Table 5-6 Lysosomal Storage Diseases

Disease	Enzyme Deficiency	Major Accumulating Metabolites
Glycogenosis		
Type 2—Pompe disease	α-1,4-Glucosidase (lysosomal glucosidase)	Glycogen
Sphingolipidoses		
G_{M1} gangliosidosis	G_{M1} ganglioside β-galactosidase	G_{M1} ganglioside, galactose-containing oligosaccharides
Type 1—infantile, generalized		
Type 2—juvenile		
G_{M2} gangliosidosis		
Tay-Sachs disease	Hexosaminidase, α subunit	G_{M2} ganglioside
Sandhoff disease	Hexosaminidase, β subunit	G_{M2} ganglioside, globoside
G_{M2} gangliosidosis variant AB	Ganglioside activator protein	G_{M2} ganglioside
Sulfatidoses		
Metachromatic leukodystrophy	Arylsulfatase A	Sulfatide
Multiple sulfatase deficiency	Arylsulfatase A, B, C; steroid sulfatase; iduronate sulfatase; heparan *N*-sulfatase	Sulfatide, steroid sulfate, heparan sulfate, dermatan sulfate
Krabbe disease	Galactosylceramidase	Galactocerebroside
Fabry disease	α-Galactosidase A	Ceramide trihexoside
Gaucher disease	Glucocerebrosidase	Glucocerebroside
Niemann-Pick disease: types A and B	Sphingomyelinase	Sphingomyelin
Mucopolysaccharidoses (MPSs)		
MPS I H (Hurler)	α-L-Iduronidase	Dermatan sulfate, heparan sulfate
MPS II (Hunter)	L-Iduronosulfate sulfatase	
Mucolipidoses (MLs)		
I-cell disease (ML II) and pseudo-Hurler polydystrophy	Deficiency of phosphorylating enzymes essential for the formation of mannose-6-phosphate recognition marker; acid hydrolases lacking the recognition marker cannot be targeted to the lysosomes but are secreted extracellularly	Mucopolysaccharide, glycolipid
Other diseases of complex carbohydrates		
Fucosidosis	α-Fucosidase	Fucose-containing sphingolipids and glycoprotein fragments
Mannosidosis	α-Mannosidase	Mannose-containing oligosaccharides
Aspartylglycosaminuria	Aspartylglycosamine amide hydrolase	Aspartyl-2-deoxy-2-acetamido-glycosylamine
Other lysosomal storage diseases		
Wolman disease	Acid lipase	Cholesterol esters, triglycerides
Acid phosphate deficiency	Lysosomal acid phosphatase	Phosphate esters

degradation of a variety of substrates, organs rich in phagocytic cells, such as the spleen and liver, are frequently enlarged in several forms of lysosomal storage disorders. The ever-expanding number of lysosomal storage diseases can be divided into rational categories based on the biochemical nature of the accumulated metabolite, thus creating such subgroups as the *glycogenoses*, *sphingolipidoses (lipidoses)*, *mucopolysaccharidoses (MPSs)*, and *mucolipidoses* (Table 5-6). Only the most common disorders are considered here.

Tay-Sachs Disease (G_{M2} Gangliosidosis: Hexosaminidase α-Subunit Deficiency)

G_{M2} gangliosidoses are a group of three lysosomal storage diseases caused by an inability to catabolize G_{M2} gangliosides. Degradation of G_{M2} gangliosides requires three polypeptides encoded by three distinct genes. The phenotypic effects of mutations affecting these genes are fairly similar, because they result from accumulation of G_{M2} gangliosides. The underlying enzyme defect, however, is different for each. Tay-Sachs disease, the most common form of G_{M2} gangliosidosis, results from mutations in the α-subunit locus on chromosome 15 that cause a severe deficiency of hexosaminidase A. This disease is especially prevalent among Jews, particularly among those of Eastern European (Ashkenazic) origin, in whom a carrier rate of 1 in 30 has been reported.

MORPHOLOGY

The hexosaminidase A is absent from virtually all the tissues, so G_{M2} ganglioside accumulates in many tissues (e.g., heart, liver, spleen, nervous system), but the **involvement of neurons in the central and autonomic nervous systems and retina dominates the clinical picture.** On histologic examination, the neurons are ballooned with cytoplasmic vacuoles, each representing a markedly distended lysosome filled with gangliosides (Fig. 5-11*A*). Stains for fat such as oil red O and Sudan black B are positive. With the electron microscope, several types of **cytoplasmic inclusions** can be visualized, the most prominent being whorled configurations within lysosomes composed of onion-skin layers of membranes (Fig. 5-11*B*). In time there is progressive destruction of neurons, proliferation of microglia, and accumulation of complex lipids in phagocytes within the brain substance. A similar process occurs in the cerebellum as well as in neurons throughout the basal ganglia, brain stem, spinal cord, and dorsal root ganglia and in the neurons of the autonomic nervous system. The ganglion cells in the retina are similarly swollen with G_{M2} ganglioside, particularly at the margins of the macula. A **cherry-red spot thus appears in the macula,** representing accentuation of the normal color of the macular choroid contrasted with the pallor produced by the swollen ganglion cells in the remainder of the retina (Chapter 29). This finding is characteristic of Tay-Sachs disease and other storage disorders affecting the neurons.