Lysosomal Storage Disease: Diagnosis and Role of Animal Models in Evaluation of Treatment
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The lysosomal storage diseases (LSDs) are a heterogeneous group of inherited disorders that affect 1 in 7,000 children. Around 50 different disorders have been identified. Most are the result of a change in an allele coding a specific lysosomal acid hydrolase, but defects in an enzyme coactivator, a membrane transporter, the targeting mechanism for protein localization to the lysosome, or intracellular vesicular trafficking can also cause LSD (Scriver et al, 2001). The defect in LSD results in failure to completely degrade one or more macromolecules and an accumulation of the undegraded substrate within lysosomes. Eventually the build up of material in lysosomes leads to cell and organ dysfunction. The particular tissue involved and the age of onset depends on which degradation pathway has been interrupted and what its importance is to the tissue.

Patients with LSD present with a broad spectrum of phenotypes characterized by progressive morbidity and mortality. Most have progressive neurological degeneration, mental retardation and deafness. A variety of musculoskeletal abnormalities includes dysostosis multiplex with short stature, coarse facial features and stiff joints. Visceral abnormalities with storage in fixed tissue macrophages lead to hepatosplenomegaly and corneal clouding.

In diagnosis, clinical findings which warrant investigation for LSD include nonimmune hydrops, progressive organomegaly, skeletal abnormalities and joint stiffness, coarse facial features, progressive dementia or loss of developmental milestones, and unexplained neuropathic extremity or bone pain. As inherited diseases, LSD are present from conception in affected patients and early diagnosis is becoming more important as effective disease specific therapy becomes available. Ideally, patients should be identified before serious mental or physical impairments have developed so newborn screening programs based on lysosomal enlargement and increased lysosomal proteins are useful. Biochemical analysis of cultured fibroblasts, leukocytes or plasma for the deficient enzyme provides a definitive diagnosis, but the clinical presentation may not provide sufficiently specific information for the clinician to identify which enzyme or gene to test for abnormality. Tissue biopsy with ultrastructural evaluation is a sensitive and relatively inexpensive tool to screen for LSD (Alroy and Ucci, 2006; Prasad et al, 1996). Many LSD have characteristic ultrastructural alterations in rectal mucosa, skin, conjunctiva and peripheral blood leukocytes that provide criteria for diagnosis. Chorionic villous samples have been used for prenatal diagnosis of LSD and bone marrow, liver, muscle and peripheral nerve biopsies may also yield diagnostic material. Electron microscopy can exclude more than 90% of suspected cases of LSD. It is particularly useful for those disorders with incompletely characterized biochemical defects and when DNA studies fail to be informative (Ceuterick-de Groote and Martin, 1998).

Ultrastructural morphology of distended lysosomes and their tissue distribution are useful characteristics for diagnosis. In some cases morphology of stored lysosomal material is characteristic for a single disorder. For example, neuronal ceroid lipofuscinosis has curvilinear and granular storage material; acid lipase deficiency/Wolman disease has cholesterol clefts and neutral lipids; Farber disease has
banana-shaped lysosomes containing small vesicles. A finding of fine fibrillar granular storage material and/or zebra bodies suggests a group of disorders which includes MPS, mucolipidoses, mannosidosis and sialadosis. In ganglioside storage diseases, glycolipids appear as lamellated membrane bound finger prints or zebra bodies.

Treatment of LSD demands arrest or reversal of established bone, visceral and CNS disease. Advances in treatment over the last 10 years has included bone marrow or hematopoietic stem cell transplantation, gene therapy with gene transduction in CNS by adenovirus (Shen et al, 2004), enzyme replacement therapy, substrate reduction therapy, and chemical chaperone therapy. Enzyme replacement is an established therapy for a number of LSDs, including Gaucher, Fabry, Pompe, MPS I, II and VI.

Animal models of LSD are useful in evaluating treatment strategies because they allow controlled therapeutic trials without the clinical and genetic heterogeneity inherent in human studies. Biochemical and morphologic correction of the phenotype forms the basis of evaluation of therapy. A number of animal models have been developed for investigation of the pathophysiology of LSDs and efficacy of treatment. Two of these will be discussed in detail, a murine model of infantile neuronal ceroid lipofuscinosis (INCL) and a murine model of mucopolysaccharidosis Type VII.

INCL, also called Santavuori-Haltia disease, is caused by a mutation in the gene encoding the lysosomal enzyme palmitoyl-protein-thioesterase (PPT1). In this disorder fatty acid modified proteins are not degraded and accumulate as granular osmiophilic deposits (GRODS) identified by electron microscopy. Incidence of GRODS is most pronounced in the CNS. Patients present with rapidly progressing disease at around 1.5 years of age resulting in blindness, motor and mental decline, and seizures. There is brain atrophy with cortical and hippocampal neuronal loss associated with astrogliosis. Death in childhood is due to neurodegenerative disease.

A murine model of INCL with a knockout mutation in the gene that encodes PPT1 shares many clinical features with the disease seen in humans. Affected mice have neurological abnormalities evident by 8 months of age and usually die by 10 months of age. The clinical features include myoclonic seizures, progressive spastic motor abnormalities (Gupta et al, 2001), and retinal degeneration (Griffey et al, 2004). Ultrastructural analysis of lysosomal storage in these mice indicates that GROD accumulates progressively in CNS neurons with widespread astrocytosis and cortical atrophy. Lysosomal storage in the form of GRODS accumulates to a lesser extent in other organs, including kidney, spleen, bone, liver, eye and heart. Storage within smooth muscle cells from the media of the aortic arch correlates with structural alterations in luminal diameter of the aorta. Gene therapy experiments with this murine model of INCL have used a rAAV vector delivered directly to the brain parenchyma by injection. The therapy resulted in reduction of storage material in CNS, increased cortical thickness relative to control, reduced seizure activity, and improved motor function (Griffey et al, 2006).

References:


