432e Lysosomal Storage Diseases

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Lysosomes are heterogeneous subcellular organelles containing specific hydrolyses that allow selective processing or degradation of proteins, nucleic acids, carbohydrates, and lipids. There are more than 40 different lysosomal storage diseases (LSDs), classified according to the nature of the stored material (Table 432e-1). Several of the most prevalent disorders are reviewed here: Tay-Sachs disease, Fabry disease, Gaucher disease, Niemann-Pick disease, lysosomal acid lipase deficiencies, the mucopolysaccharidoses, and Pompe disease. LSDs should be considered in the differential diagnosis of patients with neurologic, renal, or muscular degeneration and/or unexplained hepatomegaly, splenomegaly, cardiomyopathy, or skeletal dysplasias and deformations. Physical findings are disease specific, and enzyme assays or genetic testing can be used to make a definitive diagnosis. Although the nosology of LSDs segregates the variants into distinct phenotypes, these are heuristic; in the clinic, each disease exhibits—to some degree—a continuous spectrum of manifestations, from severe to attenuated variants.

PATHOGENESIS

Lysosomal biogenesis involves ongoing synthesis of lysosomal hydrolases, membrane constitutive proteins, and new membranes. Lysosomes originate from the fusion of trans-Golgi network vesicles with late endosomes. Progressive vesicular acidification accompanies the maturation of these vesicles; this gradient facilitates the pH-dependent dissociation of receptors and ligands and also activates lysosomal hydrolases. Lysosomes are components of the lysosome/autophagy/mitophagy system, which can be disrupted in the LSDs.

Abnormalities at any biosynthetic step can impair enzyme activation and lead to a lysosomal storage disorder. After leader sequence clipping, remodeling of complex oligosaccharides (including the lysosomal targeting ligand mannose-6-phosphate as well as high-mannose oligosaccharide chains of many soluble lysosomal hydrolases) occurs during transit through the Golgi. Lysosomal integral or associated membrane proteins are sorted to the membrane or interior of the lysosome by several different peptide signals. Phosphorylation, sulfation, additional proteolytic processing, and macromolecular assembly of heteromers occur concurrently. Such posttranslational modifications are critical to enzyme function, and defects can result in multiple enzyme/protein deficiencies.

The final common pathway for LSDs is the accumulation of specific macromolecules within tissues and cells that normally have a high flux of these substrates. The majority of lysosomal enzyme deficiencies result from point mutations or genetic rearrangements at a locus that encodes a single lysosomal hydrolase. However, some mutations cause deficiencies of several different lysosomal hydrolases by alteration of the enzymes/proteins involved in targeting, active site modifications, or macromolecular association or trafficking. All LSDs are inherited as autosomal recessive disorders except for Hunter (mucopolysaccharidosis type II), Danon, and Fabry diseases, which are X-linked. Substrate accumulation leads to lysosomal distortion, which has significant pathologic consequences. In addition, abnormal amounts of metabolites may also have pharmacologic effects important to disease pathophysiology and propagation.

For many LSDs, the accumulated substrates are endogenously synthesized within particular tissue sites of pathology. Other diseases have greater exogenous substrate supplies. For example, they are delivered by low-density lipoprotein receptor–mediated uptake in Fabry and cholesteryl ester storage diseases (CESDs) or by phagocytosis in Gaucher disease type 1. The *threshold hypothesis* refers to a level of enzyme activity below which disease develops; small changes in enzyme activity near the threshold can lead to or prevent disease. A critical element of this model is that enzymatic activity can be challenged by changes in substrate flux based on genetic background, cell turnover, recycling, or metabolic demands. Thus, a set level of residual enzyme may be adequate for substrate in some tissues or cells but not in others. In addition, several variants of each LSD exist at a clinical level. These disorders therefore represent a continuum of manifestations that are not easily dissociated into discrete entities. The bases for such variations have not been elucidated in any detail.

SELECTED DISORDERS

TAY-SACHS DISEASE

About 1 in 30 Ashkenazi Jews is a carrier for Tay-Sachs disease, which is caused by total hexosaminidase A (Hex A) deficiency resulting from defective α-chains. The infantile form is a fatal neurodegenerative disease with macrocephaly, loss of motor skills, increased startle reaction, and a macular cherry red spot. The juvenile-onset form presents as ataxia and dementia, with death by age 10–15 years. The adult-onset disorder is characterized by clumsiness in childhood; progressive motor weakness in adolescence; and additional spinocerebellar and lower-motor-neuron symptoms and dysarthria in adulthood. Intelligence declines slowly, and psychosis is common. Screening for Tay-Sachs disease carriers is recommended in the Ashkenazi Jewish population. Sandhoff disease, due to a deficiency in both Hex A and Hex B resulting from defective β-chains, is phenotypically similar to Tay-Sachs disease but also includes hepatosplenomegaly and bony dysplasias.

FABRY DISEASE

Fabry disease is an X-linked disorder that results from mutations in the α-galactosidase A gene. The estimated prevalence of hemizygous males ranges from 1 in 40,000 to 1 in 3500 in selected populations. Clinically, the disease manifests with angiokeratomas (telangiectatic skin lesions), hypohidrosis, corneal and lenticular opacities, acroparesthesia; and progressive small-vessel disease of the kidney, heart, and brain.

The angiokeratomas and acroparesthesias may appear in childhood. Angiokeratomas are punctate, dark red to blue-black, flat or slightly raised, and usually symmetric; they do not blanch with pressure. They range from barely visible to several millimeters in diameter and have a tendency to increase in size and number with age. They usually are most dense between the umbilicus and the knees—the "bathing suit area"—but may occur anywhere, including the mucosal surfaces. Angiokeratomas also occur in several other very rare LSDs. Corneal and lenticular lesions, detectable on slit-lamp examination, may help in establishing a diagnosis of Fabry disease. Debilitating episodic burning pain of the hands, feet, and proximal extremities (acroparesthesia) can last from minutes to days and can be precipitated by changes in temperature, exercise, fatigue, or fever. Abdominal pain can resemble that from appendicitis or renal colic. Proteinuria, isosthenuria, and progressive renal dysfunction occur in the second to fourth decades; ~5% of male patients with idiopathic renal failure have α-galactosidase A mutations. Hypertension, left ventricular hypertrophy, anginal chest pain, and congestive heart failure can occur in the third to fourth decades. About 1–3% of patients with idiopathic hypertrophic myocardiopathy have Fabry disease. Similarly, ~3–5% of male patients with idiopathic stroke at 35–50 years of age have α-galactosidase A mutations. Leg lymphedema without hypoproteinemia and episodic diarrhea also occur. Death is due to renal failure or cardiovascular or cerebrovascular disease in untreated male patients. Variants with residual α-galactosidase A activity may have late-onset manifestations that are limited to the cardiovascular system and resemble hypertrophic cardiomyopathy. Variants with predominant cardiac, renal, or central nervous system (CNS) manifestations are becoming better defined. Up to 70% of heterozygous females may exhibit clinical manifestations. However, in females, heart disease is the most common life-threatening manifestation, followed in frequency by stroke and then renal disease.

Phenytoin and carbamazepine diminish chronic and episodic acroparesthesia. Chronic hemodialysis or kidney transplantation can be lifesaving in patients with renal failure. Enzyme therapy clears stored lipids from a variety of cells, particularly those of the renal, cardiac, and skin vascular endothelium. Renal insufficiency appears