Long-term Stabilization After Bone Marrow Transplantation in Juvenile Metachromatic Leukodystrophy

D. Kidd, MD; J. Nelson, MD; F. Jones, MRCPth; H. Dusoir; I. Wallace, MSc; S. McKinstry, FRCR; V. Patterson, FRCP

We describe a 16-year-old boy with juvenile metachromatic leukodystrophy who was treated with bone marrow transplantation. Follow-up over 8 years showed no increase in symptoms, no progression of neurological signs, and no neuropsychological deterioration. We conclude that bone marrow transplantation may increase brain levels of arylsulfatase A enough to prevent deterioration in patients with juvenile metachromatic leukodystrophy.

Metachromatic leukodystrophy (MLD) is a disorder of autosomal recessive inheritance caused by deficiency of the lysosomal enzyme arylsulfatase A (ASA). This deficiency results in the accumulation of cerebroside sulfate (sulfatide) in the nervous system and other organs. The juvenile form, which is less common than the late infantile form, presents with the onset of educational and behavioral difficulties between 4 and 12 years of age. The intellectual deterioration is progressive and is associated with weakness, extrapyramidal signs, ataxia, and, ultimately, death.

The genetic defect has been localized to chromosome 22, and the gene itself has recently been cloned. A number of mutations have been identified; some of these have been associated with the late infantile form, some with the juvenile form, and others with the adult form of the disease. However, the same genotype has been described in both the late infantile and the juvenile forms, suggesting that genotype-phenotype correlation may not be straightforward.

Bone marrow transplantation (BMT) has been used since 1981 to treat a number of lysosomal storage diseases, but its effect on central nervous system involvement is unclear. The results of BMT in infantile MLD are conflicting, but in 1 case, clinical stabilization occurred, and it was demonstrated that donor cells had penetrated the central nervous system. There is 1 report of BMT in juvenile MLD in which, after a short follow-up, it was thought that slowing of the progression of the disease had been achieved. It was against this background that we undertook BMT in a patient with juvenile MLD.

The patient was first evaluated by us after his brother had been diagnosed as having juvenile MLD. At the age of 7 years, the brother presented with deteriorating schoolwork that progressed over the next few years, and then he developed dysarthria, bradykinesia, ataxia, extensor plantar responses, and urinary incontinence. A computed tomographic scan of the brain showed ventricular dilatation with diffuse areas of low attenuation in the white matter of both cerebral hemispheres. Visual evoked responses, electroneurograms, findings of nerve conduction velocity studies, results of cerebrospinal fluid analysis, serum and urinary copper levels, urinary amino acid levels, and serum cortisol and hexosaminidase levels were all normal. The leukocyte ASA level was 0.8 nmol/mg per hour (reference range, 24.4-50.3 nmol/mg per hour), and a skin fibroblast ASA level was 4.5 nmol/mg per hour (reference range, 263-526 nmol/mg per hour).
Our patient was 13 years old at presentation. He was thought to have developed quite normally until the age of 9 years, after which there had been a progressive deterioration in his school performance. He was easily distractible, with disinhibited behavior and poor short-term memory. His language and constructional abilities were unimpaired. Examination of the cranial nerves and the motor and sensory systems revealed no abnormalities, and there was no weakness, extensor plantar responses, ataxia, or dystonia. Reflexes were present and normal. A computed tomographic scan showed a slight increase in ventricular size and areas of low attenuation in the periventricular areas of the white matter. Leukocyte and skin fibroblast ASA levels were subnormal at 0.85 and 55 nmol/mg per hour, respectively. Over the course of the following year, the patient developed mild ataxia of his legs; his behavior became worse; and there was a small reduction in his IQ scores. After consultation with his family, it was decided that he should undergo BMT in an attempt to alter the course of the disease.

The patient underwent pretransplantation conditioning consisting of cyclophosphamide therapy (60 mg/kg per day for 2 days) and total body irradiation (8 Gy administered as a single fraction at a dose rate of 5.5 cGy/min). He received the bone marrow from his fully HLA-matched sister on September 22, 1986. Her plasma and leukocyte ASA levels were 22.0 and 30.4 nmol/mg per hour, respectively.

Posttransplantation immune suppression was initiated with cyclosporine and prednisolone and continued for 6 months. No graft-vs-host disease was observed. The patient developed cystitis despite treatment with mesna. He was discharged 32 days after transplantation. Engraftment was documented by 96% XX karyotype in a peripheral blood sample on day 70. Apart from an occurrence of localized shingles 1 year later, the patient had symptomatic juvenile MLD and, if implemented, should be carried out as early as possible in the course of the disease.

Before the BMT, our patient had symptomatic juvenile MLD with documented progression. Since the BMT, there has been no symptomatic, neurological, or neuropsychometric progression of his disease. We are not aware of any cases of juvenile MLD in which there has been documented progression followed by spontaneous arrest, so it seems likely that the disease has stabilized as a result of the BMT.

How BMT works is unclear; transplant-derived lymphoid cells may enter the brain and liberate enough ASA extracellularly to stop further neural death. This is probably more likely to happen in conditions in which a small increase in the level of an existing enzyme may be sufficient to prevent deterioration; it is known that biochemically affected siblings of patients with MLD may be clinically normal and that, therefore, a small amount of enzyme may be sufficient. Patients with no biologically active enzyme would be much less likely to benefit from the small increase provided by BMT, and this may explain its modest effect in other neuronal storage diseases. Our experience suggests that BMT is a treatment option for patients with juvenile MLD and, if implemented, should be carried out as early as possible in the course of the disease.

# REFERENCES

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