Cognitive outcomes in Hurler syndrome following transplant before age 12 months

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BACKGROUND

• Mucopolysaccharidosis (MPS) type I is a rare autosomal recessive LSD caused by deficiency in the enzyme α-L-iduronidase.
• Severe form of MPSI, Hurler syndrome, is characterized by progressive neurological involvement and multisystem disease resulting in death by end of early childhood if untreated.
• Individuals with Hurler syndrome follow a predictable trajectory of normal cognitive development in first year of life, slowing in second year, and rapid decline thereafter.
• Allogeneic hematopoietic stem cell transplantation (HCT) is the standard of care as it stabilizes deterioration and extends survival.
• Enzyme replacement therapy (ERT) as an adjunct to HCT reduces morbidity and mortality and may lead to more favorable cognitive outcomes.
• Overwhelming evidence that earlier treatment with HCT leads to improved cognitive outcomes.

OBJECTIVE

To characterize cognitive outcomes of patients with Hurler syndrome transplanted prior to 12 months of life.

METHODS

• Assessed cognitive outcomes of 8 patients with Hurler syndrome:
  • Transplanted at less than 12 months of age
  • Transplanted since 2005 to reflect modern HCT practice
  • All patients received ERT in peri transplant period
• Longitudinal cognitive follow up data available at least 2 years following HCT for all patients.
• Examined cognitive scores before transplant and at 1 and 2 years following HCT.
• Early IQ scores (IQ) were measured with the Mullen Scales of Early Learning and Bayley Scales of Infant and Toddler Development, Third Edition.
• Early IQ scores were analyzed longitudinally. Generalized estimating equations were used with robust variance estimation to determine the mean fit and p-value with an autoregressive (AR1) correlation structure to account for correlated observations.

RESULTS

Patient Characteristics

Values are mean (SD) or N (%) unless otherwise indicated.

<table>
<thead>
<tr>
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<th>MPS IH</th>
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<tbody>
<tr>
<td>N</td>
<td>8</td>
</tr>
<tr>
<td>Male</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>Age (months) at Transplant</td>
<td>8.74 (1.96)</td>
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<tr>
<td>Median (range)</td>
<td>8.76 (5.03-11.93)</td>
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<tr>
<td>ERT delivery</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>8</td>
</tr>
<tr>
<td>IV + IT</td>
<td>4</td>
</tr>
<tr>
<td>Early IQ Score:</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>91.6 (7.35)</td>
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<tr>
<td>Year 1</td>
<td>87.9 (8.55)</td>
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<tr>
<td>Missing Year 1</td>
<td>1 (12.5%)</td>
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<td>Year 2</td>
<td>93.4 (15.0)</td>
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• Five patients (62.5%) had a 2-year post-HCT IQ score equal to or higher than their baseline IQ score
  • Average change = 12.4 points
• Three patients (37.5%) had a 2-year post-HCT IQ score declined from baseline
  • Average loss = 12.7 points

DISCUSSION

• No evidence of loss in IQ points from time period prior to HCT to 2 years afterward.
• Likely cognitive benefit when transplant is conducted at younger than 12 months of life.
• Finding is different from the general literature which has a broader range of transplanted children and shows there is generally a loss of IQ points following HCT.
• Findings further support research that indicates earlier treatment leads to favorable outcomes.
• Important at the dawn of newborn screening.

FUTURE DIRECTIONS

• Longer-term analyses of a larger cohort transplanted at less than 12 months to determine if cognitive outcomes remain superior from those transplanted at older ages.
• Compare this group to children transplanted at 12 months and older while controlling for additional factors such as baseline IQ, transplant preparation, and ERT.