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UNRELATED UMBILICAL CORD BLOOD TRANSPLANT FOR JUVENILE METACHROMATIC LEUKODYSTROPHY: A FIVE-YEAR FOLLOW-UP IN THREE AFFECTED SIBLINGS

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Abstract

Unrelated umbilical cord blood transplantation (UCBT) was used to treat three siblings with juvenile metachromatic leukodystrophy (jMLD). The efficacy of this therapy was measured over a five-year period with serial neurological exams, neuroimaging, nerve conduction studies (NCS), and neuropsychological evaluations (NPE). Outcomes were a function of disease stage at time of UCBT with alteration of disease course occurring in the first two years after UCBT and then subsequent halting of progression and stabilization of symptoms and disease.

Keywords

Umbilical Cord Blood Transplant; Metachromatic Leukodystrophy; Neurological disease; neuroimaging

INTRODUCTION

MLD is a lysosomal storage disease causing widespread peripheral and central demyelination due to a deficiency of arylsulfatase A (ARSA). The neurological symptoms of MLD are the result of toxic accumulation of sulfatides [1,2]. Symptoms of jMLD generally include cognitive regression, gait disturbance, and urinary incontinence. Recent work has shown several therapies may be efficacious, including enzyme replacement, gene therapy and hematopoietic cell transplantation (HCT) [3–13]. HCT, specifically bone

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marrow and umbilical cord blood transplants, uses transplanted hematopoietic cells to deliver the deficient enzyme to the brain, with the expectation that transplanted cells migrate into the central nervous system and release enzyme, rescuing nearby neural cells [14–18]. This method has been used to treat MLD with variable results [14]. This report documents the five-year follow-up of three siblings with jMLD after umbilical cord blood transplantation at different stages of disease. A previous report documented their course two years after transplant [7].

METHODS

Methods were previously reported [7] with re-evaluation of ARSA activity, neurological exams, magnetic resonance imaging of the brain (brain MRI), NCS, and NPEs in the siblings at five years post-UCBT. ARSA assays were performed with nitrocatechol sulfate substrate.

RESULTS

Neurological Outcome

The oldest sibling (8 years old) was diagnosed with jMLD after he developed inattentiveness and urinary incontinence [7]. Subsequently, his neurologically normal 6 year-old brother and 4 year-old sister were also diagnosed with MLD. The genetic mutations of this family include two common mutations, the null A212V and the residual P426L mutation resulting in jMLD [1,7]. All underwent UCBT within 2–3 months of diagnosis [7]. There were no further complications due to the UCBT procedure after the first two years post-UCBT. The oldest sibling had rapid neurological deterioration one month after transplantation and remains in a vegetative state. The younger siblings' neurological exams have remained stable over the past three years. During the year following UCBT, the middle brother developed mild-moderate lower extremity hypertonicity and diminished ankle jerks, but otherwise has remained normal at five years post-UCBT. The youngest sibling has continued to be physically active without neurological deficits. Serum ASA activity in all children has been reasonably normal after UCBT (Table I).

Neuroimaging

The oldest child had significant WMSAs on his initial scan, which progressed to cystic changes with loss of white matter [7]. He has had no further imaging studies. The middle sibling had moderate WMSAs on initial MRI, which underwent significant improvement within one year after UCBT [7] and have remained stable (Figure 1). The youngest sibling had no WMSAs on initial exam, but six months after UCBT developed WMSAs near the occipital horns of the lateral ventricles. These changes largely resolved one year after transplant and her MRIs remained unchanged.

Neurophysiology

All three children had sensory-motor polyneuropathies with mild slowing of the nerve conduction velocities on the initial evaluation. The oldest child had NCS with minimal decreases in the sensory velocities and about a 30% decrease in motor velocities compared to the initial study. The younger children had stable NCVs over the first two years with their right median sensory conduction velocities showing a trend toward improvement. At the five-year follow-up, their median sensory NCVs have plateaued without further improvement, while the other studies remain reasonably stable (Table I).

Neuropsychological Evaluation

The middle child performed at a low-average level before UCBT; at two and five years after transplant, he had similar deficits and performed on a borderline-low average level (Table I). He required special instruction, but continued to progress in school. The youngest child's NPE results revealed average-high average ability before transplant, two and five years after transplant she still had normal ability. Notably, both had a similarly mild decrease in test scores over the first two years post-UCBT (Table I).

DISCUSSION

The use of HCT for treatment of lysosomal diseases involving the CNS has been controversial, largely due to the wide range of reported outcomes [3–6,9,10,12,16,17]. This report documents the five-year follow up evaluation of three siblings with jMLD treated with UCBT at different stages of disease. This range presented an opportunity to estimate the benefits of using UCBT at different stages of the disorder, but this estimation requires the children have similar concordance of disease severity and progression prior to UCBT. This seems to be the case. All three children developed a polyneuropathy by the time of diagnosis. The oldest child had significant WMSAs and cognitive deficits at presentation; while the youngest child had a normal MRI and NPE at that time. Importantly, the youngest child developed WMSAs at about 4 years of age during a brief period of time after UCBT (this age was similar to the age at which the older children likely developed WMSAs), while the middle sibling had findings intermediate between the other two. This information indicates these children likely would have developed disease with relatively similar rates and severity. Additionally, it indicates that UCBT likely altered their individual courses as a function of their disease state at the time treatment was initiated.

In a previous report [7], an improving trend in the younger children's NCSs was thought to be present; however, the current data indicates NCS values had plateaued without further improvement. The current data also reveal that the younger two siblings had stable neuropsychological function between two and five years; however, the two may have undergone a period of mild decline following UCBT. Whether this decline was due to further disease progression while awaiting the complete response to UCBT, or was due to the UCBT itself, or is within the normal range of variability for NPEs in chronically-ill children cannot be determined. If a delay in complete response were the cause, it would be interesting to determine whether other children treated with UCBT for neuro-metabolic disorders have a similar pattern of testing. This could indicate a need for a combination of treatment modalities to speed the action of therapy, which could include the use of UCBT to allow more rapid matching and transplantation as compared to bone marrow transplantation, adjunctive intravenous enzyme replacement therapy, or direct transplant of enzyme-secreting cells into the CNS.

CONCLUSIONS

The long-term response to UCBT in this family continues to depend upon the stage of disease in each child at the time of transplant. The oldest child gained little benefit and may have worsened [7], while the younger children's course stabilized within a year of UCBT and has continued with little change in neurological exam, NCS, and NPE. A relationship between an individual's genetic makeup and his or her response to UCBT cannot be ruled out, so we advocate caution when recommending this modality to other families with MLD.

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Figure 1.

Brain magnetic resonance images in the middle sibling (A, B, C), and youngest sibling (D, E, F, G) before and after UCBT. The middle sibling had moderate white matter changes on initial MRI (A), which showed improvement with re-imaging at two (B) and five years (C) post-transplant. There was associated enlargement of the lateral ventricles, which may represent atrophy of previously affected white matter. The youngest sibling had no initial white matter changes (D); however, 6 months after transplant she had minor WMSAs near the occipital horns of the lateral ventricles (E). These WMSAs resolved within the next 6 months (data not shown) and there has been no significant change in her neuroimaging at two (F) and five years post-transplant. Scoring with a modified Loes scoring system for MLD [21] gave estimated scores for the middle sibling (pre-transplant: 11; two-years post-transplant: 8; and five-years post-transplant: 8) and for the youngest sibling (pre-transplant: 0; two-years post-transplant: 2; and five-years post-transplant: 2). All images are FLAIR sequences and were performed on a 1.5-Tesla machine, except for the five year follow-up studies which were performed with a 3-Tesla machine (this may enhance the previously noted WMSAs, however there was no change in the size of the WMSAs from two to five years post-UBCT).

TABLE I

	Right Median Sensory	Right Sural Sensory	Right Median Motor	Right Peroneal Motor	ARSA Activity (nmol/hr/mg protein)	Full Scale IQ
Normal Range			(m/s)			
4–6 years old ¹⁹	37–54	45–63	47–66	46–65	49–65	70–130
6–14 years old ²⁰	40–58	46–62	51–64	48–66		
Age/Months Post-Transplant	Oldest Sibling					
8/6	43	39	34	35	3	-
13/59	40	34	26	24	38	-
Age/Months Post-Transplant	Middle Sibling					
6/0	-	-	-	-	5	88
6/6	33	39	38	31	-	-
8/24	42	33	41	35	44	69
10.5/59	44	35	36	30	50	73
Age/Months Post-Transplant	Youngest Sibling					
4/0	-	-	-	-	6	120
4.5/6	39	33	39	37	-	-
6.5/24	49	37	45	35	38	98
9/55	41	36	47	38	49	101