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stimulates tanning, is administered subcutaneously every 2 months and has been approved for the treatment of EPP and XLP by the EMA and the FDA. Dersimelagon, an orally administered, smallmolecule, selective melanocortin-1 receptor (MC1R) agonist that increases skin melanin without sun exposure, is currently in phase 3 clinical trials for EPP and XLP. Bitopertin, an orally administered glycine reuptake inhibitor, recently was shown to reduce blood pro toporphyrin IX levels in clinical studies and is currently in phase 3 clinical trials. Treatment of hepatic complications, which may be accompa nied by motor neuropathy, is difficult. Cholestyramine and other porphyrin absorbents such as activated charcoal may interrupt the enterohepatic circulation of protoporphyrin and promote its fecal excretion, leading to some improvement. Plasmapheresis and intra venous hemin are sometimes beneficial. Liver transplantation has been carried out in some EPP and XLP patients with severe liver complications and is often successful in the short term. However, the disease often recurs in the trans planted liver due to continued bone marrow production of excess protoporphyrin. In a retrospective study of 17 liver-transplanted EPP patients, 11 (65%) had recurrent EPP liver disease. Posttrans plantation treatment with hematin and plasmapheresis should be considered to prevent the recurrence of liver disease. However, bone marrow transplantation, which has been successful in human EPP and which prevented liver disease in a mouse model, should be considered after liver transplantation, if a suitable donor can be found. Acknowledgment The authors thank Dr. Karl E. Anderson for his review of the manuscript and helpful comments and suggestions. This work is supported in part by the Porphyrias Consortium (U54 DK083909), a part of the National Institutes of Health (NIH) Rare Disease Clinical Research Network (RDCRN), supported through collaboration between the NIH Office of Rare Diseases Research (ORDR) at the National Center for Advancing Translational Science (NCATS) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. ■ ■FURTHER READING Balwani M et al: Clinical, biochemical, and genetic characterization of North American patients with erythropoietic protoporphyria and X-linked protoporphyria. JAMA Dermatol 153:789, 2017. Balwani M et al: Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. N Engl J Med 382:2289, 2020. Bonkovsky HL et al: Ledipasvir/sofosbuvir is effective as sole treat ment of porphyria cuteanea tarda with chronic hepatitis C. Dig Dis Sci 68:2738,2023. Chen B et al: Acute intermittent porphyria: Predicted pathogenicity of HMBS variants indicates extremely low penetrance of the autoso mal dominant disease. Hum Mutat 37:1215, 2016. Kazamel M et al: Pain in acute hepatic porphyrias: Update on

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Robert J. Hopkin, Gregory A. Grabowski

Lysosomal Storage

Diseases Lysosomes are heterogeneous subcellular organelles containing specific hydrolases that allow selective processing or degradation of proteins, nucleic acids, carbohydrates, and lipids. There are >50 different lysosomal storage diseases, now termed lysosomal system diseases (LSDs), classified according to the nature of the major accumulated materials (Table 429-1). Although all are rare diseases, an overview of several are provided here: Tay-Sachs disease, Fabry disease, Gaucher disease, Niemann-Pick disease, the mucopolysaccharidoses, Pompe disease, lysosomal acid lipase deficiency (LALD), Krabbe disease, CLN2-related Batten disease, and α-mannosidosis. 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 deforma tions. 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 varying degrees—a 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 acidification accompanies the matu ration 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 that are regulated by the mTORC1 modulation, via phosphorylation, of the transcription factors TFEB/TFE3 and the resultant control of the balance between anabolic and catabolic path ways. This regulation is disrupted to varying degrees in specific tissues affected by individual LSDs. Lysosomal Storage Diseases CHAPTER 429 Abnormalities at any biosynthetic step can impair lysosomal enzyme function and lead to an LSD. After leader sequence clipping from the primary protein, remodeling of complex oligosaccharides (including the lysosomal targeting ligand mannose-6-phosphate as well as highmannose oligosaccharide chains of many soluble lysosomal hydrolases) occurs during transit through the Golgi. Lysosomal integral or associ ated membrane proteins are sorted to the membrane or interior of the lysosome by several different peptide signals. Phosphorylation, sulfa tion, additional proteolytic processing, and macromolecular assembly of heteromers occur concurrently. Such posttranslational modifica tions are critical to enzyme function, and defects in these processes can result in multiple enzyme/protein deficiencies. The final common pathway for LSDs is the accumulation of specific macromolecules within selected 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 or protein subunit. However, some mutations cause deficiencies of several different lyso somal hydrolases by alteration of the enzymes/proteins involved in targeting, active site modifications, macromolecular association, or trafficking. Nearly all LSDs are inherited as autosomal recessive disor ders, except for Hunter (mucopolysaccharidosis type II), Danon, and Fabry diseases that are X-linked, and two autosomal dominant condi tions causing Parry type neuronal ceroid lipofuscinosis (CLN) due to mutations in DNAJC5 or frontotemporal dementia and CLN11 due to GRN (progranulin) mutations. Substrate accumulations lead to lyso somal distortions/dysfunctions that have significant pathophysiologic

stiffness; distinctive DYSPLASIA OPHTHALMOLOGIC HEMATOLOGIC UNIQUE FEATURES pebbly skin lesions lymphocytes Mild coarse facies lymphocytes Mild coarse facies involvement; joint involvement; joint cardiovascular cardiovascular lymphocytes Coarse facies; lymphocytes Coarse facies; stiffness degeneration MPS I S, Scheie None degeneration +++ ++++ Corneal clouding Vacuolated Granulated degeneration + + None Granulated degeneration + + None Granulated PART 12 Endocrinology and Metabolism degeneration, no corneal clouding CLINICAL FEATURES +++ ++++ Retinal ENLARGEMENT SKELETAL (ONSET) INHERITANCE NEUROLOGIC LIVER, SPLEEN degeneration, less (SGSH) Heparan sulfate Late infantile AR Severe cognitive Heparan sulfate Late infantile AR Severe cognitive in mild form Intermediate AR Cognitive Scheie Childhood/adult Cognitive Mild juvenile X-linked Cognitive TABLE 429-1 Selected Lysosomal System Diseases (also known as Lysosomal Storage Diseases) MATERIALS CLINICAL TYPES Heparan sulfate Severe infantile Heparan sulfate Infantile [ET, HSCT] Dermatan sulfate (IDS) [ET] Dermatan sulfate ACCUMULATED PRIMARY MPS I H, Hurler α-L-Iduronidase (IDUA) ENZYME DEFICIENCY

MPS III A, Sanfilippo A Heparan-N-sulfatase MPS II, Hunter Iduronate sulfatase (GENE) [SPECIFIC glucosaminidase MPS III B, Sanfilippo B N-Acetyl-αTHERAPY] Mucopolysaccharidoses (MPS) (NGALU) MPS I H/S, Hurler/ DISORDERa

hypoplasia; aortic valve neutrophils Coarse facies; vascular hyperacusis in infantile Coarse facies; valvular fetalis in neonatal form involvement; hydrops deformity; odontoid neutrophils Distinctive skeletal lymphocytes Mild coarse facies lymphocytes Mild coarse facies infantile form None Macrocephaly; ++ ± Cherry red spot None Macrocephaly; heart disease hyperacusis disease form MPS IV B, Morquio β-Galactosidase (GLB1) Childhood AR None ± ++++ neutrophils and lymphocytes degeneration + + None Granulated degeneration + + None Granulated Chondroitin-6 sulfate Childhood AR None + ++++ Corneal clouding Granulated [ET, HSCT] Dermatan sulfate Late infantile AR None ++ ++++ Corneal clouding Granulated +++ +++ Corneal clouding Granulated None None Cherry red spot in Heparan sulfate Late infantile AR Severe cognitive 6-sulfate sulfatase (GNS) Heparan sulfate Late infantile AR Severe cognitive absent in some seizures; later degeneration, degeneration; degeneration; juvenile form AR Cognitive Juvenile AR Cognitive and B (HEXB) GM2 gangliosides Infantile AR Cognitive seizures adults Heparan sulfate Neonatal Infantile (HEXA) GM2 gangliosides Infantile Adult [ET] Dermatan sulfate Keratan sulfate MPS IV A, Morquio A N-AcetylgalactosamineSly β-Glucuronidase (GUS) Maroteaux-Lamy Arylsulfatase B (ARSB) MPS III D, Sanfilippo D N-Acetylglucosamine-

Sandhoff disease β-Hexosaminidases A Tay-Sachs disease β-Hexosaminidase A N-acetyltransferase 6-sulfate sulfatase α-glucosaminide (GALNS) [ET] MPS III C, Sanfilippo C Acetyl-CoA: (HGSNAT) GM2 Gangliosidoses MPS VI, MPS VII

Coarse facies; enlarged bone marrow Pulmonary infiltrates Types 1 and 3 highly angiokeratomas in angiokeratomas; Angiokeratomas Coarse facies; hypohydrosis juvenile form Lung failure vascular lesions None Cutaneous variable tongue Gaucher cells in bone marrow; lymphocytes; lymphocytes, lymphocytes, degeneration Foam cells in degeneration ++ ++ None Vacuolated clouding Vacuolated degeneration ++ None Vacuolated granulated neutrophils cytopenias foam cells Supranuclear gaze acroparesthesias None None Corneal dystrophy, degeneration +++ +++ Cataracts, corneal Strabismus Osteoporosis Macular None palsy ++++ None ++++ ++++ + ++++ ++++ +++ (MANBA) Oligosaccharides AR Seizures; cognitive degeneration; AR Cognitive Juvenile AR Cognitive Milder variant AR Cognitive seizures [ET, Chaperone] Globotriaosylceramide Childhood X-linked Painful –/+++ AR None ++++ Nonneuronopathic, (SMPD1) [ET] Sphingomyelin Neuronopathic, oligosaccharides Infantile (MAN2B1) [ET] Oligosaccharides Infantile type A type B Glucosylsphingosine Type 1 Type 2 Type 3 Glucosylceramide, Fucosidosis α-Fucosidase (FUCA1) Glycopeptides; Fabry disease α-Galactosidase A (GLA) A and B Acid sphingomyelinase Gaucher disease Acid β-glucosidase (GBA, a.k.a. GBA1)

α-Mannosidosis α-Mannosidase β-Mannosidosis β-Mannosidase [ET, SRT] Neutral Glycosphingolipidoses Niemann-Pick disease Glycoproteinoses

(Continued) mucopolysaccharidu ria;

Coarse facies; stiffness of hands and shoulders None None None None White matter globoid None None Optic atrophy None Gait abnormalities in gingival hypoplasia lymphocytes MPS phenotype in late infantile form Coarse facies; Coarse facies absence of type II cells and granulated lymphocytes, degeneration ± ++ None Vacuolated type I Cherry red spot Vacuolated degeneration + ++++ Corneal clouding Vacuolated neutrophils foam cells foam cells Lysosomal Storage Diseases CHAPTER 429 degeneration None +++ Corneal clouding, mild retinopathy, astigmatism hyperopic ++, less in type I ++, less in psychosis in adult dysmyelination glycolipids Late infantile AR Mild cognitive degeneration, degeneration; degeneration AR Myoclonus; CNS, PNS dementia; glycopeptides Young adult AR Cognitive glycolipids Infantile AR Cognitive Infantile AR Cognitive AR Cognitive cognitive Sialidosis Neuraminidase (NEU1) Sialyloligosaccharides Type I, congenital Type II, infantile and juvenile Juvenile leukodystrophy Arylsulfatase A (ARSA) Cerebroside sulfate Infantile Adult Galactosylsphingosine, (AGA) Aspartylglucosamine; (GALC) [BMT/HSCT] Galactosylceramide a.k.a., psychosine Glycoprotein; Glycoprotein; Aspartylglucosaminuria Aspartylglucosaminidase Krabbe disease Galactosylceramidase 1-phosphotransferase 1-phosphotransferase Acetylglucosamine-

Acetylglucosamine-

(GNPTAB) (GNPTAB) ML-II, I-cell disease UDP-Npolydystrophy UDP-NMucolipidoses (ML) ML-III, pseudo-Hurler Leukodystrophies Metachromatic

None Rare fatal neonatal liver known cellular sulfatases

subcutaneous nodules granulated cells Absent activity of all DYSPLASIA OPHTHALMOLOGIC HEMATOLOGIC UNIQUE FEATURES (LIPA) [ET] Cholesteryl esters Childhood AR None Hepatomegaly None None None Fatty liver disease; disease, cirrhosis triglycerides Infantile AR None +++ None None None Adrenal cortical (GAA) [ET] Glycogen Infantile, late onset AR Neuromuscular ± None None None Myocardiopathy degeneration None Arthropathy, calcification cirrhosis degeneration Vacuolated and PART 12 Endocrinology and Metabolism ophthalmoplegia supranuclear CLINICAL FEATURES ± None Macular hepatosplenomegaly None Vertical degeneration + ++ Retinal ENLARGEMENT SKELETAL (ONSET) INHERITANCE NEUROLOGIC LIVER, SPLEEN degeneration Variable adulthood AR Progressive CNS degeneration Juvenile AR Occasional mucopolysaccharides Late infantile AR Cognitive cognitive TABLE 429-1 Selected Lysosomal System Diseases (also known as Lysosomal Storage Diseases) (Continued) MATERIALS CLINICAL TYPES Cholesterol Childhood to (ASAH1) Ceramide Infantile (LIPA) [ET, HSCT] Cholesteryl esters; ACCUMULATED enzyme, a.k.a. FGE (SUMF1) Sulfatides; PRIMARY deficiency Formylglycine-generating Infantile-onset LALD Lysosomal acid lipase ENZYME DEFICIENCY

LALD Acid lysosomal lipase Pompe disease Acid α-glucosidase (GENE) [SPECIFIC Farber disease Acid ceramidase THERAPY] (NPC1) (NPC2) C1 and C2 NPC1 NPC2 Disorders of Neutral Lipids Disorders of Glycogen Niemann-Pick disease Childhood/adult-onset Multiple sulfatase DISORDERa

neuromuscular disease None None None None Myocardial vacuolar loss None Symmetric retinal Abbreviations: AR, autosomal recessive; BMT/HSCT, bone marrow or hematopoietic stem cell transplantation; ET, enzyme therapy; ICV ET, intracerebroventricular enzyme therapy; LALD, lysosomal acid lipase deficiency; SRT, substrate degeneration by insufficiency; degeneration aComprehensive reviews of these lysosomal storage diseases can be found in DL Valle et al: The Online Metabolic and Molecular Bases of Inherited Disease, New York, McGraw-Hill, https://ommbid.mhmedical.com/book.aspx?boo progressive to adulthood AR Neuromuscular None None None None Respiratory 4–6 years None None Progressive vision Ceroid lipofuscin Early childhood AR Neurodegenerative Wheelchair bound Loss of motor skills (?Dominant) Cardiomyopathy by adolescence Neuromuscular Cognitive loss Loss of vision degeneration Inconsistent Myoclonus cognitive to adulthood X-linked Glycogen Variable: childhood (GAA) [ET] Glycogen Variable: juvenile synthesis inhibition therapy (a.k.a., substrate reduction therapy). associated membrane peptidase 1) (TPP1) Danon disease LAMP-2 (lysosomal deficiency Acid α-glucosidase protein-2) (LAMP2) CLN2 (a.k.a. NCL2) TPP1 (tripeptidyl Neuronal Ceroid Lipofuscinoses [ICV ET] kID=2709#225069419. Late-onset GAA

consequences. In addition, abnormal amounts of metabolites may also have pharmacologic effects important to disease pathophysiology and propagation, particularly activation of the innate immune responses. For many LSDs, the accumulated substrates are synthesized within particular tissue sites of pathology. Other diseases have greater exog enous substrate supplies. For example, substrates are delivered by lowdensity lipoprotein receptor–mediated uptake in Fabry and LALD 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 that threshold can lead to or modify disease. A critical element of this model is that enzymatic activity can be challenged by changes in substrate flux based on genetic back ground, 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 the clinical level.

These disorders therefore represent a spectrum of manifestations that are not easily dissociated into discrete entities. The molecular/genetic bases for such variations have not been elucidated in any detail. Treatments approved by the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) are available for several LSDs. The first was enzyme replacement therapy (ET) for Gaucher disease; this has been followed by additional ETs, but subsequent devel opments have included modified enzyme infusion, substrate synthesis inhibition, hematopoietic stem cell transplant (HSCT), pharmacologic chaperone therapy (which use small molecules to stabilize or enhance enzyme function resulting from the mutated gene), intrathecal enzyme delivery, Trojan-horse strategies for blood-brain barrier penetration for central nervous system (CNS) delivery, and gene therapy. The technical ability to intervene for most LSDs now exists but with highly variable impact, i.e., therapeutic outcome, particularly in bones and the CNS. Significant additional research is needed to reach the goals of longterm survival with good function and quality of life. SELECTED DISORDERS ■ ■TAY-SACHS DISEASE About 1 in 30 Ashkenazi Jews is a carrier for Tay-Sachs disease (total hexosaminidase A [Hex A] deficiency), resulting from α-chain gene mutations. The infantile form is a neurodegenerative disease that results in death in infancy. It is characterized by 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 signs and dysarthria in adulthood; intelligence declines slowly, and psychiatric disorders are 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 with the addi tion of hepatosplenomegaly and bony dysplasias. ■ ■FABRY DISEASE Fabry disease, an X-linked disorder and likely the most prevalent LSD, results from mutations in GLA, which encodes α-galactosidase A. The estimated prevalence of hemizygous males ranges from 1 in 40,000 to 1 in 3500 in selected populations. Females have a higher prevalence of mutations, but more variable manifestations due to Lyonization effects. The disease manifests with angiokeratomas (telangiectatic skin lesions), hypohidrosis, corneal and lenticular opacities, acroparesthesia, and progressive disease of the kidney, heart, and brain vascular systems. Abdominal pain, recurrent diarrhea, and acroparesthesias (debilitating episodic burning pain of the hands and feet) may appear in childhood. In females, the overall manifestations vary greatly. Angiokeratomas are punctate, dark red to blue-black, and flat or slightly raised skin lesions; they do not blanch with pressure. They can be easily overlooked. They usually are most dense between the umbilicus and the knees—the “bathing suit area”—but may occur anywhere. Angiokeratomas also

occur in several other very rare LSDs. Corneal and lenticular lesions, detectable on slit-lamp examination, may help in establishing a diag nosis of Fabry disease. Acroparesthesia can last from minutes to days and can be precipitated by changes in temperature, exercise, fatigue, or fever. Abdominal pain can resemble 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 GLA 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, ~2–5% of patients with “idiopathic stroke” at 35–50 years of age have GLA mutations. Leg lymphedema occurs without hypoproteinemia. Death is due to cardiovascular, renal, or cerebrovascular disease. Variants with

residual α-galactosidase A activity may have late-onset manifestations that are most prominent in the cardiovascular system and resemble hypertrophic cardiomyopathy. Cases with predominant cardiac, renal, or CNS manifestations have been reported. Up to 70% of heterozygous females exhibit clinical manifestations. However, in females, heart dis ease is the most common life-threatening manifestation. In males, it is renal disease followed by cardiovascular disease. Lysosomal Storage Diseases CHAPTER 429 Gabapentin and carbamazepine diminish chronic and episodic acroparesthesias. Chronic hemodialysis or kidney transplantation can be lifesaving in patients with renal failure. Intravenous ET clears stored lipids from a variety of cells. More recently a chaperone therapy (migalastat) that stabilizes the residual enzyme made by the patient's body has allowed oral therapy for some patients with amenable muta tions. Renal insufficiency, cardiac fibrosis, and stroke are irreversible; therefore, early institution of therapy provides the best opportunity to prevent or slow the progression of life-threatening complications. ■ ■GAUCHER DISEASE Gaucher disease, a panethnic autosomal recessive disorder, results from defective activity of acid β-glucosidase; ~600 GBA, a.k.a. GBA1, mutations have been described in such patients. Clinically, disease variants are classified by the absence or presence and progression of primary CNS involvement. Gaucher disease type 1 is a nonneuronopathic disease (i.e., absence of early-onset or progressive CNS disease) presenting in child hood to adulthood as slowly to rapidly progressive visceral disease. About 55–60% of patients are diagnosed at <20 years of age in white populations and at even younger ages in other groups. This pattern of presentation is distinctly bimodal, with peaks at <10–15 years and at ~25 years. Younger patients tend to have greater degrees of hepato splenomegaly and accompanying blood cytopenias. In contrast, older patients have a greater tendency for chronic bone disease. Hepato splenomegaly occurs in virtually all clinically identified patients and can be minor or massive. Accompanying anemia and thrombocytope nia are variable and are not directly related to liver or spleen volumes. Severe liver dysfunction is unusual, but progressive cirrhosis can occur. Splenic infarctions can resemble an acute abdomen. Pulmonary hypertension and alveolar Gaucher cell accumulation are uncommon but life-threatening and can occur at any age; this is more common in females who have been splenectomized. GBA1 mutations in the hetero zygous or homozygous states lead to a significantly increased lifetime risk for developing Parkinson disease. The complex mechanisms for this major risk require elucidation. All patients with Gaucher disease have nonuniform infiltration of bone marrow by lipid-laden macrophages, termed Gaucher cells. This phenomenon can lead to marrow packing with subsequent infarc tion, ischemia, necrosis, and cortical bone destruction. Bone marrow involvement spreads from proximal to distal in the limbs and can involve the axial skeleton extensively, causing vertebral collapse. In addition to bone marrow involvement, bone remodeling is defective, with loss of total bone calcium leading to osteopenia, osteonecrosis, avascular infarction, and vertebral compression fractures with spinal cord involvement. Aseptic necrosis of the femoral head is common, as is fracture of the femoral neck. The mechanism by which diseased bone marrow macrophages interact with osteoclasts and/or osteoblasts

to cause bone disease is not well understood. Chronic, ill-defined bone pain can be debilitating and poorly correlated with radiographic findings. "Bone crises" are associated with localized excruciating pain and, on occasion, local erythema, fever, and leukocytosis. These crises represent acute infarctions of bone, as evidenced in nuclear scans by localized absent uptake of pyrophosphate agents. Decreased acid β-glucosidase activity (0–20% of normal) in nucleated cells establishes the diagnosis. The enzyme is not normally present in bodily fluids. The sensitivity of enzyme testing is poor for heterozygote detection; molecular testing by whole GBA1 sequencing is

the standard. The disease frequency varies from ~1 in 1000 among Ashkenazi Jews to <1 in 100,000 in other populations; ~1 in 12–15 Ashkenazi Jews carries a Gaucher disease allele. Four common mutations account for ~85% of the mutations in that population of affected patients: p.N370S (a.k.a. p.N409S), 84GG (a G insertion at cDNA position 84), p.L444P (also known as p.L483P), and IVS-2+1 (an intron 2 splice junction mutation).

PART 12 Endocrinology and Metabolism Genotype/phenotype studies indicate a significant, though not absolute, correlation between disease type and severity and the GBA1 genotype. The most common mutation in the Ashkenazi Jewish popu lation (p.N370S) shares, either homozygously or heteroallelically, a 100% association with nonneuronopathic or type 1 Gaucher disease. The N370S/N370S and N370S/other mutant allele genotypes are asso ciated with later-onset/less severe disease and with earlier-onset/severe disease, respectively. As many as 40% of individuals with the N370S/ N370S genotype do not present clinically. Other alleles include L444P (very low activity), 84GG (null), or IVS-2 (null) and rare/private or uncharacterized alleles. The L444P/L444P patients frequently have lifethreatening to very severe/early-onset disease, and many, though not all, develop CNS involvement in the first two decades of life. Symptom-based treatment of blood cytopenias and joint replace ment surgeries continue to have important roles in management. However, regular intravenous ET has been the first-line treatment for significantly affected patients and is highly efficacious and safe in diminishing hepatosplenomegaly and improving hematologic values. An oral substrate reduction therapy (SRT; eliglustat tartrate), which inhibits glucosylceramide synthesis, is approved as a first-line therapy for adults. Bone disease is decreased and can be prevented, but irre versible damage cannot be reversed, by ET. Adult patients may benefit from adjunctive treatment with bisphosphonates or other interventions to improve bone density. Adults who cannot be treated with enzyme, either because it is not effective or because they have developed an allergy or other hypersensitivities to the enzyme, may receive SRT with either eliglustat tartrate or miglustat; the latter is approved as a secondline oral therapy. Gaucher disease type 2 is a rare, severe, progressive CNS disease that leads to death by 2 years of age, depending on supportive care. Gaucher disease type 3 has highly variable manifestations in the CNS and viscera. It can present in early childhood with rapidly progressive, massive visceral disease and slowly progress to static CNS involvement that may not be evident by standard IQ evaluations; in adolescence with dementia; or in early adulthood with rapidly progressive, uncon trollable myoclonic seizures and mild visceral disease. Visceral disease in type 3 is nearly identical to that in type 1 but is generally more severe. Early CNS findings may be limited to defects in lateral gaze tracking (supranuclear lateral gaze palsy), which may remain static for decades. Cognitive degeneration can be slowly progressive or static. Type 3 is much more frequent among individuals of non–Western world descent. Visceral—but not CNS—involvement responds to ET. ■ ■NIEMANN-PICK DISEASES Niemann-Pick diseases (acid sphingomyelinase deficiency [ASMD]) are autosomal recessive disorders that result from defects in acid sphingomyelinase (ASM). Types A and B are distinguished by the early age of onset and progressive CNS disease in type A. Type A typically has its onset in the first 6 months of life, with rapidly progressive CNS deterioration, spasticity, failure to thrive, and massive hepatospleno megaly. Type B has a later, more variable onset and is characterized by a progression of hepatosplenomegaly, with eventual development of cir rhosis and hepatic parenchymal and Kupffer cell replacement by foam

cells filled with sphingomyelin. Affected patients develop potentially lethal progressive pulmonary disease with dyspnea, hypoxemia, and a reticular infiltrative pattern on chest x-ray. Foam cells are

present in alveoli, lymphatic vessels, and pulmonary arteries. Progressive hepatic or lung disease can lead to death in adolescence or early adulthood. The “type B” phenotype includes some patients with slowly progressive CNS involvement, termed A/B variant. The diagnosis is established by markedly decreased (1–10% of normal) ASM activity in nucleated cells. Intravenous ET improves nonneurologic manifestations, including pulmonary disease. The efficacies of hepatic transplant (HT) or bone marrow transplantation (BMT/HSCT) are not established. More complications than expected have occurred with these interventions due to either (1) recurrence of hepatic disease in the transplant following HT due to repopulation of bone marrow–derived ASM-deficient myeloid cells or (2) lack of clearance of sphingomyelin in hepatocytes by ASM cross-correction following the BMT/HSCT of ASM-normal bone marrow stem cells. Niemann-Pick C diseases are progressive CNS diseases due to muta tions in either of the genes encoding NPC1 or NPC2, lysosomal pro teins involved in free cholesterol and selected sphingolipid transport out of the lysosome. They can present with liver or splenic disease, but their major manifestations are progressive CNS disease over one to two decades. Treatment with substrate inhibition agents (e.g., miglustat) has shown minor CNS effects, and substrate depletion with cyclodex trin is in clinical trials for NPC1 disease. ■ ■MUCOPOLYSACCHARIDOSES Mucopolysaccharidosis type I (MPS I) is an autosomal recessive dis order caused by deficiency of α-L-iduronidase (IDU). The spectrum of involvement traditionally has been divided into three categories: (1) Hurler disease (MPS I H) for severe deficiency with neurodegen eration, (2) Scheie disease (MPS I S) for later-onset disease without neurologic involvement and with relatively less severe disease in other organ systems, and (3) Hurler-Scheie syndrome (MPS I H/S) for patients intermediate between these extremes. MPS I H/S is character ized by severe somatic disease, usually without major overt neurologic deterioration. MPS I often presents in infancy or early childhood as chronic rhinitis, clouding of the corneas, hepatosplenomegaly, and progressive dysmorphia. As the disease progresses, nearly every organ system can be affected. In the more severe forms, cardiac and respira tory diseases become life threatening in childhood. Skeletal disease can be severe, resulting in very limited mobility. There are two current treatments for the MPS I diseases. HSCT is the standard treatment for patients presenting at <2 years of age who appear to have or are at risk for neurologic degeneration. Because early diagnosis and intervention are essential, MPS I has been added to the recommended newborn screen (NBS). HSCT results in stabilization of CNS disease, reverses hepatosplenomegaly, and improves cardiac and respiratory disease. HSCT does not eliminate corneal disease or result in the resolution of progressive skeletal disease. ET effectively addresses hepatospleno megaly and alleviates cardiac and respiratory disease. The enzyme does not penetrate the blood-brain barrier and does not directly affect CNS disease. ET and HSCT appear to have similar effects on visceral signs and symptoms. ET poses a lower risk of life-threatening complications and may therefore be advantageous for patients without CNS disease. A combination of ET and HSCT has been used, with ET initiated prior to transplantation in an attempt to reduce the disease burden. The experience with this approach is not well documented, but it appears to have advantages over HSCT alone. It is clear that HSCT has benefited patients. However, late cardiac and respiratory complications of MPS I are being reported including obstructive breathing requiring pressure support, cardiomyopathy, and/or valve disease. Regular follow-up for patients with MPS I is required throughout their lives even after suc cessful HSCT. Hunter disease (MPS II) is an X-linked disorder due to deficiency in iduronate sulfate sulfatase (IDS) and has manifestations similar to those of MPS I, including some variants with neurologic degeneration. There is no corneal clouding or other eye disease. Like MPS I, MPS II is clinically variable, with CNS and non-CNS variants. HSCT has not

been successful in treating CNS disease associated with MPS II. The FDA and EMA have approved ET for the visceral manifestations of MPS II. MPS IV or Morquio syndrome is a rare autosomal recessive condi tion (1 in 200,000–300,000) and is different than the other mucopoly saccharidoses in presenting as a spondyloepiphyseal skeletal dysplasia and hyperextensibility of all joints. There are also major heart and respi ratory complications. This disorder often presents in childhood, but the age of onset and rate of progression are quite variable. Two variants, type A and type B, are caused by deficiencies in N-acetyl-galactosamine6-sulfatase (GALNS) and an acid β-galactosidase, respectively. A recom binant human GALNS ET (elosulfase alfa) is approved for the treatment of MPS IVA, making it essential to confirm the specific enzyme diag nosis. Treatment has been shown to improve ambulatory mobility and decrease pain. There is no current specific treatment for MPS IVB. ET for Maroteaux-Lamy disease (MPS VI), arylsulfatase B (ARSB) deficiency, has received FDA approval as well as approval by similar agencies in other countries. This very rare autosomal recessive disorder is characterized by hepatosplenomegaly, bone disease, heart disease, and respiratory compromise. Short stature is also an important mani festation. Visceral signs and symptoms are similar to those in MPS I; however, MPS VI is not associated with neurologic degeneration. MPS VII, Sly syndrome, is due to mutations in GUSB, which encodes β-glucuronidase. Severe deficiency in this enzyme may pres ent with fetal hydrops, which can lead to stillbirth or perinatal demise. Other patients with MPS VII may present later with short stature, coarse facial features, and hepatosplenomegaly. There is ET for this disorder (vestronidase alfa-vjbk). ■ ■POMPE DISEASE Acid maltase (acid α-glucosidase deficiency) due to GAA mutations, also called Pompe disease, is the only LSD leading to primary glyco gen storage. The classic severe infantile form presents with hypotonia, myocardiopathy, and hepatosplenomegaly, as well as total deficiency of the enzyme. This variant is rapidly progressive and generally results in death in the first year of life. However, as with other LSDs, there are early- and late-onset forms of this disorder. The late-onset variants may be as common as 1 in 40,000; patients typically present with a slowly progressive myopathy that may resemble limb-girdle muscular dystrophy. Respiratory insufficiency may be the presenting sign or may develop with advancing disease. In late stages of the disease, patients may require mechanical ventilation, report swal lowing difficulties, and experience loss of bowel and bladder control. Myocardiopathy is not usually present in late-onset variants of Pompe disease. The FDA, EMA, and similar agencies have approved ETs for Pompe disease patients of all ages. This treatment clearly prolongs life in the infantile form, consistently resulting in improved cardiac function. Respiratory function is also improved in most treated infants if insti tuted before age 6 months. Some infants demonstrate marked improve ment in motor functions, while others have minor changes in muscle tone or strength. Many states have instituted NBS for Pompe disease. In addition, newer protocols for treatment with methotrexate and ritux imab have greatly decreased antidrug antibody reactions, particularly in the enzyme-absent infantile variants. The combination of NBS and immunomodulation preceding ET has greatly improved therapeutic response and long-term survival. Prevention of deterioration has been shown with GAA ET in the late-onset forms. Early intervention with acid a-glucosidase ET in such patients may limit or prevent dete rioration, but very advanced disease will have significant irreversible components. ■ ■LYSOSOMAL ACID LIPASE DEFICIENCY Wolman syndrome (now infantile-onset LALD) and cholesterol ester storage disease (now childhood/adult-onset LALD) are caused by defi ciency of lysosomal acid lipase (LAL) due to autosomal recessive muta tions in LIPA. The diagnosis is established by enzyme or gene analyses of LAL or LIPA in serum/plasma or nucleated cells, respectively. LAL hydrolyzes cholesterol esters (CEs) and triglycerides (TGs)

delivered to the lysosome via the LDLR pathway. Accumulation of these in the tissues leads to progressive organ dysfunction includ ing liver disease, intestinal malabsorption, heart dysfunction, and other manifestations. The most severe form presents in early infancy as a medical emergency with severe failure to thrive, vomiting, and hepatosplenomegaly. The infantile-onset LALD patients die without specific treatment by age 1 year (median age of death, 3.7 months) from tissue accumulations of CEs and TGs and near total absence of LAL. Childhood/adult-onset LALD can have a variable age of initial presentation with nonspecific signs but often involves elevated liver enzymes, microvesicular fatty liver disease, cryptogenic cirrhosis, and varying severities of hepato-/splenomegaly, due to massive accumula tions of CEs secondary to the LAL substrate preference for TGs by the low LAL levels. Importantly, neither clinical variant manifests primary CNS disease. Without treatment, disease progresses throughout life and may result in early (adolescence, mean ~13 years) liver cirrhosis and (early adulthood) atherosclerosis or early death. Importantly, statins can decrease the hypercholesterolemia but do not alter the basic progressive tissue (e.g., liver) pathology. The majority of the later onset patients are evaluated by hepatology or lipidology physicians. ET for LALD has major effects in reversing disease manifestations and is approved for patients at all ages by the EMA, FDA, and several other country agencies.

Lysosomal Storage Diseases CHAPTER 429 ■ ■KRABBE DISEASE Deficiency in β-galactocerebrosidase (GALC) causes Krabbe disease, an autosomal recessive neurodegenerative disorder due to mutations in GALC. Krabbe disease is panethnic but quite rare. The early infantile form presents at an average age of 4 months and progresses rapidly, with death at an average age of 18 months. Later onset forms also exist and have onsets and survival that are highly variable. The early-onset form presents with hyperirritability, feeding problems, fever, seizures, and neurodegeneration. Blindness, hypotonia, and loss of voluntary movement develop over time. Later onset forms present with spasticity, ataxia, vision loss, and behavioral problems and progress to dementia and early death. There is no FDA-approved treatment, but early, i.e., first or second month after birth, presymptomatic HSCT has been used. This results in improved survival, but neurologic problems are still common and slowly progressive in the CNS and more severe in the peripheral nervous system. More recently, studies in mouse and dog models have used gene therapy with dramatic improvement in both neurologic function and survival. Human studies are in clinical trials. ■ ■NEURONAL CEROID LIPOFUSCINOSIS TYPE 2 (NCL2 OR CLN2) There are at least 13 mutant genes that have been associated with storage of neuronal ceroid lipofuscin. CLN2 is due to mutations in TPP1 and deficiency in tripeptidyl peptidase 1. This autosomal reces sive neurodegenerative disorder typically presents between age 2 and 4 years, most commonly with seizures, ataxia, myoclonus, and vision loss. Motor skill losses include sitting, walking, speech, and feeding and lead to severe disability and eventually death at an average age of 12 years. Intellectual disability and behavioral problems also become increasingly severe with age. Most affected children are wheelchair bound in late childhood, and survival beyond adolescence is rare. There are also later onset patients, and there is significant clinical over lap between CLN2 and other CLNs; confirmation of the diagnosis by gene sequencing is essential. FDA/EMA-approved treatment of CLN2 is with cerliponase alfa, an ET that is administered by intracerebroven tricular infusions over several hours every 2 weeks. Administration of cerliponase alfa is facilitated by placement of an indwelling intracere broventricular port to allow reliable access. Currently, this is the only approved ET that is intrathecally administered. CLN2 is the only neu ronal ceroid lipofuscinosis that has a specific treatment. Several others are in preclinical development. ■ ■ALPHA MANNOSIDOSIS Alpha mannosidosis is a very rare disorder caused by deficiency in α-d-mannosidase due to biallelic loss of function of MAN2B1. This leads to buildup of mannose-rich

oligosaccharides in the cells, blood,

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