA at baseline</th>
<th>CA at last visit</th>
<th>DA at baseline</th>
<th>DA at last visit</th>
<th>Change in DA</th>
<th>DQ at base line</th>
<th>DQ at last visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS1</td>
<td>G140V</td>
<td>28</td>
<td>47</td>
<td>24</td>
<td>26</td>
<td>2</td>
<td>86</td>
<td>55</td>
</tr>
<tr>
<td>MS2</td>
<td>K234N</td>
<td>15</td>
<td>78</td>
<td>11</td>
<td>39</td>
<td>28</td>
<td>73</td>
<td>50</td>
</tr>
<tr>
<td>MS3</td>
<td>R468Q</td>
<td>45</td>
<td>116</td>
<td>30</td>
<td>27</td>
<td>3</td>
<td>67</td>
<td>23</td>
</tr>
<tr>
<td>MS4</td>
<td>K236N</td>
<td>46</td>
<td>60</td>
<td>36</td>
<td>38</td>
<td>2</td>
<td>78</td>
<td>63</td>
</tr>
<tr>
<td>MS5</td>
<td>R88H</td>
<td>37</td>
<td>69</td>
<td>18</td>
<td>19</td>
<td>1</td>
<td>49</td>
<td>28</td>
</tr>
<tr>
<td>MS6</td>
<td>Q121R</td>
<td>30</td>
<td>95</td>
<td>18</td>
<td>16</td>
<td>-2</td>
<td>60</td>
<td>17</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>37.2</td>
<td>77.5</td>
<td>22.8</td>
<td>27.5</td>
<td>4.7</td>
<td>68.8</td>
<td>39.4</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>8.3</td>
<td>24.9</td>
<td>9.1</td>
<td>9.5</td>
<td>11.6</td>
<td>13.3</td>
<td>19.2</td>
</tr>
</tbody>
</table>

- All patients in Group MS demonstrate little change in developmental age over time, all falling within 3 months gain or loss with the exception of patient MS2 who was the youngest in that group at baseline (15 months) who continued to show cognitive developmental gain over time.
- In Group NT, with the exception of patient NT7 (who was 6 months of age and showed a developmental gain) and patient NT4 (who lost cognitive skills), patients also showed little change over time.
- Two patients (NT3, NT4) with deletions showed decline to a very low level by age 5.

Fig2. Growth curve of the developmental age of each patient.
Results (2)

Fig 3. Growth curve of the developmental age by the group.

- The patients as a whole demonstrated cognitive growth until about 36~42 months of age, followed by a plateau in development, and decline starts at about 48~60 month of age.
- While the decline was slow for the entire group, the patients in Group NT show a more rapid decline than do those in Group MS (p=0.00033).

Fig 4. Growth curve of the developmental age by the group (Group MS + Group NT)
Conclusion

- The natural history of cognitive growth in the neuronopathic form of Mucopolysaccharidosis type II (MPS II) is not well defined especially their patterns of development and decline. The ability to predict the developmental course of the neurologically impaired patient is necessary to assess treatment outcomes aimed at the brain.

- We have shown the difference of rate of cognitive decline by genotype of IDS gene. Patients in Group MS shows slower rate of decline than those in Group NT. These differences could be partially explained by cross-reactive immunological material (CRIM) status of the mutant IDS enzyme. To evaluate CRIM status and enzyme activity accurately, further analysis using skin culture fibroblasts is necessary.

- The limitation of this study is that the patients were seen at different intervals and frequencies. Overall, despite this limitation, the pattern of long plateaus in development was apparent and consistent with other studies.

- This is the first demonstration that different mutation types within the neuronopathic MPS II patients are associated with different rates of decline. We also were able to identify the chronological age before which a trial would need to start in order to maintain cognitive growth and a ceiling beyond which a relatively normal outcome would not be likely.

Acknowledgements

The authors would like to thank Eisuke Inoue and Masashi Mikami for their support of statistical analysis.