

MIXED DONOR CHIMERISM AND LOW LEVEL IDURONIDASE EXPRESSION MAY BE ADEQUATE FOR NEURODEVELOPMENTAL PROTECTION IN HURLER SYNDROME

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Hurler syndrome is a lysosomal storage disease resulting in fatal cardiac or neurologic sequelae unless alpha-iduronidase production is reconstituted with hematopoietic stem cell transplantation. We report on a 4-year, 6-month-old boy with mixed donor chimerism and low enzyme levels but a normal neurodevelopmental trajectory. (*J Pediatr* 2005;147:106-8)

Children with Hurler syndrome lack the lysosomal enzyme alpha-L-iduronidase. This results in glycosaminoglycan (GAG) accumulation with progressive mental retardation and death.^{1,2} Recombinant alpha-L-iduronidase appears to ameliorate some of the systemic effects in Hurler syndrome, but hematopoietic stem cell transplantation remains the only means of preventing the neurologic deterioration.³

Children with Hurler syndrome have normal intelligence at birth, but on average their IQ declines by 2 standard deviations within the first 2 years of life (30-point decrease in IQ).⁴ The negative correlation between age and IQ has been found to be significant ($r = -0.82$, $P \leq .0003$).² Good neuropsychological outcomes after bone marrow transplantation (BMT) are dependent on multiple factors including age at transplantation (<24 months), mental developmental indexes >70 before transplantation, adequate engraftment (as measured by full donor chimerism), and posttransplantation iduronidase activity.⁴⁻⁶ We report the case of a patient with Hurler syndrome in whom a good neurologic outcome was achieved in spite of poor sustained engraftment and very low serum alpha-L-iduronidase activity after BMT.

CASE REPORT

At 9 months of age, the patient presented with coarse facies and a lumbar gibbus. He had dysostosis multiplex and a positive mucopolysaccharide (MPS) screen result. Hurler syndrome was confirmed by the absence of alpha-L-iduronidase activity in peripheral blood leukocytes. He had a homozygous mutation of his IDUA gene, W402X, common to those with a severe Hurler phenotype.

At 15 months of age, the patients underwent BMT from a male matched related donor. Conditioning regimen included cyclophosphamide (50 mg/kg \times 4 doses), busulfan (based on targeted AUC 18mg/kg divided every 6 hours over 4 days), and low-dose total body irradiation (300 cGy). The patient was transplanted with 5.6×10^8 nucleated cells/kg. He had no unexpected transplant-related toxicity and specifically no central nervous system complications.

After BMT, his musculoskeletal abnormalities persisted but were stable, his facial features softened, and airway obstruction resolved. An echocardiogram obtained 2 years after transplantation showed resolution of both his atrial septal defect and mild valvular regurgitation.

Initially he fully engrafted. He was followed by chimerisms on whole blood and alpha-L-iduronidase levels on unfractionated peripheral leukocytes. He expressed normal levels of alpha-L-iduronidase after transplantation but failed to sustain these beyond 4 months after BMT. The patient has remained at very low levels of activity (Table).

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BMT	Bone marrow transplantation	CNS	Central nervous system
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Based on clinical evaluation and developmental achievements, it was felt that his pretransplantation development was normal. He sat at 6½ months, stood at 7 months, had single words at 10 months, and walked at 13 months. Two years after BMT (age 3 years, 3 months), a formal neuropsychological evaluation demonstrated development in the normal range. Full Scale intelligence testing revealed average intelligence (45th percentile). There was a minor discrepancy between his verbal (average range) and performance intelligence (low-average range). He had mild difficulties with visual spatial skills, primarily with block design. His language skills were normal on the Token Test for children.

His most-recent evaluation at age 4 years 5 months revealed dramatic improvements on the Peabody Developmental Motor Skills, with an age equivalent of 41 months. (This minor delay was attributed to his Hurler syndrome-induced flexion contractures of his fingers). He continued to do well in school and was communicating in both English and French. Repeat neuropsychological testing at that time revealed average full-scale intelligence with no discrepancy between his verbal and performance skills.

DISCUSSION

Hurler syndrome is a progressive disease that leads to coarse facial features, corneal clouding, hernias, hepatosplenomegaly, skeletal deformities, and progressive mental retardation.^{1,2} Death results from heart disease or respiratory failure in the first decade of life.

Cleary and Wraith¹ showed that normal developmental milestones over the first year of life were achieved by all of their patients. However, neurodevelopment does not continue along a normal trajectory after the first year.^{2,4,7} Therefore our patient should have had evidence of neurologic deterioration if there were inadequate cerebral alpha-L-iduronidase activity.

The rationale for BMT lies in the provision of donor histiocytes that migrate to the central nervous system (CNS), differentiate into microglial cells, and provide an ongoing source of functional enzyme.^{7,8} We postulate that this occurred in our patient at sufficient levels to provide neuroprotection in spite of an inadequate peripheral engraftment.

Peters et al⁵ showed that iduronidase activity post BMT less than or equal to that of a heterozygous carrier donor (~50%) was associated with a poor neurologic outcome (Mental Development Index [MDI] ≤80). A statistically significant correlation was subsequently found between MDI at follow-up and peripheral enzyme activity in these patients (0.59, *P* = .02). Other studies have reported adequate developmental outcomes in children with less than 90% chimerism (although all had at least 50% chimerism).^{6,9-11} Our patient's outcome suggests that even very low levels of peripheral enzyme activity level can be associated with normal development.

Data regarding the presence of alpha-iduronidase activity in the CNS after BMT is indirectly derived from cerebrospinal fluid and neuroimaging studies.¹¹ Takahashi et al¹⁰ used magnetic resonance spectroscopy to measure

Table. Measured levels of alpha-L-iduronidase and donor engraftment over time

	Alpha-L-iduronidase *	Chimerism % [†]
Pretransplantation	0	
Posttransplantation	Normal 14-41 nmol/h/mg protein	Ideal >90%
1 month	28	90
4 months	0	45
6 months	14	30
1 year	3	15
1 year 5 months	2	15
1 year 8 months	3	10
2 year 1 month	73 [‡]	15
2 year 6 months	4	10
3 year 2 months	3	10

*Alpha iduronidase enzyme activity was measured using a standardized assay on unfractionated peripheral blood leukocytes.

†Chimerism was determined by restriction fragment length polymorphism on the recipient's whole blood sample.

‡Believed to be secondary to assay problems.

central levels of GAGs before and after BMT in a patient with Hurler syndrome. After BMT, peripheral enzyme activity was greater than 50% of normal (13 nmol/mg/protein/h with normal 28 ± 7) but never achieved complete engraftment. At the patient's 2-year follow-up, in spite of low enzyme activity, the levels of central GAGs were stable, routine neuroimaging results were normal, and the child had a 28-point increase in IQ.¹⁰ This is the first neuroimaging evidence that peripheral enzyme activity may be limited in predicting CNS enzyme activity. Our case adds support to this notion.

Limitations of this report include that it may be too early to predict our patient's ultimate neurologic outcome, although if enzyme activity in the CNS were inadequate, he should have shown cognitive decline by age 4. Although delayed or minimal cognitive problems are seen in attenuated forms of MPS1, such as Hurler-Scheie syndrome, our patient presented with significant symptoms before 1 year of age, and his IDUA mutations are associated with a severe MPS1 phenotype. Thus we are confident he has Hurler syndrome.

Our case illustrates that normal peripheral blood alpha-L-iduronidase levels may not be required to sustain normal neuropsychological development in patients with Hurler syndrome after BMT. If techniques can be developed to identify prospectively those patients who are destined to have a good neurologic outcome in spite of low peripheral blood alpha-L-iduronidase levels (for example by functional neuroimaging or other central nervous system biochemical markers), we may avoid the morbidity and mortality of a second BMT.

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