State of Illinois
Illinois Department of Public Health

Krabbe Disease and Other Leukodystrophies

Pursuant to House Joint Resolution 13
97th Illinois General Assembly

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Illinois Department of
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Illinois Department of Public Health
Office of Health Promotion
Division of Health Assessment and Screening
535 W. Jefferson St.
Springfield, Illinois 62761-0001

Introduction

Pursuant to House Joint Resolution 13 by the 97th General Assembly, the Illinois Department of Public Health prepared the following report on Krabbe disease and related leukodystrophies regarding incidence, treatment options, state or federal research projects, disease registries and biobanks, diagnostic tests and their usage, access and availability of drugs, and economic impact of the diseases on families.

Background

Krabbe disease, a lysosomal storage disease (LSD) (also referred to as a globoid cell leukodystrophy), is a rare, inherited degenerative disorder of the central and peripheral nervous systems that is often fatal. LSDs result from dysfunction of enzymes produced in the lysosomes, cellular organelles responsible for metabolism and waste management of lipids (fats) and glycoproteins (proteins containing sugars) within the cells of the body. The cellular dysfunction of LSDs is usually due to a genetic defect causing a deficiency of a single enzyme produced within the lysosomes.

The term leukodystrophy refers to a progressive degeneration of myelin, the white matter of the brain, due to improper growth or gradual destruction of the myelin sheath, a protective, fatty covering that insulates axons (nerve fibers). Myelin is a complex organic substance composed of at least 10 different chemicals. Leukodystrophies, including Krabbe disease, metachromatic leukodystrophy, adrenoleukodystrophy, Pelizaeus-Mersbacher disease, Canavan disease, childhood ataxia with central nervous system hypomelination (also known as vanishing white matter disease), Alexander disease, Refsum disease and cerebrotendinous xanthonmatosis, are each distinct types of leukodystophy caused by an inherited genetic defect specific to one, and only one, of the 10 chemicals. In these types of leukodystrophy, a defective gene disrupts the production or metabolization of myelin. Although there are variations among the leukodystrophies, the disease processes cause progressive deterioration of individual nerves and the central nervous system, or impair nervous system function due to the accumulation of metabolic waste products and, in the most severe forms, such as early onset infantile Krabbe, result in death in very early childhood.

The most common symptom of leukodystrophy is a gradual decline of an infant or child who previously appeared well. There may be progressive losses in body tone, movements, gait, speech, ability to eat, vision, hearing or behavior, with increasing irritability. Although early symptoms may be difficult to recognize, often there is slowing of mental and physical development. Diagnosis of some leukodystrophies, such as Krabbe disease, is made by DNA testing for the actual genetic defect, and is specific to each

leukodystrophy. Other tests may include retinal exams for optic nerve damage, analysis of specific enzyme activity levels in white blood cells, cerebrospinal fluid total protein, magnetic resonance imaging (MRI) of the head, and nerve conduction velocity testing.

The symptoms of Krabbe disease usually begin before the age of 1 (infantile form). Initial signs and symptoms typically include irritability, muscle weakness, feeding difficulties, episodes of fever without sign of infection, stiff posture, and slowed mental and physical development. As the disease progresses, muscles continue to weaken, impacting the infant's ability to move, chew, swallow, and breathe. Affected infants also experience vision loss and seizure.

Less commonly, onset of Krabbe diseases can occur in childhood, adolescence, or adulthood (late-onset forms). Visual problems and walking difficulties are the most common initial symptoms in this form of the disorder, however, signs and symptoms vary considerably among affected individuals.

The prognosis for leukodystrophies varies according to the specific type of the disease. Treatment is primarily symptomatic and supportive, and may include medications, physical, occupational and speech therapies, nutritional, educational and recreational programs. While there is no cure for these diseases, recently, in some cases, hematopoietic stem cell transplants performed very early in life, or before symptoms have progressed, have shown limited success, but not without inherent risks. Infantile Krabbe disease is generally fatal before age 2. Persons with juvenile- or adult-onset cases of Krabbe disease often have a milder course of the disease and have survived into adulthood with nervous system disease.

Disease Incidence

True incidence of Krabbe disease and other leukodystrophies in Illinois is unknown, as all cases may not be recognized and additional cases may be misdiagnosed. The incidence of Krabbe disease in the United States is estimated at 1 in 100,000 live births, and the projected annual birthrate for Illinois is 160,000 births. The estimated incidence for all types of leukodystrophies, of which there are around 50 types, is 1 in 1,500 to 7,000 live births. Overall population incidence may be higher than generally appreciated, at 1 in 7,663 live births, although most leukodystrophies remain undiagnosed. Metachromatic leukodystrophy appears to be the most commonly diagnosed leukodystrophy.

In Illinois, screening of all newborns for seven LSDs or leukodystrophies, including Krabbe disease, is scheduled to commence in 2014. In addition to Krabbe disease, screenings will be conducted for Pompe, Gaucher, Fabry, Niemann-Pick, MPS (mucopolysaccharide)-1 (also known as Hurler) and MPS-2 (also known as Hunter).

Treatment

Most treatments for Krabbe disease and other leukodystrophies are primarily symptom-based and supportive in nature. Options include medications and diet modifications that may help reduce the accumulation of substrates in body tissues for some types of leukodystrophies. Only supportive care to improve nutrition, and to control seizures, irritability and spasticity, along with education and occupational services, is available for children in the later stages of these diseases. Bone marrow transplants may help in some types of leukodystrophy; hematopoietic stem cell transplantation for Krabbe disease has been attempted in presymptomatic infants and older individuals with mild symptoms. Early stem cell transplantation may improve and preserve cognitive function of newborn infants with Krabbe disease, but may not prevent subsequent peripheral nervous system function deterioration. The clinical variability in late-onset forms of leukodystrophies makes evaluation of transplant effectiveness difficult.

Clinical Trials

The National Institutes of Health lists 16 clinical trials associated with the study of leukodystrophies that are actively recruiting participants. These studies address causes of leukodystrophy types that are currently unknown, imaging studies of children with metachromatic leukodystrophy (MLD), biomarkers for MLD and Krabbe disease, natural history of infantile globoid cell leukodystrophy, gene therapy for MLD, and intrathecally administered enzyme replacement for MLD. In addition, several studies are underway of fetal umbilical cord and hematopoietic stem cell transplant for inborn errors of metabolism and LSDs, and allogenic bone marrow transplant for inherited metabolic disorders. Ten other studies have been completed, including several studies of experimental drug treatment for MLD with Metazym, effects of warfarin in treatment of MLD, stem cell transplants for inborn errors of metabolism, and magnetic stimulation of the human nervous system.

Disease Registries and Biobanks

Genetic Alliance Registry and BioBank www.geneticalliance.org/biobank
HJK Research Institute (Hunter's Hope Foundation) www.huntershope.org
Myelin Project www.myelin.org

Additional Resources

National Center for Biotechnology Information www.ncbi.nlm.nih.gov
United Leukodystrophy Foundation www.ulf.org
National Organization for Rare Disorders (NORD) www.rarediseases.org
National Tay-Sachs and Allied Diseases Association www.ntsad.org
Metachromatic Leukodystrophy Foundation www.mldfoundation.org

Diagnostic Tests

Clinical Examination
Initial diagnostic work-ups for possible leukodystrophies begin with clinical examination and family history. While age of onset and symptoms for leukodystrophy may vary, initial presentation may include physical deformities, hypotonia, nystagmus, seizures, motor delay and/or regression, ataxia, dysarthria, cognitive regression, or psychiatric manifestations and behavioral abnormalities.

Brain Imaging
The next step toward diagnosis includes brain MRI and computerized tomography (CT) scan. Distinct patterns of leukodystrophy that appear on brain scans assist clinicians in differentiation of leukodystrophy disease type, and are helpful in determining which molecular testing should be instituted.

Molecular Testing
While molecular testing is not available for all types of leukodystrophy, DNA analysis can confirm mutations in the galactocerebrosidase (GALC) gene that causes Krabbe disease, although the relationship between genotype and disease phenotype (infantile, early or late onset) is not always clear. Molecular diagnostic, carrier, and prenatal testing also are available for several of the leukodystrophies.

Enzyme Activity
Detection of reduced activity levels of specific enzymes in white blood cells, such as the reduced galactocerebrosidase enzyme activity associated with Krabbe disease, assists clinicians in determining the type of leukodystrophy.

Blood, Spinal Fluid and Urine Analysis
Analysis of body fluids can be performed. The presence of unusual proteins or biochemicals, such as proteins in cerebrospinal fluid in Krabbe disease; sulfatides in urine associated with metachromatic leukodystrophy; phytanic acid in blood and body tissues associated with Refsum disease; and the bile alcohols associated with cerebrotendinous xanthonmatosis; can be quantified to assist clinicians in diagnosing the leukodystrophies.

Neurological Examination and Testing
Electroencephalograms (EEG), nerve conduction velocity testing, brainstem auditory evoked response (BAER), and visual evoked response (VER) are additional tests that may be performed to evaluate severity of neurological regression and/or disease progression.

Availability of Drug Therapies

Most drug therapies available for leukodystrophies are for comfort measures, and are supportive in nature for treating the physical symptoms of the diseases, such as spasticity,

seizures, nutritional deficits, psychiatric disturbances, pain, and irritability. These are not considered therapeutic in treatment of the disease, although clinical trials of some new drug therapies that may prove more promising in disease management are being conducted.

Economic Impact to Families

Knowing there is no cure and no reliably effective treatment for their child's condition, along with the knowledge their child will most likely have a very brief life, is an undeniably heavy burden for parents. As these diseases progress, most children with leukodystrophy will require continuous 24 hour care in the home or another facility. Some of these children will need frequent hospitalizations, the care of numerous medical specialists, specialized therapies and medications to keep them as comfortable as possible, and special supportive educational and occupational care services. Estimates of care cost vary with the severity of the disease, but in one study of 122 children diagnosed with a form of leukodystrophy, the average yearly cost of hospital care was $22,579, excluding out-patient costs. However, 10 percent of the children in this group accounted for a disproportionate amount of the total costs, and averaged greater than $500,000 per year for hospital care. Some, but not all of these children, had undergone hematopoietic stem cell transplant. Half of the children with the highest annual costs of care were diagnosed with metachromatic leukodystrophy and of the remaining half the type of leukodystrophy was undetermined (Bonkowsky and Nelson, 2010).

Children with leukodystrophies may suffer a great deal of discomfort during their short lives, despite the best efforts of their caregivers. While parents devote their lives to providing selfless care for their children, the economic impact of lost wages, financial hardships, and personal stresses cannot be overestimated. While treatment options, such as bone marrow or hematopoietic stem cell transplants (associated costs ranging $50,000 to $150,000), have shown cognitive improvements in some children with leukodystrophy, these are not considered curative. Decisions regarding transplants also may create additional financial and psychological burdens as parents are forced to choose a treatment that could prove life threatening in terms of risk of complications that may or may not be successful, or be forced to helplessly stand by while their child's condition continues to deteriorate.

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