

## HEMATOPOIETIC STEM-CELL TRANSPLANTATION IN GLOBOID-CELL LEUKODYSTROPHY

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**ABSTRACT**

**Background** Globoid-cell leukodystrophy is caused by a deficiency of galactocerebrosidase, which results in progressive central nervous system deterioration. We investigated whether allogeneic hematopoietic stem-cell transplantation can provide a source of leukocyte galactocerebrosidase and thereby prevent the decline of central nervous system function in patients with the disease.

**Methods** Five children with globoid-cell leukodystrophy (one with the infantile type and four with late-onset disease) were treated with allogeneic hematopoietic stem-cell transplantation. Measurement of leukocyte galactocerebrosidase levels, neurologic examinations, neuropsychological tests, magnetic resonance imaging of the central nervous system, cerebrospinal fluid protein assays, and neurophysiologic measurements were performed before and after transplantation, with follow-up ranging from one to nine years.

**Results** Engraftment of donor-derived hematopoietic cells occurred in all patients and was followed by restoration of normal leukocyte galactocerebrosidase levels. In the four patients with late-onset disease, the central nervous system deterioration was reversed, and in the patient with the infantile form of the disease, signs and symptoms have not appeared. Magnetic resonance imaging showed a decrease in signal intensity in the three patients with late-onset disease who were assessed both before and after transplantation. Abnormalities in cerebrospinal fluid total protein levels were corrected in three patients with late-onset disease and substantially reduced in the patient with the infantile form.

**Conclusions** Central nervous system manifestations of globoid-cell leukodystrophy can be reversed by allogeneic hematopoietic stem-cell transplantation. (N Engl J Med 1998;338:1119-26.)

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**G**LOBOID-CELL leukodystrophy is an autosomal recessive disease due to greatly diminished or absent activity of the lysosomal enzyme galactocerebrosidase.<sup>1</sup> The disease is characterized by the progressive loss of central and peripheral myelin and by spasticity, dementia, and peripheral neuropathy. It ends in a chronic vegetative state and early death. The more common form begins in early infancy and is rapidly progressive, often leading to death within two years. The late-onset form typically begins later in child-

hood, has a more insidious onset, and progresses over a period of several years to death.<sup>2,3</sup>

Hematopoietic stem-cell transplantation has been shown to alter the course of some but not all lysosomal and peroxisomal disorders.<sup>4</sup> Donor leukocytes provide the deficient enzyme, which enters the central nervous system.<sup>5,6</sup> We used transplantation with allogeneic hematopoietic stem cells to treat five patients with globoid-cell leukodystrophy. In four of these patients, clinical central nervous system abnormalities were present before transplantation. The anticipated development or progression of signs and symptoms was arrested after engraftment, thus supporting the hypothesis that allogeneic hematopoietic stem-cell transplantation can be effective in patients with globoid-cell leukodystrophy.

**METHODS**

The patients were referred for treatment to the University of Minnesota at Minneapolis, the Université Catholique de Louvain in Brussels, Belgium, or Duke University School of Medicine in Durham, North Carolina, where approval by the institutional review boards and parental consent for participation in the study were obtained. Table 1 shows the characteristics of the five patients. Four of the patients received marrow from an HLA-identical sibling; one was treated with unrelated umbilical-cord blood (with one HLA-DR mismatch). The preparative regimens for each patient are listed in Table 1. All patients received cyclosporine with or without methylprednisolone for prophylaxis against graft-versus-host disease. Engraftment status was studied immediately after transplantation and annually thereafter by quantitation of leukocyte galactocerebrosidase activity. We confirmed engraftment by DNA analysis or determination of the sex chromosomes of leukocytes in the recipient's blood.

Leukocyte galactocerebrosidase levels were analyzed by established techniques based on the hydrolysis of radioactively labeled galactocerebrosidase.<sup>2,3,7</sup> The values were recorded in nanomoles per hour per milligram of protein in peripheral leukocytes. The mean ( $\pm$ SD) normal range for leukocyte galactocerebrosidase activity is  $2.6 \pm 1.8$  nmol per hour per milligram of protein.

Neuropsychological examinations were performed in three of the patients with late-onset disease. The tests, which were part of an established battery used for patients with storage diseases, in-

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**TABLE 1.** CHARACTERISTICS OF THE FIVE PATIENTS WITH GLOBOID-CELL LEUKODYSTROPHY.\*

PATIENT NO.	ONSET	FIRST SYMPTOM (AGE AT DIAGNOSIS)	CENTER†	DONOR	AGE AT TRANSPLANTATION	PREPARATIVE REGIMEN	CURRENT AGE
1	Late	Optic atrophy (5 yr)	Minneapolis	ID	11.1 yr	B (18), C (200)	20 yr
2	Late	Poor vision (4 yr)	Brussels	ID	7.3 yr	B (16), C (200)	14 yr
3	Late	Family history	Minneapolis	ID	8.2 yr	B (18), C (200)	13 yr
4	Late	Family history	Minneapolis	UCB	2.6 yr	B (320‡), C (100), TBI	5.8 yr
5	Infantile	Family history (1 mo)	Duke	ID	2 mo	B (16), C (200)	16 mo

\*ID denotes an HLA-identical sibling, B busulfan (total doses in milligrams per kilogram of body weight are given in parentheses), C cyclophosphamide (total doses in milligrams per kilogram are given in parentheses), UCB umbilical-cord blood from an unrelated donor with 1 HLA-DR mismatch, and TBI total-body irradiation (750 cGy given in one fraction).

†Minneapolis denotes the University of Minnesota at Minneapolis; Brussels, the Université Catholique de Louvain; and Duke, Duke University School of Medicine.

‡This dose is expressed in milligrams per square meter of body-surface area.

cluded measures of intelligence, language, perception, attention, memory, and motor function.<sup>4</sup> Each of the tests measures specific areas of brain function and has established normal values. A composite listing of the test manuals we used is available elsewhere.\*

Neurologic examinations were performed at each visit. Neurophysiologic studies included standardized electroencephalography, measurement of visual evoked responses, and studies of nerve conduction velocity.<sup>8</sup> Magnetic resonance imaging (MRI) scans were reviewed and severity scores were calculated to provide a numerical statement of areas of brain involved (higher scores indicate more severe disease, with 0 denoting normal and 30 denoting the most severe disease).<sup>9</sup> Cerebrospinal fluid total protein, the albumin index (a measure of the integrity of the blood-brain barrier), and the IgG index (a measure of central nervous system synthesis of IgG) were measured by standard techniques.<sup>10-13</sup>

## RESULTS

All five children tolerated transplantation with relative ease. The absolute neutrophil count rose to 500 per cubic millimeter or higher by day 11, day 19, day 15, day 20, and day 12 after transplantation in Patients 1 through 5, respectively. DNA analysis or sex-chromosome analysis of peripheral-blood leukocytes or both were performed immediately after the transplantation and throughout follow-up. Of the cells examined, all were of donor origin for the first four patients and 85 percent were the donor's in the case of the fifth patient. Graft-versus-host disease did not occur in Patients 2 and 5. Grade II acute graft-versus-host disease of the skin was noted in Patient 1. Minimal skin involvement of chronic graft-versus-host disease, lasting for three months,

occurred in Patient 3 after grade I acute graft-versus-host disease. Patient 4 had grade I graft-versus-host disease (with skin involvement only).

Figure 1 shows leukocyte galactocerebrosidase levels at the time of diagnosis and after transplantation. The recipients' leukocyte enzyme activity, although greater than the levels in the donors during the first year after transplantation, became equivalent to those of the donors in subsequent years. Donor enzyme levels were measured before transplantation.

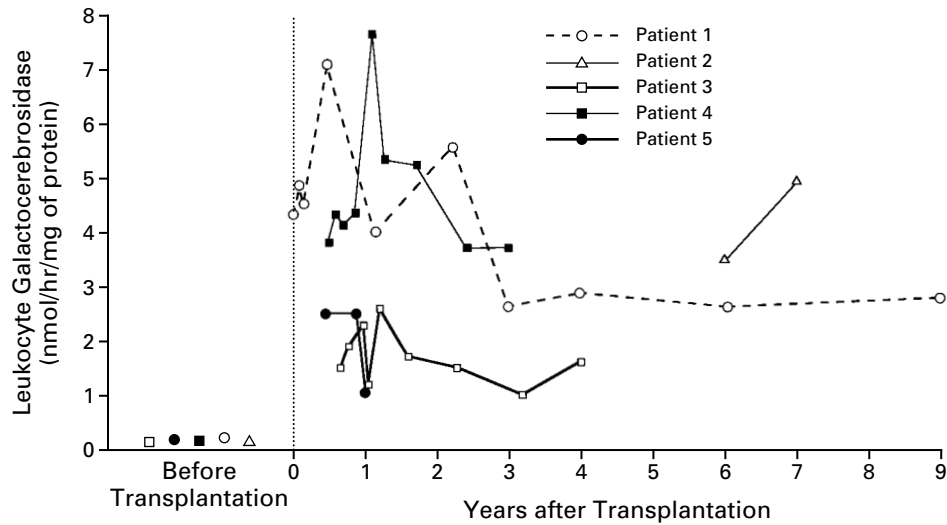
### Patient 1

At the age of five years, Patient 1 had decreased visual acuity, and optic atrophy was diagnosed. Her school performance gradually deteriorated after eight years of age. The diagnosis of globoid-cell leukodystrophy was established by enzymatic assay when she was eight years old. Hand tremors and ataxia began at nine years of age, and a positive Romberg's test, diminished vibratory and positional sensation in the legs and feet, and hypothener muscle atrophy were noted on neurologic examination. At the age of 11 years she received a marrow transplant from an HLA-identical sibling who had normal enzymatic activity (2.4 nmol per hour per milligram of protein) but who was demonstrated by genomic testing to be a carrier of globoid-cell leukodystrophy.

The patient's tremors and ataxia disappeared by six months after engraftment.<sup>14</sup> One year later, motor incoordination and stumbling were no longer evident. Nine years after transplantation, her neurologic condition remains stable. She works as a credit-control clerk and telephone receptionist. She is independent in the activities of daily living.

Before transplantation, Patient 1 had been failing in school and was unable to identify common objects in pictures (visual agnosia). Subsequently, her schoolwork improved, and she graduated from high school. She continues to have difficulties in visual-

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**Figure 1.** Leukocyte Galactocerebrosidase Activity in Five Patients with Globoid-Cell Leukodystrophy before and after Hematopoietic Stem-Cell Transplantation. The dotted line indicates the time of transplantation.

**TABLE 2.** STANDARD SCORES OF PATIENTS 1, 3, AND 4 AT BASE LINE AND AT THE MOST RECENT VISIT, FOR EACH NEUROPSYCHOLOGICAL DOMAIN.\*

DOMAIN	PATIENT 1		PATIENT 3		PATIENT 4	
	11 YR	20 YR	8 YR	13 YR	2 YR	5 YR
Verbal intelligence	102	109	95	93	116	110
Nonverbal intelligence	72†	71†	102	130	116	97
Reading	102	ND	67‡	85	NAA	108
Math	104	ND	101	100	110	92
Receptive vocabulary	84†	ND	86	89	117	121
Expressive vocabulary	ND	ND	89	103	117	117
Expressive fluency	79†	98	93	ND	NAA	112
Spatial perception	105	109	87	97	NAA	NAA
Face perception	50§	75†	100	112	110	90
Global perception	60‡	ND	102	130	135	110
Short-term memory	ND	ND	69‡	102	119	98
Verbal learning	100	134	67‡	90	NAA	114
Motor speed and coordination	51§	61‡	79†	93	NAA	NAA
Graphomotor coordination	WNL	WNL	119	116	NAA	81†

\*The mean ( $\pm$ SD) score for this battery is  $100 \pm 15$ . Ages are reported in years at base line and follow-up for each patient. ND denotes not done, NAA not age-appropriate, and WNL within normal limits.

†This score is  $>1$  SD below the mean for age.

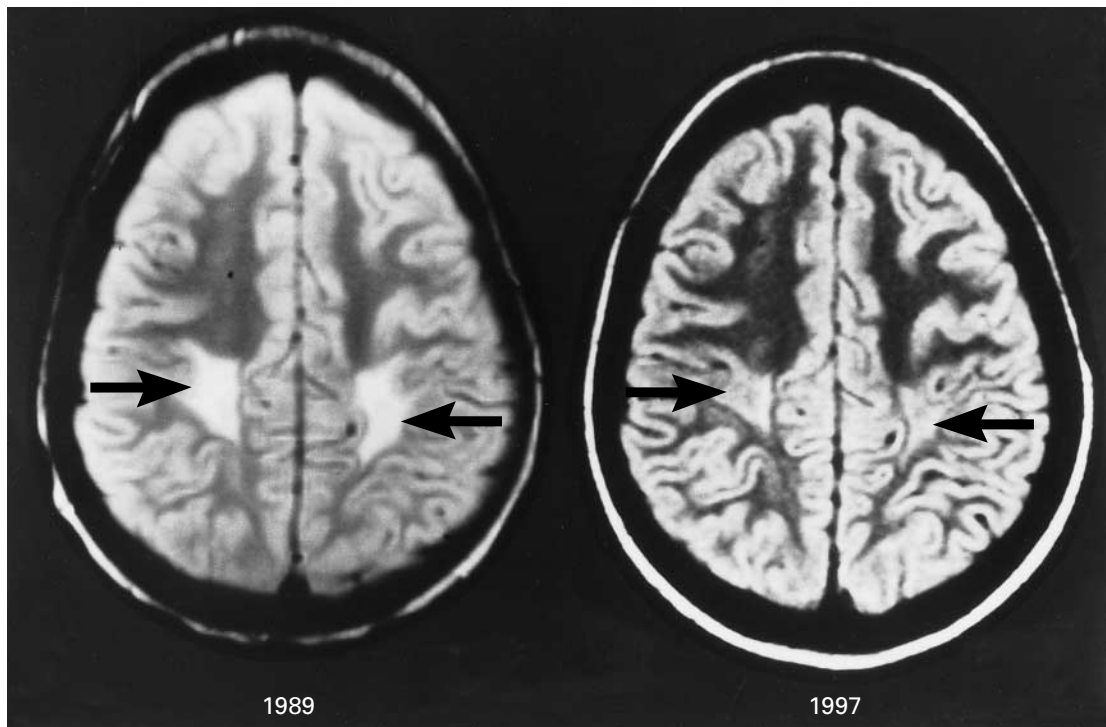
‡This score is  $>2$  SD below the mean for age.

§This score is  $>3$  SD below the mean for age.

spatial perception. The neuropsychological data indicate improving skills and no signs of deterioration (Table 2).

Before transplantation, visual evoked responses (an electroencephalographic measurement of the response to light) in the patient were significantly prolonged at 177 msec.<sup>15</sup> After transplantation, visual

evoked responses decreased to 130 msec (normal  $+3$  SD,  $<105$  msec). These recorded times were p100 measurements (i.e., measurements of the time required for impulses to travel from the retina to the occipital region). Electroencephalographic wave forms in response to visual stimuli were easier to identify after transplantation, and their amplitude increased.



**Figure 2.** Axial T<sub>2</sub>-Weighted Spin-Echo Magnetic Resonance Images in Patient 1 before and after Transplantation. In the image on the left, from 1989, abnormal areas of increased white-matter signal intensity are evident just before transplantation (arrows); in the image on the right, obtained eight years later, there is a reduction in the abnormal signal intensity (arrows).

The patient's visual acuity is now 20/40 in the right eye and 20/70 in the left.

MRI after transplantation showed a reduction in the abnormal myelin pattern (Fig. 2). Motor-nerve conduction velocity has remained stable at 30 m per second. Epileptiform activity was noted on electroencephalographic examination before transplantation and was absent 10 months thereafter. Cerebrospinal fluid total protein levels declined gradually after transplantation (Fig. 3).

#### Patient 2

The clinical course in Patient 2 began with deterioration of her vision at four years of age. One year later, a gait disturbance indicative of left-sided corticospinal dysfunction was apparent. At seven years of age, she received a marrow transplant from an HLA-identical homozygous normal sibling who had a galactocerebrosidase level of 3.9 nmol per hour per milligram of protein.

During the next seven years, the patient's gait became normal.<sup>16</sup> Although formal neuropsychological testing has not been performed, she is now maintaining normal school performance, whereas before transplantation she was failing in school. She is independent in the activities of daily living. Areas of

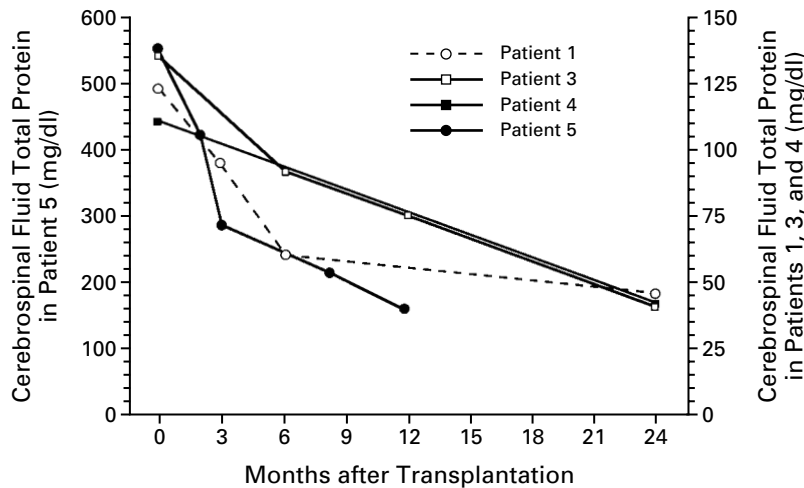
increased signal intensity noted in MRI scans decreased from 1992 to 1997. Defects in visual acuity have remained stable.

#### Patient 3

After the diagnosis of globoid-cell leukodystrophy in two siblings, Patient 3, a seven-year-old asymptomatic boy, was found to have an abnormal leukocyte galactocerebrosidase level. He received a marrow transplant at eight years of age from an HLA-identical sibling, a carrier of the disease, who had a leukocyte galactocerebrosidase level of 2.1 nmol per hour per milligram of protein.

Neuropsychological testing indicated average intelligence before transplantation. However, reading ability, visual memory, and motor abilities were below normal before transplantation and improved after engraftment (Table 2). The patient's nonverbal IQ increased remarkably beginning one year after transplantation. His adaptive skills are normal, and he is attending school. The results of the neurologic examination remain normal.

MRI revealed areas of increased signal intensity, which have decreased since engraftment (Fig. 4). Figure 3 shows the levels of total protein in cerebrospinal fluid; the IgG level in cerebrospinal fluid was



**Figure 3.** Cerebrospinal Fluid Total Protein Levels in Four Patients with Globoid-Cell Leukodystrophy before and after Hematopoietic Stem-Cell Transplantation.

11.9 mg per deciliter before transplantation and decreased to 2.6 mg per deciliter two years afterward (normal, <4.6 mg per deciliter).

#### Patient 4

Patient 4, a two-year-old boy, was found to have galactocerebrosidase deficiency after globoid-cell leukodystrophy developed in his younger brother at four months of age and rapidly progressed to death 10 months later. Our patient underwent transplantation at the age of two years eight months with umbilical-cord blood from an unrelated donor, in which the leukocyte galactocerebrosidase level was 2.7 nmol per hour per milligram of protein.

Neuropsychological assessment before and three years after transplantation showed above-average intelligence with no abnormalities of motor, language, or perceptual function (Table 2). Although his scores relative to normal scores are lower at follow-up than at base line on the tests of nonverbal intelligence, short-term memory, and global perception, he continues to acquire skills in these areas, albeit at a slower-than-normal rate.

The neurologic examination was and continues to be normal except for Achilles-tendon contractures leading to walking on tiptoes at 10 months of age. The patient's walking and running are now approaching normal, after the injection of botulinum toxin into the gastrocnemius muscles and the use of nighttime leg splinting at five years of age. He is attending a school appropriate for his age, and his attainment of developmental milestones is normal.

The pattern of demyelination on MRI has not changed. Median nerve conduction velocity was 13 m per second before transplantation and has in-

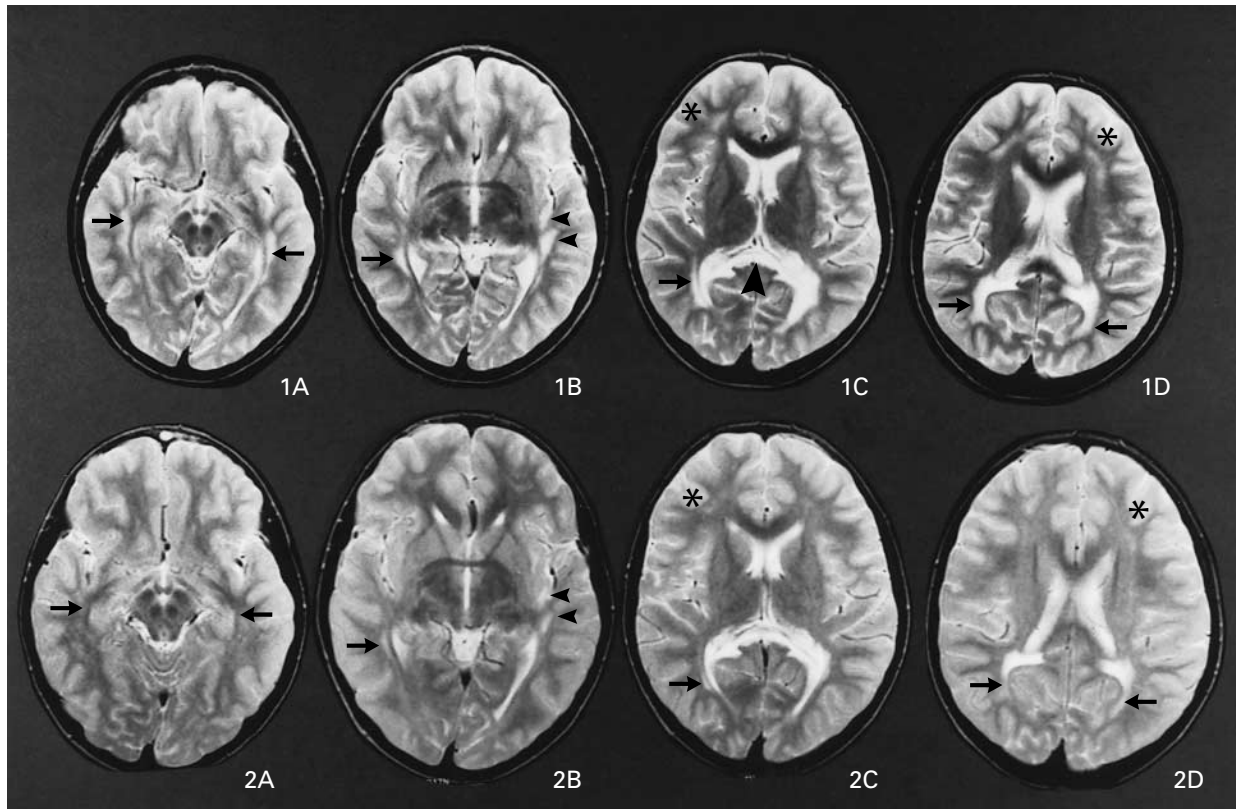
creased to 30 m per second three years after transplantation (Fig. 5). Total protein levels in cerebrospinal fluid have decreased (Fig. 3). The IgG level in cerebrospinal fluid was 8.2 mg per deciliter before hematopoietic stem-cell transplantation and 5.3 mg per deciliter two years later.

#### Patient 5

Globoid-cell leukodystrophy was diagnosed in Patient 5 at one month of age. He was investigated because a brother had died from the disease at 13 months of age. Patient 5 underwent transplantation at two months of age with marrow from an HLA-identical twin sister who was a heterozygote with a level of enzyme activity of 1.6 nmol per hour per milligram of protein. His clinical course and condition at 16 months of age have diverged in a favorable manner from those of the older, untreated brother.

In contrast to his condition before transplantation, the patient now neither clenches his fists nor arches. There is a tendency to hyperextend his legs, and there is rigidity in all extremities. Deep-tendon reflexes are more easily elicited on the right side. No seizures have occurred. Fine-motor skills include a neat pincer grasp. He is able to reach and grab a ring without difficulty. His gross-motor skills include the ability to reach above shoulder level. He has nearly complete head control. He sits without support and assumes a crawling position. In language development, he recognizes his name, turns appropriately, and has several syllables in his age-appropriate vocabulary. Personal and social skills include playing patty-cake, waving bye-bye, and drinking from a cup.

MRI, first performed when the patient was nine months of age, showed areas of increased signal in-



**Figure 4.** Axial T<sub>2</sub>-Weighted Spin-Echo Magnetic Resonance Images Obtained 6 Months (Top) and 26 Months (Bottom) after Transplantation in Patient 3.

The images obtained at six months show abnormal signal intensity in the periventricular white matter adjacent to the optic radiations (arrows in images 1A, 1B, and 1C), in the anterior left temporal periventricular white matter (arrowheads in image 1B), in the splenium of the corpus callosum (arrowhead in image 1C), in the parietal periventricular and central white matter (arrows in image 1D), and in the frontal central white matter (asterisks in images 1C and 1D). The images obtained 26 months after transplantation show a reduction in the abnormal signal intensity in the periventricular white matter adjacent to the optic radiations (arrows in images 2A, 2B, and 2C), in the anterior left temporal periventricular white matter (arrowhead in image 2B), in the parietal periventricular and central white matter (arrows in image 2D), and in the frontal central white matter (asterisks in images 2C and 2D).

tensity in the internal capsule and frontal-parietal white matter as well as the cerebellum. Figure 3 shows the decrease in total protein in cerebrospinal fluid. The albumin index in the cerebrospinal fluid was 97.4 before transplantation and 24.2 11 months after engraftment (normal, <9). The rate of cerebrospinal fluid IgG synthesis was 106 mg per deciliter before transplantation and had decreased to 14.9 mg per deciliter by 13 months of age (normal, <8.0 mg per deciliter).

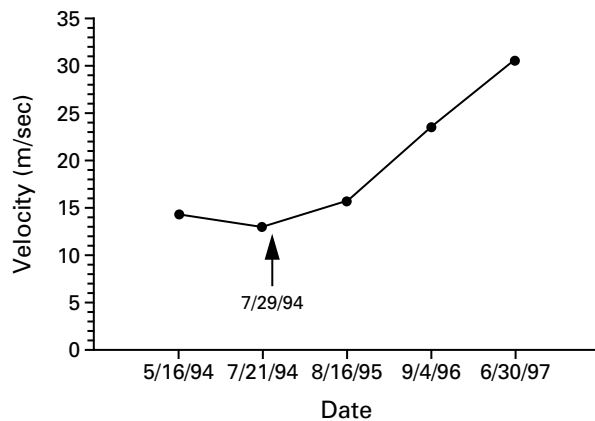
#### DISCUSSION

We treated five children with globoid-cell leukodystrophy with allogeneic hematopoietic stem-cell transplantation. Two patients (Patients 1 and 2) with late-onset globoid-cell leukodystrophy had substantial neurologic disability before transplantation. Preliminary reports on both have been published

elsewhere.<sup>14,16</sup> The obvious difficulties, which included ataxia, tremors, motor incoordination (in Patient 1), and gait dysfunction (in Patient 2) resolved after transplantation. In three patients with late-onset disease who had serial evaluations (Patients 1, 3, and 4), cognition, language, and memory continue to develop normally. Patients 1, 2, 3, and 4 have demonstrated increased academic abilities in school.

MRI in two patients (Patients 1 and 3) has shown smaller areas of signal intensity since transplantation. The severity score (based on a review of the MRI scans) decreased from 10 to 9.5 in Patient 1 (from 1989 to 1997) and from 7.5 to 5.0 in Patient 3 (from 1995 to 1997).<sup>9</sup> The severity score has remained stable in Patient 2 even though some areas of demyelination have become smaller. The MRI findings in Patient 4 have remained stable.

Cerebrospinal fluid protein levels decreased in



**Figure 5.** Median Nerve Conduction Velocity Measured before and after Hematopoietic Stem-Cell Transplantation in Patient 4. The arrow shows the date of transplantation.

four patients (Patients 1, 3, 4, and 5) after transplantation (Fig. 3). Cerebrospinal fluid was not examined in Patient 2. Median nerve conduction velocity rose from 13 m per second to 30 per second in Patient 4 but did not change significantly in Patients 1 and 3. Such studies were not performed in Patients 2 and 5.

These signs of improvement in the central nervous system in the patients with late-onset disease are without precedent in the natural history of globoid-cell leukodystrophy.<sup>1-3,7,17,18</sup> The normalization of enzyme activity must be considered the factor most likely to be responsible for this improvement. Another, though less likely, explanation would be that the chemotherapeutic agents used to prepare the patients for transplantation altered the rate of synthesis of toxic compounds, such as psychosine.

Heterogeneity of the disease is another explanation, because globoid-cell leukodystrophy can vary in age at onset and rate of progression among siblings, despite similar reductions in leukocyte galactocerebrosidase levels.<sup>1-3,7,19,20</sup> In the family of Patient 1, two older sisters have leukocyte galactocerebrosidase levels that are diagnostic of globoid-cell leukodystrophy and similar to the level in the patient. These sisters are free of severe neurologic disease. The sister of Patient 3 is severely affected intellectually, and a brother has uncontrolled seizures with continued neurologic deterioration. The course of disease in Patient 4 was considerably slower than that in the brother who had the infantile form. An explanation for this heterogeneity has been sought in analysis of mutations in the galactocerebrosidase gene,<sup>21</sup> but no differences have been found to explain the discordance. Variations in the clinical manifestations are common in milder or later-onset forms of disease in

which there are slightly higher levels of residual enzyme activity.<sup>22,23</sup>

The course of the disease in Patient 5, who had the infantile form, diverges from that in his brother, but this finding should be interpreted cautiously because of the clinical variability of onset and progression of signs and symptoms.

The "twitcher" mouse, an animal model of globoid-cell leukodystrophy, has been used to study the effects of bone marrow transplantation. Despite normal enzyme activity after engraftment in this mouse model, the symptoms of hind-limb paralysis continue, although they are somewhat attenuated. Life span in this mouse is prolonged to only 100 days, despite evidence of decreased "globoid cell" neuropathology and reduced accumulation of psychosine.<sup>24-26</sup>

The differences in the results of transplantation between patients with late-onset disease and those with onset during infancy may be due to the different rates of entry of donor-derived mononuclear leukocytes, perivascular cells, and microglia into the central nervous system, which is slow and occurs over a period of months to a year after engraftment.<sup>27,28</sup> Normal enzyme levels can be expected to be present only after such cellular changes are established.<sup>5,6,29</sup> The balance between correction due to engraftment and ongoing destruction due to disease would be more favorable in the late-onset than in the infantile form of the disease.

The risks of hematopoietic stem-cell transplantation have decreased as a result of improved HLA tissue typing with molecular methods, depletion of T lymphocytes from the donor's marrow,<sup>30</sup> and the use of umbilical-cord blood.<sup>31,32</sup> Before these advances, as reports show, the results were less favorable. Teenage twins with late-onset globoid-cell leukodystrophy who were treated with allogeneic marrow transplantation died of graft-versus-host disease.<sup>20</sup> Two patients treated in Minneapolis who had the infantile form of the disease died after transplantation, because engraftment was not sustained.<sup>14</sup> Two other severely affected patients with infantile-onset disease, who underwent transplantation at eight and nine months of age, had progressive disease despite complete engraftment. One of these patients, from Minneapolis, has died.<sup>14</sup> The other, treated at Duke University, has shown continued deterioration.

The infantile form of globoid-cell leukodystrophy presents a clinical dilemma, since deterioration occurs rapidly. Immediate postnatal hematopoietic stem-cell transplantation has been advocated, as has transplantation in utero.<sup>33,34</sup>

On the basis of the results in the five children described in this report, we conclude that globoid-cell leukodystrophy, especially the late-onset form, can be treated effectively with hematopoietic stem-cell transplantation.

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