to be irreversible. Early institution of enzyme therapy may prevent or slow the progression of life-threatening complications.

GAUCHER DISEASE

Gaucher disease is an autosomal recessive disorder that results from defective activity of acid β-glucosidase; ~400 mutations have been described at the *GBA1* locus of such patients. Disease variants are classified by the absence or presence and progression of neuronopathic involvement.

Gaucher disease type 1 is a nonneuronopathic disease that can present in childhood 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 a greater degree of hepatosplenomegaly and accompanying blood cytopenias. In contrast, the older group has a greater tendency for chronic bone disease. Hepatosplenomegaly occurs in virtually all symptomatic patients and can be minor or massive. Accompanying anemia and thrombocytopenia are variable and are not directly related to liver or spleen volumes. Severe liver dysfunction is unusual. 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. *GBA1* mutations in the hetero- or homozygous state are a significant risk factor for early-onset or more rapidly progressive Parkinson disease.

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 infarction, 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 and 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 present in bodily fluids. The sensitivity of enzyme testing is poor for heterozygote detection; molecular testing by *GBA1* sequencing is preferred. The disease frequency varies from about 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: N370S (1226G), 84GG (a G insertion at cDNA position 84), L444P (1448C), and IVS-2 (an intron 2 splice junction mutation).

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 population (N370S) shares a 100% association with nonneuronopathic or type 1 Gaucher disease. The N370S/N370S and N370S/other mutant allele genotypes are associated with later-onset/less severe disease and with earlier-onset/severe disease, respectively. As many as 50–60% of individuals with the N370S/N370S genotype are asymptomatic. Other alleles include L444P (very low activity), 84GG (null), or IVS-2 (null) and rare/private or uncharacterized alleles. The L444P/L444P patients almost always have life-threatening 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 replacement surgeries continue to have important roles in management. However, regular intravenous enzyme therapy is currently the treatment of choice in significantly affected patients and is highly efficacious and safe in diminishing hepatosplenomegaly and improving hematologic values. Bone disease is decreased but not eliminated by enzyme therapy. Adult patients may benefit from adjunctive treatment with bisphosphonates to improve bone density. Patients who cannot be treated with enzyme, either because it is not effective or because they have an allergy or other hypersensitivities, may be receive *substrate reduction therapy* with medications that decrease the production of the complex lipid molecules that are broken down by acid β-glucosidase.

Gaucher disease type 2 is a rare, severe, progressive CNS disease that leads to death by 2 years of age. 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; in adolescence with dementia; or in early adulthood with rapidly progressive, uncontrollable 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, which may remain static for decades. Mental retardation can be slowly progressive or static. This variant is most frequent among individuals of Swedish descent. Visceral—but not CNS—involvement responds to enzyme therapy.

NIEMANN-PICK DISEASE

Niemann-Pick diseases are autosomal recessive disorders that result from defects in acid sphingomyelinase. 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 hepatosplenomegaly. Type B has a later, more variable onset and is characterized by a progression of hepatosplenomegaly, with eventual development of cirrhosis and hepatic replacement by foam cells. Affected patients develop 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 leads to death in adolescence or early adulthood.

The diagnosis is established by markedly decreased (1–10% of normal) sphingomyelinase activity in nucleated cells. There is no specific treatment for Niemann-Pick disease. The efficacy of hepatic or bone marrow transplantation has not been clearly established. Clinical trials of enzyme therapy are in phases 2 and 3.

Niemann-Pick C diseases are progressive CNS diseases due to mutations in either NPC1 or NPC2. They 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) and substrate depletion with cyclodextrin have shown promise.

LYSOSOMAL ACID LIPASE

Lysosomal acid lipase deficiency may result in Wolman disease (severe deficiency) or CESD, which presents later and has some (3–10%) residual enzyme activity. Wolman disease presents in early infancy with hepatosplenomegaly, diarrhea, vomiting, and abdominal distention, sometimes accompanied by adrenal calcification, anemia, and mixed hyperlipidemia. Death occurs before the age of 1 year and is often due to severe intestinal malabsorption. CESD is heterogeneous and presents with hepatomegaly and hepatosteatosis at any age in childhood or adulthood. CESD should be included in the differential diagnosis for all patients with isolated hypercholesterolemia. The disease may progress to hepatic fibrosis, cirrhosis, and liver failure. In addition, patients often develop very early-onset atherosclerotic vascular disease, which may be life-threatening in childhood. Preliminary results of treatment with enzyme replacement therapy are promising for Wolman disease and CESD.

MUCOPOLYSACCHARIDOSES

Mucopolysaccharidosis type I (MPS I) is an autosomal recessive disorder caused by deficiency of α-L-iduronidase. The continuum of