Therapy for the Sphingolipidoses

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Sphingolipidoses are human metabolic storage disorders characterized by the accumulation of harmful quantities of glycosphingolipids and phosphosphingolipids. These lipids have in common a hydrophobic portion of their structure called ceramide. In glycosphingolipids, various oligosaccharides are linked to ceramide through glycosidic bonds. An example is glucocerebroside, composed of ceramide and 1 molecule of glucose. Large quantities of glucocerebroside accumulate in tissues in patients with Gaucher disease. Higher oligosaccharide homologues contain additional neutral and acidic oligosaccharides. Among these are gangliosides that have 1 or more molecules of N-acetylneuraminic acid. A ganglioside called GM₂ accumulates in Tay-Sachs disease. Sphingomyelin is a phosphosphingolipid that accumulates in patients with Niemann-Pick disease.

Sphingolipids are primarily membrane lipids. The synthesis of these lipids is required when cells are formed. When cells such as red and white blood cells become senescent, they are removed from the circulation. Their membrane components are sequentially biodegraded by hydrolytic enzymes located in lysosomes within phagocytic cells. As the brain develops and synapses are formed, the structures of sphingolipids may be simplified or their quantity reduced. Both of these processes require sequential activity of a series of sphingolipid hydrolases. Deleterious mutations occasionally occur in genes that code for sphingolipid catabolizing enzymes that cause a reduction of their catalytic activity. When such an alteration occurs, there is an accumulation of a lipid that normally would be completely degraded. The accumulation can be rapid or slow depending largely on the nature of the mutation and its effect on the activity of the enzyme. For example, some patients with Gaucher disease with very low glucocerebrosidase activity have rapid and extensive accumulation of glucocerebroside throughout the body. The brains of these infants are extensively damaged, and cortical neuronophagia is widespread. Patients exhibiting this phenotype are classified as having type 2 Gaucher disease. Patients with type 3 Gaucher disease exhibit neuropathic signs at a later time. Most patients with Gaucher disease, designated as type 1, do not have evidence of central nervous system involvement.

At this time, only a limited number of strategies are available to treat patients with metabolic storage disorders. Among them are organ transplantation, bone marrow transplantation, enzyme replacement, and gene therapy. Organ allografts have been largely ineffective. Bone marrow transplantation can cure patients with type 1 Gaucher disease. Because of the risks currently associated with this procedure, only a small number of patients with type 1 Gaucher disease have received bone marrow transplants. Several patients with type 3 (chronic neuronopathic) Gaucher disease have been treated in this fashion, with variable clinical benefit.

Enzyme replacement therapy is highly effective for patients with type 1 Gaucher disease. A lengthy series of investigations was required to bring this treatment to fruition. It was necessary to develop methods to purify the requisite quantities of glucocerebrosidase from a human tissue source such as placenta and to target it to lipid-storing cells. Eventually, beneficial responses were achieved in patients. Recipients exhibited marked improvement of their anemia, thrombocytopenia, hepatosplenomegaly, skeletal damage, and in the quality of their lives. More than 2000 patients with Gaucher disease are currently benefiting from enzyme replacement therapy. Recombinant glucocerebrosidase is as ef-
istered intravenously, intrathecally, and intracisternally. In 1 case, the enzyme was administered intravenously into the left hemisphere only (G. C. Zirzow, BS, O. A. Sanchez, MD, G. J. Murray, PhD, et al, unpublished data, 1998).

The response to enzyme replacement therapy was subsequently assessed in patients with type 3 (chronic neuronopathic) Gaucher disease. Once again, hematologic and systemic manifestations improved dramatically. There is, however, considerable uncertainty concerning the effect of this treatment on neurologic manifestations. Only a small amount of intravenously administered glucocerebrosidase could be detected in the cerebrospinal fluid, and it occurred only with high doses of glucocerebrosidase. In some patients, there were biochemical indications of a reduction of the burden of Gaucher cells in the brain cerebrospinal fluid compartment. Moreover, a few patients who exhibited horizontal gaze palsy appeared to have an improvement of this abnormality. However, no significant benefit has been seen in patients with severe myoclonic seizures. The long-term effects of enzyme replacement therapy in patients with type 3 Gaucher disease remain to be established.

A few patients with type 2 (acute neuronopathic) Gaucher disease have received macrophage-targeted glucocerebrosidase. In 1 case, the enzyme was administered intravenously, intrathecally, and intracisternally. In both instances, there was no indication of long-term improvement of the central nervous system manifestations, and both patients died in infancy. It is not surprising that the heroic efforts in the first trial were ineffective since a similar attempt to treat infants with Tay-Sachs disease with hexosaminidase A was without benefit. Because of these difficulties, Sanchez et al have explored an alternative procedure to deliver glucocerebrosidase to the brain of experimental animals. The enzyme was infused under a slight hydrostatic pressure directly into the striatal region of the brain of rats. Mannose-terminal glucocerebrosidase is comparatively stable under these conditions. It was gradually distributed from the site of injection along white matter fiber tracts to the cortex (Figure). Of considerable significance was the demonstration of high concentrations of the exogenous enzyme in cortical neurons by immunocytochemistry.

Another promising illustration of the benefit of enzyme replacement therapy has recently appeared. We conducted a phase 1 safety and dose-response enzyme therapy trial in patients with Fabry disease. The findings of this investigation were encouraging. One patient reported that he spontaneously discontinued treatment with carbamazepine (Tegretol) that he had been taking for his painful acroparesthesias for 6 weeks following a single intravenous injection of purified ceramidetrihexosidase (α-galactosidase A). A full-scale efficacy trial of enzyme replacement in Fabry disease will be implemented. It appears likely that patients with this sphingolipid storage disorder will derive considerable benefit from this therapy.

Many investigators are becoming interested in gene therapy. This approach seems particularly appealing for patients with type 1 Gaucher disease since bone marrow transplantation can be curative. We carried out a number of preclinical studies on gene therapy for Gaucher disease in rodents and nonhuman primates. Encouraged by our findings, we undertook a gene therapy trial in 3 patients with type 1 Gaucher disease. We observed transient marking of a small percentage of peripheral blood cells with the normal glucocerebrosidase transgene. We believe that significant improvements in the delivery of genes to stem and progenitor cells are required before clinical benefit can be expected. Moreover, novel techniques may have to be developed for the delivery of therapeutic genes into nondividing cells such as neurons. Recent investigations reveal that pseudotyped non-pathogenic lentiviruses may prove useful in this regard.

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