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Enzyme replacement is associated with better cognitive outcomes after transplant in Hurler syndrome

Julie B. Eisengart, PhD^{1,2}, Kyle D. Rudser, PhD³, Jakub Tolar, MD, PhD^{1,4}, Paul J. Orchard, MD^{1,4}, Teresa Kivisto, RN^{1,4}, Richard S. Ziegler, PhD^{1,2}, Chester Whitley, PhD, MD^{1,5}, and Elsa Shapiro, PhD^{1,2}

¹Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota

²Division of Pediatric Clinical Neuroscience, University of Minnesota, Minneapolis, Minnesota

³Division of Biostatistics, University of Minnesota, Minneapolis, Minnesota

⁴Division of Hematology, Oncology, Blood and Marrow Transplantation, University of Minnesota, Minneapolis, Minnesota

⁵Institute of Human Genetics, University of Minnesota, Minneapolis, Minnesota

Abstract

Objective—To investigate whether intravenous enzyme replacement therapy (ERT) benefits cognitive function in patients with mucopolysaccharidosis Type IH (Hurler syndrome, MPS IH) undergoing hematopoietic cell transplantation (HCT).

Study design—Data were obtained for nine children treated with HCT + ERT (ERT group) and ten children with HCT only (No ERT group) from neuropsychological evaluations prior to HCT and at 1 and 2 years follow-up.

Results—Two years following HCT, children in the ERT group lost 9.19 fewer IQ points per year than children in the No ERT group ($P=0.031$). Further, the ERT group improved in nonverbal problem solving and processing, whereas the No ERT group declined, resulting in a difference of 9.44 points between the groups per year ($P<0.001$).

Conclusion—ERT in association with HCT enhances cognitive outcomes, providing new evidence that ERT is a valuable addition to the standard transplant protocol. Although the mechanism for this improved outcome is unknown, both direct benefits and indirect effects must be considered.

Keywords

mucopolysaccharidosis; hematopoietic cell transplantation; blood brain barrier

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Mucopolysaccharidosis (MPS) type I is a lysosomal storage disease characterized by a deficiency in the enzyme α -L-iduronidase with consequent progressive accumulation of glycosaminoglycans (GAGs) in nearly all organ systems, leading to a myriad of complications, including ophthalmologic, airway, pulmonary, cardiac, and orthopedic difficulties. MPS type IH (MPS IH), the most severe form, is fatal if untreated within the first decade of life. MPS IH has central nervous system (CNS) involvement in early childhood resulting in cognitive deterioration.¹

Enzyme replacement therapy (ERT) alone is used to treat only less severe forms of MPS I because intravenous enzyme is thought to be ineffective in treating cognitive decline. Hematopoietic cell transplantation (HCT) is the standard of care for MPS IH patients in order to treat CNS disease. HCT appears to provide enzyme to the CNS and arrest neurologic deterioration, likely by engraftment of donor-derived macrophages and microglia within the brain parenchyma.² However, HCT should be performed early in the child's life (within the first 2 years) before the accumulation of irreversible damage.

As part of the preparative conditioning for HCT, the agent busulfan, known to be neurotoxic, eliminates existing marrow to make way for donor cells. Monitoring of busulfan is now the standard of care in order to limit excessive toxicity by determining metabolism of the first dose and adjusting all subsequent doses based on patient-specific pharmacodynamics.² As a result of monitoring busulfan, neurotoxicity is decreased.⁹

Although HCT slows or halts progression of cognitive decline, even with improved treatment approaches many children with MPS IH continue to show cognitive and other physical impairments.^{3,4} Intravenously delivered ERT used in combination with HCT decreases morbidity and mortality,^{5-7,29} However, it is not the universal treatment approach;⁸ some have argued that ERT provides no benefit in a healthy MPS IH child and that ERT could alter rates of engraftment.³⁰ Even though the use of ERT with HCT improves transplant survival,^{5,29} no studies have investigated whether combined treatment affects CNS function measured by neuropsychological evaluation.

Methods

All children with MPS IH who were treated with HCT beginning in 2002 were included (N=19). The year 2002 was selected because busulfan monitoring was initiated as part of the treatment protocol, which afforded some control over its neurotoxic effects. Nine of these children received combined HCT + ERT (ERT group) at the University of Minnesota Blood and Marrow Transplant Service and had neuropsychological evaluations prior to and at 1 and 2 years post transplant. All assessments occurred as part of prescribed multidisciplinary clinical protocols. Ten children were treated with HCT only, had the same evaluations, and were used for comparison (No ERT group). Since 2005, all children undergoing HCT have received ERT at this institution. Thus, the two groups (ERT and No ERT) necessarily were serially recruited for the study, from 2002 to 2005 (No ERT), and from 2005 onward (ERT). Transplant preparative regimens have remained relatively unchanged since 2002. Consents were obtained for sharing medical, clinical, and neurobehavioral functioning results from medical files.

HCT protocols

The HCT protocol for all but three patients included a fully myeloablative protocol including cyclophosphamide (50 mg/kg x 4 daily doses) and intravenous busulfan (1.1 mg/kg/dose every 6 hours for 16 doses), with the busulfan dose adjusted as necessary to maintain an area under the curve of 900–1500 uM*minute (cumulative dosing).

Three patients received a reduced intensity transplant regimen due to concern regarding increased risk based on pre-transplant measures.¹⁰ These three patients were all in the No ERT group. The reduced intensity regimen consisted of intravenous busulfan (0.5 mg/kg/dose every 6 hours for 8 doses), fludarabine 35 mg/m² daily x 5 doses, and 200 cGy of total body irradiation. Two of the three patients received the reduced intensity procedure because of an older age at the time of transplant (31 and 34 months)³, and the third due to cardiac related concerns. The latter patient was shown to have a low ejection fraction (27%), and required support with digoxin prior to transplant. Within this group of three, one older patient with a sibling donor successfully engrafted. The other older patient and the cardiac patient received cord blood grafts and did not achieve engraftment with the reduced intensity regimen. They were subsequently re-transplanted with the same transplantation regimen using unrelated grafts, and both subsequently engrafted. In addition, 16 of the 19 patients (excluding the three that received the reduced intensity regimen) received either anti-thymocyte globulin (ATG n=15) or Campath-1H (n=1) as immunotherapy prior to transplantation. Graft versus host disease prophylaxis included cyclosporine in all cases, with mycophenolate mofetil (MMF; n=10) or methylprednisolone (n=5) for cord blood recipients, and cyclosporine and methotrexate for two patients transplanted with related marrow grafts. In one case of transplantation with a sibling donor and a reduced intensity preparative regimen, cyclosporine and MMF were used.

ERT Protocol

Patients enrolled on a prospective, IRB-approved protocol received weekly ERT, totaling 10–14 doses of 0.58 mg/kg intravenous laronidase prior to, and eight doses following transplantation. Post-transplantation doses were designed to provide a source of enzyme until a time when it was anticipated that donor engraftment would be achieved, as previously described.⁶

Measure of Neurocognitive Development

A standard neuropsychological evaluation protocol, used for all patients being assessed before and after HCT, included assessment of cognitive developmental status with the Mullen Scales of Early Learning,¹¹ normed in the United States for children from birth to 68 months. The Mullen yields an age-based standard score ($M = 100$, $SD = 15$), known as the Early Learning Composite (ELC) reflecting overall cognitive development and is an early estimation of the intelligence quotient (IQ). The ELC represents the aggregate of the child's scores in separate functional domains including Visual Reception (nonverbal problem solving and processing), Fine Motor (finger/hand strength and dexterity), Receptive Language (listening and understanding what is spoken), and Expressive Language (spoken language proficiency) skills. The Gross Motor domain was not included as it does not contribute to the ELC. Cognitive developmental functioning was assessed at baseline before HCT, as well as at 1 year and 2 years post-HCT.

Treatment Related Variables

The following treatment-related data were used in adjusted analyses: age at transplant, baseline ELC, and number of inpatient days in the acute post-transplant period. We also recorded type of donor (cord blood or sibling), presence of chronic graft versus host disease (GVHD), percent donor engraftment, and post-transplant enzyme levels.

Analytic Approach

Baseline characteristics were tabulated with respect to ERT use. Unadjusted longitudinal analyses present the average scores for each group at each point over time. Generalized estimating equations (GEE)¹² were used with exchangeable working correlation structure to

account for correlated observations. Covariates were selected *a priori* to be potential confounders or independent predictors of outcomes. Robust variance estimation was used for confidence intervals and P-values. A sensitivity analysis was examined to evaluate the dependence of results on choice of working correlation structure; use of an independence working structure did not appreciably change the results. All statistical analyses were performed using R v2.9.2¹³ with the ‘gee’ library v4.13-14.¹⁴

Results

Patient characteristics at baseline and during HCT can be found in Table I. No children died in the ERT group, but in the No ERT group, two of the ten patients died after transplant: one at 104 days, due to reactive airway disease and aspiration pneumonia, and one at 231 days due to refractory autoimmune hemolytic anemia. In both groups, all surviving patients achieved at least 80% donor engraftment by 2 years post transplant, except one patient in the ERT group who engrafted at 47% donor. In addition, by 2 years post-transplant, all patients had normal enzyme levels, except for the child who was 47% engrafted (enzyme levels in the “carrier range”). In an effort to follow an intent-to-treat type of analysis, analyses were evaluated both with and without the two patients who died. When the patients who died were included, their values were set to zero at 1 and 2 years follow-up.

Unadjusted analyses

Trajectories of ELC scores for ERT versus No ERT groups from baseline to 1 and 2 years post-HCT are presented in Figure 1. Although the ERT group began with lower ELC scores than the No ERT group, they showed a less dramatic decline, and at 2 years post-HCT, their ELC scores were higher on average than the No ERT group, regardless of inclusion of deaths (trajectories for individuals are presented in Figure 2; available at www.jpeds.com).

A breakdown of the Mullen by domain is presented in Table II (available at www.jpeds.com). At baseline the ERT group was average in Visual Reception and Expressive language, but below average in Receptive Language and Fine Motor. Likewise, the No ERT group was average in Visual Reception and Expressive language, and below average in Receptive Language. However, the No ERT group had a better baseline Fine Motor score (average range) than the ERT group. One year following transplant, both groups were below average for overall ELC, as well as the individual Mullen domains. Two years after transplant, the groups continued to be below average for overall ELC. They were also below average across Mullen domains, with one exception: the ERT group improved to the average range for the Visual Reception. Further, the No ERT group fell to the impaired range in the Fine Motor domain. When patients who died were included in the analyses, all scores for the No ERT group fell even further. Thus, the analysis that excludes them is likely an overly optimistic representation of the No ERT group’s trajectory, which is still significantly lower than that of the ERT group.

Adjusted analyses

The rate of decline in ELC scores over 2 years was significantly less in the ERT group as compared with the No ERT group, after adjusting for baseline ELC score (i.e., pre-HCT) and the number of days spent in the hospital (Table III). Being in the No ERT group was associated with a loss of 12.84 points per year (95% CI: (−20.21, −5.46); $P<0.001$), and being in the ERT group was associated with losing only 3.64 points per year (95% CI: (−7.57, 0.28); $P=0.069$). The difference in rates was calculated based on these estimated rates of decline for the ERT and No ERT groups and indicated that children in the ERT group lost 9.19 fewer points per year (95% CI: 0.85, 17.54); $P=0.031$). When the two patients in the No ERT group who died were excluded, this difference was reduced to 5.40

points per year (95% CI: 0.5, 10.29), yet remained clinically and statistically significant ($P=0.031$). Given the progressive cognitive deterioration associated with the disease, an additional sensitivity analysis was conducted wherein patients whose baseline evaluations occurred more than 3.5 months prior to HCT were also excluded due to the possibility that their ELCs might have declined in the time between evaluation and HCT (Table IV; available at www.jpeds.com). Again the difference in the rate of decline between the ERT and No ERT groups remained significant.

Two patients required re-transplantation, which resulted in a larger time interval between evaluation and HCT. Given possible differential effects on CNS outcomes, the rate of change in ELC was re-examined after excluding these patients and the results remained robust. In addition, with adjustment for the reduced intensity preparative regimen, results yet again remained significant (Table V; available at www.jpeds.com).

Figure 3 presents the analyses for the four Mullen domains that comprise the ELC. These analyses both adjusted for baseline score and days in the hospital and excluded deaths. There was a significant difference in the rate of change for ERT compared with No ERT of 9.44 points per year (95% CI: (4.98, 13.90); $P<0.001$), nearly a full standard deviation, for Visual Reception. Further, in this domain the ERT group actually showed a statistically significant *improvement* over two years of 3.01 per year (95% CI: (0.05, 5.97); $P=0.046$). There were no significant differences in slopes of change among any of the other domains, although there was a trend toward more favorable outcomes for the ERT group in the Fine Motor domain. An intent-to-treat type of analysis was used to compare results when deaths were included versus excluded. Analyses both including and excluding deaths showed statistically significant differences between treatment groups, with the ERT group consistently performing better when differences were found.

Discussion

We report an association of short-term cognitive benefits with enzyme replacement therapy (ERT) in patients with MPS IH undergoing transplantation. All patients with MPS IH who were treated at our institution beginning in 2005 were given ERT in addition to HCT with the original intention to improve mortality and morbidity.⁵⁻⁷ Improvement in cognitive functioning was not initially predicted at the onset of this protocol.

Neuropsychological testing results indicated that the children who received the combined treatment of ERT + HCT lost fewer ELC points in the 2 years following transplant than children who underwent HCT alone. Given that ELC (equivalent to an IQ in older persons) actually represents an age-based aggregate of diverse abilities (e.g., visual, verbal, etc.), we were also able for the first time to examine the domains separately to reveal what functional areas may be more or less affected.

Children who received ERT showed significant improvement on the Visual Reception domain, which measures the construct of nonverbal problem-solving, not of perception. The improvement in the ERT group contrasts, and significantly differs from, the No ERT group's decline in this domain.

For the Visual Reception tasks, children are presented with visual information in various forms and patterns, involving localizing, tracking, scanning, matching, and memorizing. Instructions are given verbally and paired with gesture, but speaking is not required for responses. The Visual Reception domain, because it measures nonverbal problem solving skills, is a proxy for nonverbal cognitive ability. Nonverbal problem solving has often been used as an estimation of general intellectual ability (e.g., Ravens Progressive Matrices test¹⁵). Improvement on the Visual Reception scale likely translates to an improvement in

nonverbal reasoning. It may reflect the fact that such functions are widely distributed in the CNS, with over 50% of the human brain dedicated to processing of visual information¹⁶ and therefore with more physical opportunity for benefits from enzyme. An unanswered question is whether there are areas of the CNS that are affected differentially.

Why was language unaffected by ERT? Children with MPS disorders have generally been thought to have early language impairment due to both neurological impairment as well as hearing loss (mixed conductive and sensorineural).¹⁷ Language is dependent on environmental input, which is obstructed due to hearing loss. We were unable to control for the effects of environmental variables in this study.

Another possibility is that language is intrinsically impaired in MPS disorders early in development and consequently does not have potential for recovery of function. The development of early language may be also be disrupted by the neurotoxic preparative regimen of transplant. From her longitudinal studies of perinatal focal injury, Stiles notes that language is a system that is widely distributed in the brain in early development and that damage in a variety of regions can impede its development; lateralized specific language systems may not develop normally as the neural substrate of language has little plasticity.¹⁸ The windows of development of language and visual problem solving have different time courses, and visual-spatial cognition may have more potential for recovery. Stile states that the “capacity for reorganization and functional compensation is retained” in the case of visual-spatial cognition.

Did hydrocephalus contribute to outcomes? Only one child had a shunt and was diagnosed with hydrocephalus (ERT group). The other children in the study, equivalent in both groups, had mildly enlarged ventricles that did not change substantially over the course of time. Was the benefit due to the use of cord blood? No statistical differences in outcomes of cord blood compared with marrow transplant were found.

Is the benefit due to enzyme crossing the blood-brain barrier? The blood-brain-barrier, built of capillary endothelial cells connected with tight junctions,¹⁹ has long been an issue of focus and concern when treating MPS IH patients with intravenous ERT, because the enzyme is not expected to enter the CNS in clinically beneficial levels.^{20,21} The neurological benefit that recipients of HCT derive from the procedure has been thought to be a consequence of donor microglial engraftment in the brain with subsequent secretion of iduronidase, and local, paracrine, cross-correction of the iduronidase-deficient neurons and glia.²² Irradiation has been shown to enhance donor microglial engraftment in the brain,^{23–25} and it is possible that chemotherapy-based regimens may also increase CNS engraftment of donor microglia. In animal models, chemotherapy and radiation have been shown to increase the permeability of the blood-brain barrier,²⁴ but no conclusive evidence has been demonstrated in humans. Thus, it is possible that the administration of intravenous ERT following transplantation may result in increased penetration of enzyme into the CNS due to the effect of the transplant regimen. In addition, in animal models, the blood-brain-barrier may be permeable to very high doses of lysosomal enzyme in the peripheral circulation.²⁸ One hypothesis is that high concentrations of lysosomal enzyme in the blood may engage non-mannose 6 phosphate receptor-mediated transport mechanisms and thus encourage more enzyme to be transported into the CNS in very young patients.

In contrast to this direct effect of donor cells, it has been hypothesized that somatic improvements from intravenous ERT indirectly support developmental functioning.²⁶ A healthier child may interact with his environment more actively and experimentally, thus promoting the learning process that underlies development.²⁷ The trend toward better Fine

Motor outcomes for the ERT group is consistent with such a theory, as children may use their hands to engage their surroundings and learn.

Accounting for patient deaths complicates this analysis. An intent-to-treat analysis is the well-recognized and accepted standard for randomized clinical trials but the corresponding analysis here is inhibited by incomplete observations due to death. If the deaths were completely independent, then the analysis in which they are excluded entirely would represent an unbiased estimate. However, if missing data due to death is not at random, then ignoring them introduces bias and may not represent what would be observed for the group without ERT therapy, with no occurrence of death. As such, results are presented when patients who die are included (assigned a value of 0) and also when they are excluded. Both showed meaningful differences between treatment groups. Although an appropriate value to assign patients who die is unclear, we have presented intent-to-treat type results for a plausible choice (value of 0) in an effort better to characterize the potential magnitude of treatment effect.

Despite the small sample size, which is inherent in rare diseases, we find compelling differences between our ERT and No ERT groups. However, there is always the real possibility that our sample is not representative of MPS IH or its true course following either HCT or HCT+ERT treatments.

The serial recruitment of participants for this study was a limitation, as unknown or subtle differences in multidisciplinary treatment, or even historical factors, may explain between-group differences in response to treatment. As these are serially recruited, participant matching across groups was not possible. It is important to note that there was no bias in group selection, as all participants were included.

Another limitation is the effect of re-transplantation of children in the No ERT group on their cognitive outcomes. Repeated exposure to procedures that are known adversely to affect the CNS certainly affect cognitive developmental functioning. Further, because MPS IH is a progressive disease, the additional time lapse for these children before successful engraftment translated to a delay in the arrest of the disease, likely causing further cognitive decline. Yet excluding these subjects from the analysis did not change the findings in this study.

This study provides new evidence that ERT is a valuable addition to the standard transplant protocol for MPS IH. It also raises new questions regarding the permeability of the blood-brain-barrier and the effects of high concentration of enzyme in the blood on brain function during the peri-transplant period in young patients with MPS IH. Given that MPS IH children with combined ERT + HCT treatment remain below average, earlier treatment as a result of newborn screening may point the way to even better developmental outcomes. These findings are short-term outcomes in the lives of these children. It will be important to continue to follow these children to determine whether differences in cognitive functioning persist in the long term.

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Abbreviations and Acronyms

CNS	central nervous system
ELC	Early Learning Composite
ERT	enzyme replacement therapy
HCT	hematopoietic cell transplantation
MPS IH	Mucopolysaccharidosis type IH

References

1. Shapiro E, Lockman L, Balthazor M, Krivit W. Neuropsychological outcomes of several storage diseases with and without bone marrow transplantation. *J Inherit Metab Dis.* 1995; 18:413–29. [PubMed: 7494400]
2. Boelens J, Prasad V, Tolar J, Wynn R, Peters C. Current International Perspectives on Hematopoietic Stem Cell Transplantation for Inherited Metabolic Disorders. *Pediatr Clin North Am.* 2010; 57:123–45. [PubMed: 20307715]
3. Peters C, Balthazor M, Shapiro E, King R, Kollman C, Hegland J, et al. Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. *Blood.* 1996; 87:4894. [PubMed: 8639864]
4. Peters C, Shapiro E, Anderson J, Henslee-Downey P, Klemperer M, Cowan M, et al. Hurler syndrome: II. Outcome of HLA-genotypically identical sibling and HLA-haploidentical related donor bone marrow transplantation in fifty-four children. *Blood.* 1998; 91:2601. [PubMed: 9516162]
5. Tolar J, Grewal S, Bjoraker K, Whitley C, Shapiro E, Charnas L, et al. Combination of enzyme replacement and hematopoietic stem cell transplantation as therapy for Hurler syndrome. *Bone Marrow Transplant.* 2007; 41:531–5. [PubMed: 18037941]
6. Tolar J, Orchard P. alpha-L-iduronidase therapy for mucopolysaccharidosis type I. *Biologics.* 2008; 2:743–51. [PubMed: 19707455]
7. Wynn R, Mercer J, Page J, Carr T, Jones S, Wraith J. Use of enzyme replacement therapy (Laronidase) before hematopoietic stem cell transplantation for mucopolysaccharidosis I: experience in 18 patients. *J Pediatr.* 2009; 154:135–9. [PubMed: 19187736]
8. Cox-Brinkman J, Boelens J, Wraith J, O'meara A, Veys P, Wijburg F, et al. Haematopoietic cell transplantation (HCT) in combination with enzyme replacement therapy (ERT) in patients with Hurler syndrome. *Bone Marrow Transplant.* 2006; 38:17–21. [PubMed: 16715104]
9. Russell J, Kangaroo S. Therapeutic drug monitoring of busulfan in transplantation. *Curr Pharm Design.* 2008; 14:1936–49.
10. Orchard P, Milla C, Braunlin E, DeFor T, Bjoraker K, Blazar B, et al. Pre-transplant risk factors affecting outcome in Hurler syndrome. *Bone Marrow Transplant.* 2010; 45:1239–46. [PubMed: 19898501]
11. Mullen, E. Mullen Scales of Early Learning. Circle Pines, MN: American Guidance Service; 1995.
12. Diggle; Heagerty; Liang; Zeger. *Analysis of Longitudinal Data.* New York: Oxford University Press; 2002.
13. R Development Core Team. *R: A language and environment for statistical computing.* Vienna, Austria: R Foundation for Statistical Computing; 2009.
14. Carey, V. Ported to R by Thomas Lumley (versions 3.13, 4.4) and Brian Ripley (version 4.13). *gee: Generalized Estimation Equation Solver.* 2009. R package version 413-14 <http://CRAN.R-project.org/package=gee>
15. Raven, J. *Manual for Raven's progressive matrices and vocabulary scales.* Oxford: Oxford Psychologists Press; 1998.
16. Zeki, S.; Marg, E. *A Vision of the Brain.* Oxford: Blackwell; 1993.
17. Neufeld E, Muenzer J. The mucopolysaccharidoses. The metabolic and molecular bases of inherited disease. 2001; 8:3421–52.

18. Stiles J. Neural plasticity and cognitive development. *Developmental Neuropsychology*. 2000; 18:237–72. [PubMed: 11280966]
19. Ueno M. Molecular anatomy of the brain endothelial barrier: an overview of the distributional features. *Current Medicinal Chemistry*. 2007; 14:1199–1206. [PubMed: 17504140]
20. Thomas J, Jacobs S, Kierstein J, Hove J. Outcome after three years of laronidase enzyme replacement therapy in a patient with Hurler syndrome. *J Inherit Metab Dis*. 2006; 29:762. [PubMed: 17089217]
21. Tokic V, Barisic I, Huzjak N, Petkovic G, Fumic K, Paschke E. Enzyme replacement therapy in two patients with an advanced severe (Hurler) phenotype of mucopolysaccharidosis I. *Eur J Pediatr*. 2007; 166:727–32. [PubMed: 17043838]
22. Krivit W, Sung J, Shapiro E, Lockman L. Microglia: the effector cell for reconstitution of the central nervous system following bone marrow transplantation for lysosomal and peroxisomal storage diseases. *Cell Transplant*. 1995; 4:385–92. [PubMed: 7582569]
23. Ajami B, Bennett J, Krieger C, Tetzlaff W, Rossi F. Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. *Nat Neurosci*. 2007; 10:1538–43. [PubMed: 18026097]
24. Kennedy D, Abkowitz J. Kinetics of central nervous system microglial and macrophage engraftment: analysis using a transgenic bone marrow transplantation model. *Blood*. 1997; 90:986. [PubMed: 9242527]
25. Mildner A, Schmidt H, Nitsche M, Merkler D, Hanisch U, Mack M, et al. Microglia in the adult brain arise from Ly-6ChiCCR2+ monocytes only under defined host conditions. *Nat Neurosci*. 2007; 10:1544–53. [PubMed: 18026096]
26. Wraith J, Beck M, Lane R, van der Ploeg A, Shapiro E, Xue Y, et al. Enzyme replacement therapy in patients who have mucopolysaccharidosis I and are younger than 5 years: results of a multinational study of recombinant human [alpha]L-iduronidase (laronidase). *Pediatrics*. 2007; 120:e37. [PubMed: 17606547]
27. Bushnell E, Boudreau J. Motor development and the mind: The potential role of motor abilities as a determinant of aspects of perceptual development. *Child Dev*. 1993; 64:1005–21. [PubMed: 8404253]
28. Vogler C, Levy B, Grubb J, Galvin N, Tan Y, Kakkis E, et al. Overcoming the blood-brain barrier with high-dose enzyme replacement therapy in murine mucopolysaccharidosis VII. *Proceedings of the National Academy of Sciences of the United States of America*. 2005; 102:14777. [PubMed: 16162667]
29. Wynn RF, Mercer J, Page J, Carr TF, Jones S, Wraith JE. Use of enzyme replacement therapy (Laronidase) before hematopoietic stem cell transplantation for Mucopolysaccharidosis I: Experience in 18 patients. *J Pediatr*. 2009; 154:135–39. [PubMed: 19187736]
30. Boelens J. Trends in haematopoietic cell transplantation for inborn errors of metabolism. *J Inherit Metab Dis*. 2006; 29:413–20. [PubMed: 16763911]

Figure 1.
Change in cognitive developmental status following HCT.

Figure 2. Change in cognitive developmental status following HCT. Individual trajectories are presented with overall group averages.

Figure 3.
Comparison of domains comprising cognitive developmental status 2 years following HCT.

Table 1

Patient characteristics.

Covariate	Overall (N=19)	ERT (N=9)	No ERT (N=10)
Male	11 (57.9%)	5 (55.6%)	6 (60.0%)
Age at Transplant (mos)	17.5 (7.9)	18.0 (6.8)	17.1 (9.1)
Time Since Evaluation (days)	54.6 (72.2)	17.1 (2.2)	88.3 (88.0)
Cord Blood Donor	15 (78.9%)	6 (66.7%)	9 (90.0%)
Sibling Donor	4 (21.1%)	3 (33.3%)	1 (10.0%)
GVHD Prophylaxis			
- CSA/MMF	10 (52.6%)	6 (66.7%)	4 (40.0%)
- CSA/MTX	3 (15.8%)	3 (33.3%)	0 (0.0%)
- MP/CSA	6 (31.6%)	0 (0.0%)	6 (60.0%)
Ablation			
- ATG	15 (78.9%)	8 (88.9%)	7 (70.0%)
- Campath	1 (5.3%)	1 (11.1%)	0 (0.0%)
- No ATG	3 (15.8%)	0 (0.0%)	3 (30.0%)
No GVHD	15 (78.9%)	7 (77.8%)	8 (80.0%)
GVHD grade 2	3 (15.8%)	2 (22.2%)	1 (10.0%)
GVHD grade 4	1 (5.3%)	0 (0.0%)	1 (10.0%)
Days in Hospital	47.6 (21.8)	46.0 (19.3)	49.5 (25.6)
Baseline Scores			
- Early Learning Composite *	87.6 (16.4)	84.0 (15.0)	90.8 (17.7)
- Visual Reception T-score †	44.2 (10.9)	40.6 (10.0)	48.4 (10.9)
- Fine Motor T-score †	42.8 (10.8)	39.9 (9.8)	46.1 (11.6)
- Receptive Language T-score †	39.4 (11.2)	39.7 (9.6)	39.0 (13.4)
- Expressive Language T-score †	42.1 (9.8)	40.0 (8.7)	44.5 (10.9)

* Mean = 100, SD = 15

† Mean = 50, SD = 10

Table 2

Unadjusted Early Learning Composite and domain T-Scores across visits.

Score	Baseline (prior to HCT)	One Year Post-HCT	Two Years Post-HCT
Early Learning Composite [*]			
- ERT	84.0 (15.0)	74.1 (11.3)	76.2 (14.2)
- No ERT	91.8 (18.5)	70.9 (12.5)	71.3 (12.8)
Visual Reception Domain [†]			
- ERT	40.6 (10.0)	38.0 (10.4)	46.0 (12.9)
- No ERT	48.4 (10.9)	35.2 (8.89)	33.5 (6.95)
Fine Motor Domain [†]			
- ERT	39.9 (9.75)	34.6 (7.63)	30.6 (9.44)
- No ERT	46.1 (11.6)	33.1 (7.03)	29.0 (11.6)
Receptive Language Domain [†]			
- ERT	39.7 (9.64)	39.7 (12.5)	38.9 (8.98)
- No ERT	39.0 (13.4)	36.1 (10.1)	35.3 (9.05)
Expressive Language Domain [†]			
- ERT	40.0 (8.66)	35.3 (10.1)	33.6 (9.19)
- No ERT	44.5 (10.9)	32.5 (10.4)	37.6 (8.85)

^{*} Mean = 100, SD = 15[†] Mean = 50, SD = 10

Table 3

Adjusted analysis results for Early Learning Composite (ELC). First including deaths (follow-up values at one and two years post HCT imputed as zero), then excluding the two patients who died.

Covariate	Estimate (95% CI)	P-value
Baseline ELC	0.78 (0.56, 0.99)	<0.001
Days in Hospital	-0.32 (-0.61, -0.03)	0.029
No ERT (per yr)	-12.84 (-20.21, -5.46)	<0.001
ERT (per yr)	-3.64 (-7.57, 0.28)	0.069
Difference in Rate [‡] ; ERT vs. No ERT	9.19 (0.85, 17.54)	0.031
Excluding Deaths		
Baseline ELC	0.70 (0.55, 0.86)	<0.001
Days in Hospital	-0.06 (-0.16, 0.03)	0.199
No ERT (per yr)	-8.91 (-12.06, -5.76)	<0.001
ERT (per yr)	-3.51 (-7.33, 0.30)	0.071
Difference in Rate [‡] ; ERT vs. No ERT	5.40 (0.50, 10.29)	0.031

[‡]The difference was calculated based on the estimated rate of each group.

Table 4

Excluding patients whose baseline evaluations occurred more than 3.5 months prior to HCT and excluding patients who underwent a second transplant

Covariate	Estimate (95% CI)	P-value
Baseline ELC	0.82 (0.53, 1.11)	<0.001
Days in Hospital	-0.32 (-0.60, -0.05)	0.020
No ERT Rate (per yr)	-13.65 (-21.82, -5.47)	0.001
ERT Rate (per yr)	-3.63 (-7.59, 0.33)	0.072
Difference in Rate [‡] : ERT vs. No ERT	10.01 (0.94, 19.09)	0.031
Excluding Deaths		
Baseline ELC	0.67 (0.48, 0.85)	<0.001
Days in Hospital	-0.05 (-0.15, 0.05)	0.361
No ERT Rate (per yr)	-9.18 (-12.74, -5.63)	<0.001
ERT Rate (per yr)	-3.51 (-7.28, 0.27)	0.068
Difference in Rate [‡] : ERT vs. No ERT	5.68 (0.59, 10.76)	0.029

[‡]The difference was calculated based on the estimated rate of each group.

Table 5

Adjustment for the reduced intensity preparative regimen

Covariate	Estimate (95% CI)	P-value
Baseline ELC	0.94 (0.55, 1.32)	<0.001
Days in Hospital	-0.27 (-0.50, -0.05)	0.015
Special Prep	13.76 (-0.94, 28.47)	0.067
No ERT Rate (per yr)	-12.94 (-20.38, -5.50)	<0.001
ERT Rate (per yr)	-3.56 (-7.62, 0.49)	0.085
Difference in Rate [‡] : ERT vs. No ERT	9.37 (0.92, 17.83)	0.030
Excluding Deaths		
Baseline ELC	0.76 (0.51, 1.01)	<0.001
Days in Hospital	-0.06 (-0.16, 0.03)	0.197
Special Prep	4.39 (-6.75, 15.52)	0.440
No ERT Rate (per yr)	-8.97 (-12.15, -5.80)	<0.001
ERT Rate (per yr)	-3.49 (-7.35, 0.36)	0.076
Difference in Rate [‡] : ERT vs. No ERT	5.48 (0.61, 10.35)	0.027

[‡]The difference was calculated based on the estimated rate of each group.