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Serial MR after Bone Marrow Transplantation in Two Patients with Metachromatic Leukodystrophy

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Summary: Two children with metachromatic leukodystrophy underwent bone marrow transplantation. In both patients MR subsequently showed, first, white matter changes, then later, lack of change as the patients stabilized clinically.

Index terms: Bone marrow transplantation; Degenerative disease; Brain, diseases; Brain, magnetic resonance; Pediatric neuroradiology

Bone marrow transplantation is a promising treatment for metachromatic leukodystrophy (1). We present two patients with metachromatic leukodystrophy who underwent bone marrow transplantation and have been serially followed by magnetic resonance (MR).

Case Reports

Case 1

L.K.B. has a low level of aryl sulfatase A, consistent with a homozygotic state for metachromatic leukodystrophy. The patient had normal initial development, but by age 3 she had developed an intention tremor and abnormal nerve conduction velocity measurements. The patient underwent bone marrow transplantation at age 4³/₄ years from her HLA-matched healthy sibling. Complete engraftment was achieved. Restitution of normal levels of aryl sulfatase A has been documented for the past 8 years.

MR was first obtained at age 5 years 8 months (Fig 1A). Diffuse increased periventicular white matter changes were present. MR 1 year later showed decreased white matter abnormalities. Subsequent yearly MR studies have shown no evidence of progression or significant change (Fig 1B).

Neuropsychological testing demonstrated a decrease in intelligence quotient and lack of new learning from age 4 to 6 years. The patient has remained stable in her Wechsler verbal IQ, which has been in the 80 range since she was 8 years old. She now reads and comprehends at a normal level at 12½ years of age. She continues to demonstrate a static pattern of deficits, including dysarthric

speech, bilateral dysmetria, intention tremor, and a widebased ataxic gait. This is in marked contrast to her older affected sister, who became vegetative by age 6 and died at age 8 years.

Case 2

W.L.V. had a low level of aryl sulfatase A consistent with homozygosity for metachromatic leukodystrophy at age 14 when she had evidence of early dementia. She received a bone marrow transplantation from an HLA-identical sibling ½ year later. Engraftment was verified by both complete restitution of enzymatic activity of aryl sulfatase A and by DNA analysis of leukocytes.

The patient's sister and brother were both affected. The sister began her clinical course of disease similar to W.L.V. and by age 18 became bedridden and died at age 20 years. The brother began his clinical course of metachromatic leukodystrophy at 8 years of age and now at 12 years is wheelchair bound, spastic, and unable to talk. In contrast, the intellectual achievements of W.L.V. have been followed for 3 years. Both verbal and performance IQs have remained in the 75 range. Her neurologic examination remains normal. Thus, there is no evidence of clinical progression.

The MR examinations have demonstrated mild increased white matter changes and volume loss over the past 2 years, with no significant change over the past year (Fig 2). The volume loss may be caused by steroids used for treatment of clinical graft-versus-host disease.

Discussion

Metachromatic leukodystrophy is inherited in an autosomal recessive pattern. A deficiency of the lysosomal enzyme cerebroside sulfatase (aryl sulfatase A) leads to an accumulation of the sulfate ester of galactose cerebroside in various tissues, including the brain, peripheral nerves, kidneys, liver, and gall bladder. Accu-

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Fig 1. A, T2-weighted (1500/70 [repetition time/echo time], 0.35 T) axial image of L.K.B. 1 year after bone marrow transplantation. Increased abnormal signal is present adjacent to both anterior and posterior horns of the lateral ventricles.

B, T2-weighted (2500/90, 1.5 T) image approximately 6 years later. Other than technical differences, there is no significant change. *C*, Computed tomographic scan of the sister of L.K.B. at 8 years 11 months of age. Marked cerebral and cerebellar atrophy and ventricular dilatation are present.

mulation in cerebral tissues produces progressive degeneration of myelin, loss of neurologic function, and eventual death. Biochemical diagnosis is made by decreased activity of aryl sulfatase A in leukocytes, fibroblasts, and urine.

Three forms of metachromatic leukodystrophy have been differentiated according to the age of onset: late infantile, juvenile, and adult (2). The juvenile form may be further subdivided into early and late forms because of differences in symptoms and pathophysiology (3). The late-infantile form has a relatively predictable inexorable course (4), whereas the others vary in phenotypic expression both within and between families (5, 6). The characteristic course of the late-infantile form of metachromatic leukodystrophy consists of progressive decline in cognitive skills and motor dysfunction leading to quadriparesis. Death occurs within a few years of the first symptoms.

Bone marrow transplantation has been shown to correct the enzymatic deficiency. To date, there have been eight patients with metachromatic leukodystrophy who have been successfully engrafted and have been followed for a sufficient period of time to assess the benefit of this treatment on neurologic manifestations. Disease progression in all of these patients has either slowed or stabilized (7–10).

The serial neuropsychological (11) and neurophysiologic (12) testing of case 1 have been reported elsewhere. MR was first obtained in this patient at 5 years 8 months of age (8 months after bone marrow transplantation engraftment). The high-intensity confluent areas in the periventricular white matter are typical of metachromatic leukodystrophy. One year later, however, the sizes of these abnormal areas were noted to be decreased. The MR examinations have remained stable since this time, with no evidence of disease progression. This improvement may be secondary to either remyelination or a decreased inflammatory reaction with lymphocytic infiltration of the white matter. The MR findings parallel the patient's neuropsychological studies and clinical course.

The comparison with the older sister who was similarly affected by metachromatic leukodystrophy is critical for appropriate analysis. The sister died before MR was available at our facility. Her axial computed tomographic examination was done at 8 years 11 months of age. Marked cerebral and cerebellar atrophy and ventricular dilatation were present (Fig 1C). In comparison, our patient does not have similar evidence of ventricular size change and/or generalized atrophy even though she is 4 years



Fig 2. *A*, T2-weighted (2700/90, 1.0 T) axial image of W.L.V. several months before bone marrow transplantation. Abnormal signal is present adjacent to both frontal and posterior horns of the lateral ventricles.

B, One year after bone marrow transplantation, there is some ventricular enlargement and increased white matter abnormality (2500/90, 1.0 T).

C, Three years after bone marrow transplantation there, is slight widening of the subarachnoid space but no significant progression of the white matter abnormality (2500/90, 1.5 T). The images have not significantly changed from those obtained 2 years after bone marrow transplantation (not shown).

older than her sister was when she had her computed tomographic examination.

The patient in case 2 has the juvenile form of metachromatic leukodystrophy. Although this form has a less-predictable course than the lateinfantile form of the disease, clinical progression would have been expected over the 3 years that she has been followed. The patient has been treated for chronic graft-versus-host disease with steroids for most of this time. There has been some generalized volume loss noted over the first 2 years seen by MR, but there has been no significant further volume loss over the past year. The volume loss may be secondary to the underlying disease. In our experience, however, the volume loss is not disproportionate to that which we have seen in other patients who underwent bone marrow transplantation who have been engrafted for nonneurologic disease or other patients who do not have metachromatic leukodystrophy and have been taking similar doses of steroids. Moreover, there has been no interval progression of the white matter abnormality. This again argues in favor of steroid effect rather than disease progression. That she remains clinically stable with no significant progression of disease on her MR examinations is noteworthy. Ultimately, further serial studies will clarify the issue of possible disease progression.

The role of sequential MR in these patients may be questioned. We find neuropsychological and neurophysiological testing to be reliable indicators of disease progression. MR does provide an independent assessment of the disease status and may improve confidence in subtle changes.

We will continue to observe and evaluate our patients who have uncertain prognoses. However, we do believe that the arrest of MR changes after bone marrow transplantation treatment of these patients should be of interest to radiologists, and we think that reporting our patients in fullest detail will provide a complete database for other physicians and parents to make appropriate decisions.

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