Improve of White Matter Changes on Neuroimaging Modalities After Stem Cell Transplant in Metachromatic Leukodystrophy

Martje E. van Egmond, MD; Petra J. W. Pouwels, PhD; Jaap-Jan Boelens, MD, PhD; Caroline A. Lindemans, MD, PhD; Frederik Barkhof, MD, PhD; Martijn D. Steenwijk, MSc; Peter M. van Hasselt, MD, PhD; Marjo S. van der Knaap, MD, PhD; Nicole I. Wolf, MD, PhD

**Importance:** We sought to illustrate improvement of cerebral white matter changes in metachromatic leukodystrophy after treatment with hematopoietic stem cell transplant (HSCT).

**Observations:** We conducted serial magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (1H-MRS) as standard follow-up after HSCT with cord blood in 1 patient with juvenile metachromatic leukodystrophy diagnosed before frank degenerative symptoms developed. We measured MRI and 1H-MRS changes. The white matter changes first increased after HSCT, then decreased in relation to the pre-HSCT MRI and 1H-MRS.

**Conclusions and Relevance:** Hematopoietic stem cell transplant, if performed early in metachromatic leukodystrophy, can not only stabilize but even improve cerebral white matter abnormalities. Our findings suggest a biological effect of HSCT.


**METACHROMATIC LEUKODYSTrophy (MLD) is an inherited white matter disorder with deterioration of motor and cognitive capabilities. The following 3 different forms of the disease are distinguished: late infantile (onset before 30 months of age), juvenile (onset before 16 years of age), and adult. The disease is caused by deficiency of the enzyme aryl-sulfatase A, leading to progressive demyelination of the central and peripheral nervous systems. At present, no curative therapy exists for MLD. The only treatment option for juvenile and adult patients with an early diagnosis is hematopoietic stem cell transplant (HSCT).**

Controversy remains about the efficacy of HSCT for MLD because the procedure carries a high risk, and sound evidence of a significant effect is difficult to obtain in a disorder with a variable age at onset and rate of progression, even without treatment and within the same family. Some groups advocate the concurrent infusion of mesenchymal stem cells, but no data have proven their efficacy. Patients with an unsatisfactory outcome after HSCT have been described in published reports, but these patients often underwent transplant at a later stage, making it difficult to predict the effect of HSCT in patients with mild disease or in those who are unaffected. The current assumption is that HSCT can at best stabilize neurodegeneration but not reverse cerebral damage already present before this procedure.

**REPORT OF A CASE**

A 14-year-old girl presented with headache and concentration difficulties after minor head trauma. Results of the neurological examination showed mild distal motor weakness and slight muscle atrophy in the arms and legs. Deep tendon reflexes were absent, and she had mild cerebellar ataxia. She had difficulties in social interaction and behavioral problems. Her total IQ score was 94 (Wechsler Intelligence Scale for Children–Third Edition). Cerebral magnetic resonance imaging (MRI) revealed symmetrical periventricular white matter hyperintensities on T2-weighted sequences (Figure, A-C), suggesting MLD. The MLD magnetic resonance (MR) severity score was evaluated by an experienced neuroradiologist (F.B.) blinded to the acquisition dates, with a finding of 14 of 34 points (Table). Demyelination load was quantified manually using the proton density T2-weighted images by a rater (M.D.S.) blinded to acquisition date.
Proton magnetic resonance spectroscopy (1H-MRS) of white matter was characterized by a decreased concentration of N-acetylaspartate (NAA) most pronounced in the frontal affected white matter, increased myo-inositol level, slightly increased levels of choline-containing compounds, and no detectable lactate level (Figure, M-O). The diagnosis was confirmed by demonstrating reduced activity of arylsulfatase A in leukocytes and homozygosity for the known mutation c.1277C>T (p.Pro426Leu) in the ARSA gene (OMIM 607574).
Because the patient was in an early stage of the disease, she was treated with HSCT in an attempt to stabilize neurodegeneration. She underwent conditioning with busulfan combined with fludarabine phosphate and antithymocyte globulin. Allogeneic cord blood transplant was performed with cord blood matched for 5 of 6 HLA antigens. The transplant was uncomplicated, with 100% donor-cell engraftment and minor posttransplant complications.

Six months after HSCT, MRI of the brain showed progression of white matter abnormalities (Figure, D-F) and mild atrophy. The MLD MR severity score was 18 (Table); the demyelination load had increased to 71.3 mL.

At the neurological examination 1 year after HSCT, the distal muscle weakness and cerebellar ataxia had improved. She was treated with sertraline hydrochloride because of depressive symptoms and behavioral problems, with good effect. Her total IQ was stable at 93.

Eighteen months after HSCT, MRI of the brain demonstrated clear improvement of white matter abnormalities, especially in the centrum semiovale (Figure, G-I). The MLD MR severity score was 15 (Table); the demyelination load had decreased to 25.5 mL. Slight improvement was observed in the 'H-MRS of white matter. The NAA concentration had increased in all areas and was now slightly below the reference range only in the frontal white matter. The myo-inositol level was unchanged and remained elevated. The ratios of choline-containing compounds to NAA and myo-inositol to NAA, which are sensitive markers for disease stage, had diminished and thus improved (Figure, P-Q). The latest MRI took place 27 months after transplant. White matter and 'H-MRS abnormalities were stable; a demyelination load of 21.1 mL confirmed further improvement (Figure, J-L and S-U).

Our case demonstrates that MRI and 'H-MRS of the brain can improve after HSCT in juvenile MLD. This finding is important because it shows that MR abnormalities in MLD may be at least partially reversible. The neuroimaging results were consistent with the clinical observation of gradually improving motor and behavioral functions and stable cognition in the 27 months after HSCT. These observations suggest that the HSCT not only stabilized the demyelinating process of MLD but also allowed some recovery.

**COMMENT**

Deterioration of MRI abnormalities after HSCT has been reported in several patients with MLD, with stabilization also reported. Cable et al described 1 case with improvement of MRI abnormalities after HSCT but did not provide detailed imaging; the child was clinically unaffected at the time of the transplant and also received cord blood from an unrelated donor. Since the acceptance of this manuscript, a report of another patient with improvement of MRI changes after HSCT early in the disease course has been published.
To quantify brain MRI abnormalities, we used the MLD MR severity scoring method described by Eichler et al. In addition, lesions were manually outlined to measure the demyelination load. In our patient, MRI abnormalities progressed in the first months after HSCT, with a clear increase in the severity score. This deterioration probably was the result of the HSCT itself and further disease progression before the complete response to HSCT. Subsequently, significant improvement of white matter abnormalities was seen on MRI imaging and 1H-MRS, not only compared with the results 6 months after HSCT but also compared with the neuroimaging before HSCT. This improvement was not represented in the overall severity score, also because of cerebral atrophy after the procedure, which might indicate limited sensitivity of the scoring method. Quantification of the demyelination load, however, clearly reflected the reduction in volume of the white matter lesions. Thus, our case demonstrates that brain MRI and 1H-MRS can improve after HSCT in juvenile MLD, suggesting a biological effect of this treatment.

Accepted for Publication: August 29, 2012.
Published Online: April 22, 2013. doi:10.1001/jamaneurol.2013.629

Correspondence: Nicole I. Wolf, MD, PhD, Department of Child Neurology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands (n.wolf@vumc.nl).

Author Contributions: Study concept and design: van Egmond, Boelens, Lindemans, and Wolf. Acquisition of data: van Egmond, Pouwels, Boelens, Lindemans, van Hasselt, van der Knaap, and Wolf. Analysis and interpretation of data: van Egmond, Pouwels, Barkhof, Steenwijk, van Hasselt, van der Knaap, and Wolf. Drafting of the manuscript: van Egmond, Boelens, Lindemans, Steenwijk, and Wolf. Critical revision of the manuscript for important intellectual content: van Egmond, Pouwels, Boelens, Lindemans, Barkhof, van Hasselt, van der Knaap, and Wolf.

Conflict of Interest Disclosures: None reported.

REFERENCES