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.1

The genetic defect has been localized to chromosome 22, and the gene itself has recently been cloned.2 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.3

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.4 The results of BMT in infantile MLD are conflicting,5 but in 1 case, clinical stabilization occurred, and it was demonstrated that donor cells had penetrated the central nervous system.7 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.8 It was against this background that we undertook BMT in a patient with juvenile MLD.

REPORT OF A CASE

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, electroretinograms, 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).
lary, and the levels have been consistently higher than they were before BMT (Figure). Psychometric testing has also been carried out at yearly intervals, and the results have shown no deterioration (verbal IQ/performance IQ, 75/51 before BMT; 71/56 eight years after BMT). Subsequent computed tomographic scans have shown a small increase in the amount of cerebral atrophy but no change in the white matter abnormalities.

Comments

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 neuronal death.66 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 normal66 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.

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REFERENCES


Graph of leukocyte arylsulfatase A (ASA) level (ordinate) against time (days after bone marrow transplantation [BMT]) (abscissa). Reference range (shaded area), 24.4 to 50.3 nmol/mg per hour.