Understanding the Nurse's Role in Managing Gaucher Disease

How advances in screening, diagnosis, and treatment affect patient care.

ABSTRACT: Lysosomal storage disorders (LSDs) are a group of inherited metabolic conditions, the overall incidence of which is estimated to range from one in 5,000 to one in 7,000 live births. Gaucher disease, the most common LSD, is of autosomal recessive inheritance. It results from a deficiency of acid β-glucocerebrosidase and can affect the spleen, liver, bone, bone marrow, and central nervous system. Gaucher disease is clinically classified into one of three phenotypes, depending on the absence or presence of neurodegenerative disease and the rate of disease progression. Although there is no cure for Gaucher disease, it may be treated with enzyme replacement and substrate reduction therapy. With the development of enzyme testing through dried blood spots, Gaucher disease may now be detected at birth through newborn screening. The purpose of this article is to review the epidemiology and pathophysiology of Gaucher disease, update nurses on advances in newborn screening, diagnosis, and management of this genetic disorder, and highlight the role of nurses in the diagnosis and care of patients with Gaucher disease.

Keywords: Gaucher disease, genetics, lysosomal storage disorders, newborn screening

Suzy was five years old when her pediatrician, suspecting splenomegaly and pancytopenia, referred her to a hematologist for evaluation. (This case is a composite based on my experience.) Since the age of two, she had experienced frequent nosebleeds and bruised easily. The hematologist confirmed Suzy's pancytopenia and hepatosplenomegaly by ultrasound but identified no leukemic processes. The hematologist continued to monitor Suzy's blood counts and investigated various infectious etiologies, including Epstein–Barr virus and cytomegalovirus, all of which were negative. Given Suzy's persistent pancytopenia and hepatosplenomegaly, the hematologist referred her to a gastroenterologist, who found Suzy's liver enzymes to be normal and determined her abdominal ultrasound to be unremarkable. Ten months after Suzy's initial referral to the hematologist, her gastroenterologist ordered a liver biopsy, which revealed the lipid-laden, striated Kupffer cells associated with Gaucher disease. A subsequent blood enzyme assay confirmed that Suzy had type 1 Gaucher disease. Suzy's diagnostic odyssey is typical of that experienced by far too many patients affected with Gaucher disease, who often wait years from the

onset of symptoms, undergoing multiple unnecessary invasive procedures, before obtaining a diagnosis.

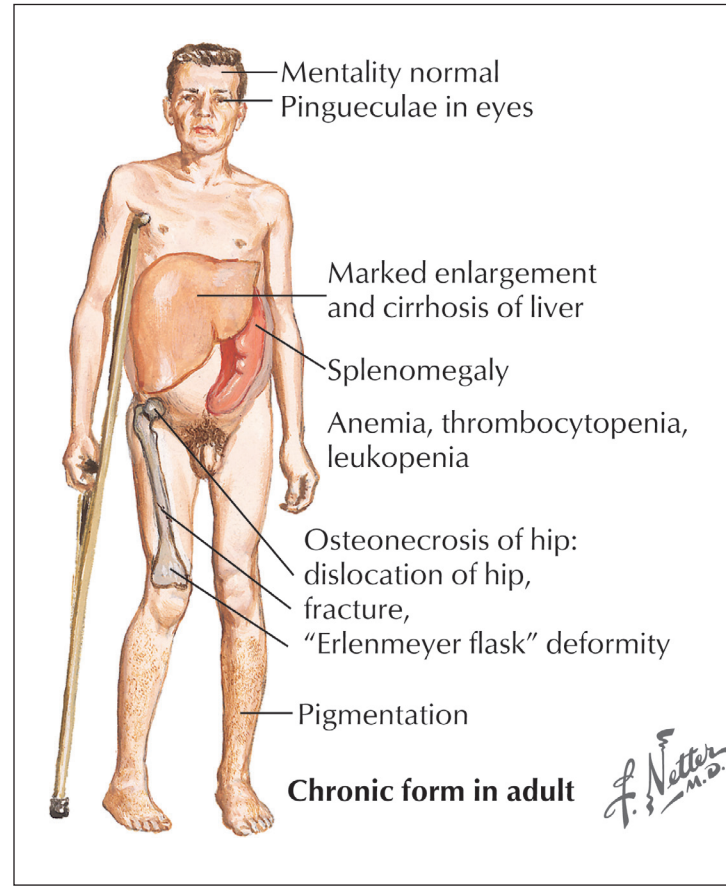
As an autosomal recessive condition requiring both parents to be carriers, Gaucher disease is rare; to appropriately include Gaucher disease in the differential diagnosis of affected patients, health care providers must familiarize themselves with its epidemiologic and clinical characteristics. This article discusses the epidemiology and pathophysiology of Gaucher disease, as well as recent advances in Gaucher disease screening, diagnosis, and management. It further underscores the important role of nurses in providing counsel and support to affected patients and their families throughout the diagnostic and treatment phases of care.

EPIDEMIOLOGY OF GAUCHER DISEASE

Gaucher disease is the most common of the lysosomal storage disorders (LSDs), which are metabolic conditions caused by genetic defects in the lysosomal system. The lysosome is an internal cell structure that contains numerous enzymes responsible for degrading complex cellular components. LSDs result from the absence or deficiency of a lysosomal enzyme and the subsequent accumulation of the enzyme's particular substrate in the body. The incidence of LSDs is estimated to range from one in 5,000 to one in 7,000 live births.[1] Worldwide, Gaucher disease has a prevalence estimated to range from one in 40,000 to one in 60,000 in the general population and, though it is a panethnic disorder, in the Ashkenazi Jewish population its frequency is markedly higher, ranging from one in 400 to one in 1,000 live births.[2] Carrier frequency in those of Ashkenazi descent is estimated to be as high as one in 18.[3]

GAUCHER DISEASE PATHOPHYSIOLOGY

An inherited autosomal recessive disorder, Gaucher disease is caused by mutations in the *GBA* gene, which encodes the lysosomal enzyme acid β-glucocerebrosidase (GCase).[4] This means that affected individuals inherited nonworking copies of the *GBA* gene from both parents (see Figure 1). Deficiency or absence of GCase in individuals with Gaucher disease disrupts the breakdown of the lipid glucocerebroside, which causes it to accumulate in the lysosomes.[2,5] These lipid-laden cells, which are found predominately in the spleen, liver, bone marrow, and bone tissue, are the catalyst for the widespread, multisystemic symptoms of the disease.[2,6] While such organ involvement occurs in all cases of Gaucher disease, the severity of involvement and the rate of progression are multifactorial and highly variable, influenced by the type of mutation as well as environmental factors.[7]



The genetic mutations that cause Gaucher disease result in widespread damage affecting multiple organ systems.

Massive hepatosplenomegaly, presenting as abdominal distention or pain, may result from the accumulation of glucocerebroside in the cells of the liver and spleen. Patients may report early satiety, bloating, and episodes of nausea or vomiting. Spleen enlargement is typically greater than liver enlargement and is often reflective of disease severity. According to data collected in the International Collaborative Gaucher Group (ICGG) Gaucher Registry, about 30% of patients have a splenic volume greater than 15 multiples of normal and approximately 55% have volumes that are five to 15 multiples of normal.[8]

Cytopenia also occurs as a result of displacement of healthy red bone marrow by lipid-filled Gaucher cells. The resulting anemia can cause fatigue. Thrombocytopenia can present in early childhood as easy bruising, epistaxis, and excessive bleeding after trauma or surgery.[9]

The skeletal manifestations of Gaucher disease are often the most debilitating, yet the pathogenesis

of bone changes are not fully understood.[2] Between 70% and 100% of patients with type 1 Gaucher disease have clinical or radiographic evidence of bone disease.[3] Irreversible complications may influence long-term mobility and quality of life. The spine, pelvis, and femurs are usually affected; several different mechanisms of bone injury have been identified.[2] The displacement of yellow marrow with red marrow because of Gaucher cell infiltration produces both physical and biochemical changes in the bone marrow microenvironment that can affect bone marrow vascularity and pressure, potentially causing thrombosis, infarction, and impaired hematopoiesis.[2]

Impaired growth. Gaucher cell marrow infiltration also leads to changes that can impair growth.[2] Using *z* scores generated from the growth charts of the Centers for Disease Control and Prevention and the ICGG Gaucher Registry, Kaplan and colleagues demonstrated that height for sex and age was in the lower fifth percentile for 34% of children with type 1 Gaucher disease at the time of diagnosis.[10,11] Reduced bone density, which is seen in approximately 20% of patients at diagnosis, puts patients at elevated risk for fractures. The mechanism to which osteopenia is attributed is osteoblastic dysfunction caused by accumulation of the lipid glucocerebroside.[2] As a result of bone remodeling abnormalities, about 40% of patients develop the Erlenmeyer flask deformity, which is a widening of the distal femur, creating an Erlenmeyer flask–like appearance.[8]

Acute bone crises present as a sudden onset of severe localized pain with swelling, tenderness, and erythema, often accompanied by fever, leukocytosis, and elevated erythrocyte sedimentation rate. When osteomyelitis occurs in Gaucher disease, it is usually aseptic, though it's difficult to exclude pyogenic osteomyelitis at onset. Eventually, negative blood cultures allow clinicians to differentiate aseptic from pyogenic osteomyelitis.[2] While it is impossible to predict major bone complications in patients with Gaucher disease, risk factors include anemia and splenectomy.[12] In untreated patients, bone crises are reported to occur in 55% of splenectomized patients and 22% of patients with an intact spleen.[13] Osteonecrosis is irreversible and often precipitates fracture and joint collapse.[2]

Central nervous system involvement in Gaucher disease is rare, with an estimated incidence of less than one in 100,000 live births.[14] Patients with the neurologic forms have specific mutations in the gene that drastically reduces GCase activity. Studies suggest that in the absence of this enzyme, neuroinflammation, neuronal dysfunction, and cell death occur.[15]

DISEASE CLASSIFICATION

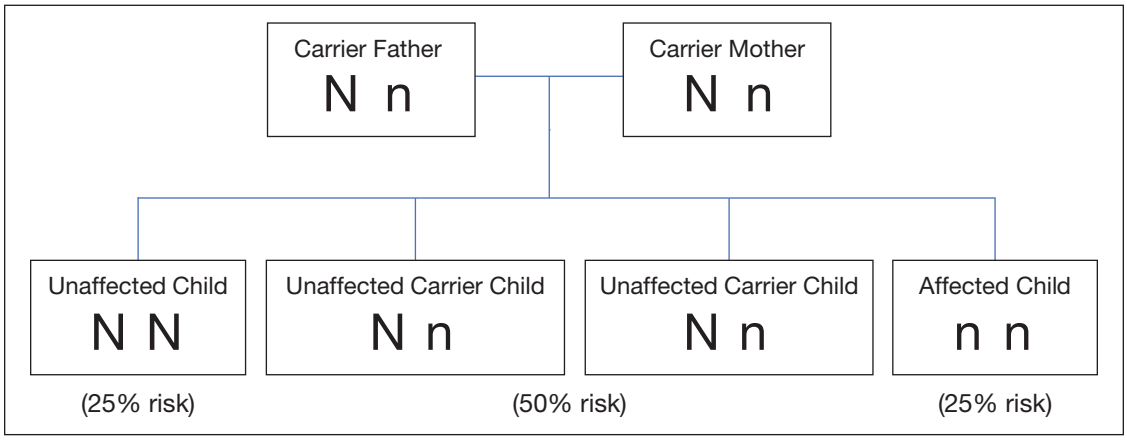
Gaucher disease manifests along a continuum and is classified clinically into three phenotypes based on the absence or presence of neurologic disease and the rate of disease progression.[12] Type 1 Gaucher disease primarily involves the visceral organs—the liver, spleen, and bone marrow—and is defined by the lack of central nervous system involvement; types 2 and 3 represent the neuronopathic forms of the disease (see Table 1). Type 1 Gaucher disease accounts for approximately 94% of diagnoses in the Western hemisphere.[14]

Type 1 is often considered the "mild" form of Gaucher disease. Onset and severity are highly variable. The majority of patients with type 1 Gaucher disease develop symptoms in the first or second decade; others remain asymptomatic well into adulthood with onset as late as the fifth to eighth decade.[8]

Types 2 and 3. Neuronopathic Gaucher disease is divided into types 2 and 3, though it exists as a phenotypic continuum, with manifestations ranging from mild oculomotor abnormalities to hydrops fetalis (in which the fetus or newborn develops an abnormal fluid buildup under the skin or in the tissue surrounding the lungs, heart, or abdomen).[16]

Type 2 has a very predictable phenotype with severe visceral involvement and neurologic disease

Figure 1. Autosomal Recessive Inheritance



presenting in early infancy and progressing rapidly until death by age two.[9,15] Early neurologic signs, such as hypertonia, irritability, and supranuclear gaze palsy (loss of the ability to look in a particular direction), arise from brain stem dysfunction.[14] Other manifestations include microcephaly, myoclonic jerks, seizures, and profound developmental delays. Brain stem deterioration is rapid, with death occurring as a result of aspiration and respiratory compromise.[14]

Type 3, considered the chronic neurologic form, follows a less predictable course than type 2. Some patients with type 3 may have generalized or myoclonic seizures, whereas in others the only neurologic manifestation is slowed saccadic (discontinuous or sporadic) eye movements.[14] Patients with type 3 Gaucher disease typically develop visceral manifestations, including moderate to severe hepatosplenomegaly, before age two, and about half will have their first neurologic finding by this age as well.[8] Neurologic progression is slow, and life span extends into the fourth or fifth decade.[9]

DIAGNOSIS OF GAUCHER DISEASE

It is often challenging to diagnose Gaucher disease, as it affects multiple tissues and organs, producing many symptoms that are common to other disorders as well. Patients with type 1 Gaucher disease are often misdiagnosed with hematologic malignancies or liver disease. In a single-center retrospective review of 86 patients with type 1 disease, almost 19% reported a diagnostic delay of at least five years.[17] This can lead to unnecessary invasive medical procedures such as bone marrow or liver biopsies as was described in the opening scenario. Delayed diagnosis increases the risk of complications, such as avascular necrosis and fractures.

The gold standard diagnostic assay for Gaucher disease measures GCase activity in peripheral blood leukocytes, confirmed by molecular analysis. In patients with Gaucher disease, enzyme activity is typically 0% to 15% of normal.[9] Health care providers need to be aware of the availability and relative ease of this diagnostic method in order to advocate for patients who are manifesting symptoms but remain undiagnosed. Measuring GCase activity should be considered first-line testing for any patient of Ashkenazi origin presenting with splenomegaly; for patients not of Ashkenazi origin in whom two or more manifestations of Gaucher disease are evident, Gaucher enzyme testing should be considered after malignancies have been ruled out.[18] (See *Diagnosing Gaucher Disease*.[18])

Enzyme testing for carrier detection is unreliable and not recommended. Carriers often have reduced enzyme activity at levels between those of unaffected and affected individuals, but they may also have normal enzyme activity. The level of enzyme activity does not reliably distinguish between disease types or correlate with disease severity.[9]

Table 1. Comparison of Gaucher Subtypes

Clinical Features	Type 1	Type 2	Type 3
Age of onset	Childhood/ adulthood	Infancy	Childhood/ adolescence
Clinical variability	High	Minimal	High
Bone disease	Mild to severe	Absent	Mild to very severe
Hepatosplenomegaly	Mild to severe	Mild to severe	Mild to very severe
Neurodegeneration	Absent	Very severe	Mild to severe
Life expectancy	Normal/ near normal	2 years of age	Middle adulthood

Adapted with permission from Grabowski GA. *Lancet* 2008;372(9645):1263-71.

NEWBORN SCREENING

The development of a newborn screening test for GCase activity using dried blood spot specimens marked a milestone in the crusade to reduce Gaucher patients' diagnostic odysseys. At this writing, the screening test is available in all hospitals in Illinois, Missouri, Tennessee, and Pennsylvania, and in select hospitals in New York. Nursing responsibilities for these patients start with screening and diagnosis. Primary care and acute care nurses who are involved in specimen collection or result disclosure must familiarize themselves with their state's newborn screening panel and practitioner manual. (To learn what conditions are included in your state's panel, visit http://genes-r-us.uthscsa.edu/resources/consumer/statemap.htm or www.babysfirsttest.org/#.)

Diagnosis of Gaucher disease through newborn screening reduces unnecessary, invasive testing and delayed diagnosis, allowing for early intervention, which may provide significant improvements in patient outcomes. As a progressive condition, if Gaucher disease is undiagnosed for an extensive period in a mildly affected patient or for a short period in a severely affected patient, irreversible damage may occur.[19] Since Gaucher disease is a genetic condition, identifying affected patients shortly after birth also allows other at-risk family members, such as older siblings, to be identified.

NURSING IMPLICATIONS FOR SCREENING AND DIAGNOSIS

Nurses need to consider the psychosocial implications of early diagnosis in patients at risk for Gaucher disease. There is no cure and the impact of having a lifelong, chronic condition can be overwhelming for both patients and their families. While the future holds great promise for a cure for this disease, curative therapies have yet to be developed.

Monitoring psychosocial effects. Nurses are ideally positioned to assess the risks and benefits of a

Gaucher diagnosis and monitor the subsequent psychosocial effects, particularly anxiety and distress, on patients and family members. While early diagnosis may eliminate the distress of a delayed diagnosis, concerns about the future persist. It is vital to assess both the patient's and the family's coping capacity.

Ethical issues. The addition of LSDs to newborn screening panels has raised multiple ethical issues. Newborn screening identifies the presence or absence of Gaucher disease, but does not distinguish among phenotypes. Since all *GBA* mutations have not been clearly associated with a particular type of Gaucher disease, health care providers are challenged in communicating genetic testing results to families with a newborn who has screened positive for Gaucher disease. The prognosis for a newborn who ultimately develops type 1 is vastly different from that of one who goes on to develop the neuropathic manifestations of type 2 or 3, as there is no treatment for the neurologic involvement seen in the latter types of Gaucher disease. Children with type 1, who may be mildly affected or asymptomatic, essentially become "patients in waiting," given the unclear genotype–phenotype correlation and our inability to predict clinical disease course by genetic mutation. Although those with a neuronopathic form of the disease may obtain a diagnosis of Gaucher disease as newborns, their prognosis will not be apparent until later in life and cannot be altered by current available therapies, especially if they have type 2.

Effective management of Gaucher disease requires a multidisciplinary team approach, which in addition to medical and nursing specialists often includes social workers, genetic counselors, and physical and occupational therapists. Once a diagnosis has been made, collaboration between the patient's family and members of the interdisciplinary care team is essential. Nurses not only provide support to cope with the diagnosis but help patients and family members understand and carry out the plan of care.

TREATMENT AVAILABILITY

Although early treatment provides a clear benefit in slowing nonneuronopathic disease progression, often with nearly complete resolution of disease-related symptoms,[13] there are currently no widely accepted standardized treatment guidelines for Gaucher disease. Currently, two types of therapy are approved by the U.S. Food and Drug Administration (FDA) for the treatment of type 1 Gaucher disease: enzyme replacement therapy, which breaks down glucocerebroside, and substrate reduction therapy, which partially blocks the body from producing this lipid. Although treatment is costly and requires prior authorization, given the extensive evidence of treatment efficacy on nonneuronopathic symptoms, most insurance plans will cover treatment costs for type 1 and often for types 2 and 3, though it may require more work on the part of the prescriber—submitting letters of medical necessity and appealing denials. When coverage is denied, patients can often receive help covering costs through programs sponsored by the drug manufacturers or through the National Organization for Rare Disorders (NORD). To investigate NORD's patient assistance programs, visit https://rarediseases.org/for-patients-and-families/help-access-medications/patient-assistance-programs-2.

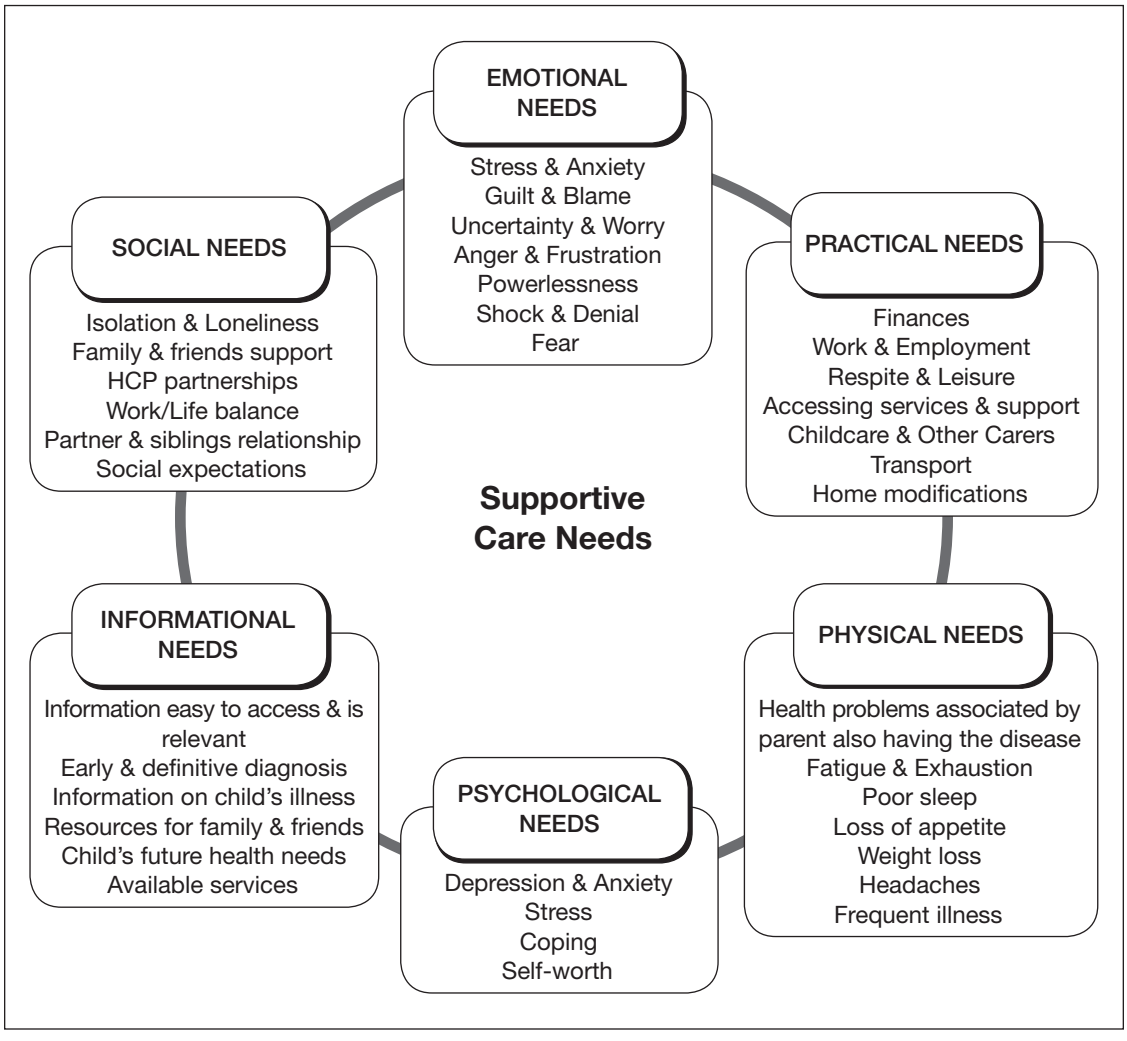
Enzyme replacement therapy for the treatment of Gaucher disease became available in 1991 with the development of alglucerase (a placenta-derived GCase). Today, however, treatment involves the IV infusion of recombinant GCase enzyme, which breaks down the accumulating lipid. Infusions are administered every two weeks. Three FDA-approved enzyme replacement therapies are currently available in the United States: imiglucerase (Cerezyme), velaglucerase alfa (Vpriv), and taliglucerase alfa (Elelyso). Enzyme replacement therapy has been shown to reduce the incidence of hepatosplenomegaly, normalize hematologic values, and improve osteopenia.[20] Risks of treatment include infusion reactions and antibody formation, which has the potential to render the drug inactive.[20] Immunoglobulin G antibodies should be monitored routinely during the first year following diagnosis, with a baseline blood sample drawn before the patient's first infusion and blood draws repeated every three to six months. If antibody production is high, there is a risk of anaphylaxis.[20] Overall, infusions are well tolerated, with the most common adverse effects being hypersensitivity reactions, which can be managed effectively with antihistamine premedication.[5]

Infusion nurses play a critical role in providing routine patient assessment throughout infusion sessions. For patients who are transitioned to home therapy, the role of the nurse is even greater as she or he is the sole health care provider in regular communication with the patient. Infusions are given over a one-to-two-hour period every other week and treatment is required for life. Infusion nurses thus have an opportunity to develop strong therapeutic relationships with patients and their families and to identify unmet care needs over the long term.

Diagnosing Gaucher Disease[18]

Gaucher disease should be considered in the differential diagnosis of
- any patient of Ashkenazi descent who presents with splenomegaly
- any patient not of Ashkenazi origin with two or more of the following manifestations after malignancies have been ruled out:
  - hepatosplenomegaly
  - hematologic abnormalities
  - characteristic bone lesions or bone pain
  - signs of central nervous system involvement

Figure 2. The Supportive Care Framework



HCP = health care professional.
Reprinted with permission from Pelentsov LJ, et al. *Disabil Health J* 2015;8(4):475-91.[22]

Use in types 2 and 3 Gaucher disease. Since the enzymes used in this type of therapy cannot cross the blood–brain barrier, enzyme replacement therapy can help treat only the visceral organ involvement of patients affected by neurologic forms of Gaucher disease; there is no treatment for the progressive neurologic degeneration associated with types 2 or 3. This does not, however, negate the value of enzyme replacement therapy in enhancing quality of life in type 3 disease through reduction of organ size and improvement of hematologic parameters.[13] In deciding to initiate enzyme replacement therapy in patients with type 2 Gaucher disease, parents need to weigh the quality of life benefits against the treatment burden, given the inability of treatment to slow disease progression or affect type 2 prognosis. It is critical that palliative care be initiated as soon as type 2 Gaucher disease is diagnosed. Both supportive and end-of-life care are important aspects of nursing management in type 2 Gaucher disease.

Substrate reduction therapy is taken orally with frequency determined by the patient's cytochrome P-450 metabolizer status. The therapy contains a glucocerebroside synthase inhibitor, which reduces production and storage of the lipid glucocerebroside. Two FDA-approved substrate reduction therapies are currently available in the United States: eliglustat (Cerdelga) and miglustat (Zavesca). This therapy is contraindicated in ultrarapid metabolizers because the swift breakdown of the drug may prohibit it from reaching therapeutic levels. Overall, substrate reduction therapy is well tolerated. The most common adverse effects are fatigue, headache, nausea, diarrhea, and arthralgias.[20] Like its predecessor enzyme replacement therapy, substrate reduction therapy effectively reduces nonneuronopathic symptoms

in type 1 Gaucher disease, as was demonstrated in an 18-month, phase 3, placebo-controlled trial that enrolled 38 adults with type 1 Gaucher disease.[21]

SUPPORTIVE CARE

In caring for patients with Gaucher disease, nurses can help shape the supportive care framework, which must address the social, emotional, practical, informational, psychological, and physical needs of the patient and family.[22] (See Figure 2.[22]) In a qualitative study exploring the supportive care needs of parents who have a child with a rare disease, the identified needs focused on three major themes: social isolation, perceived lack of provider knowledge, and impact on family relationships.[23]

Social isolation. Parents often report difficulty in maintaining social relationships. This was reported more often by families who identified themselves as social people prior to their child's diagnosis. Parents reported that their lives were vastly different from those of their family and friends, a perception that exacerbated their feelings of isolation.[23]

Perceived lack of provider knowledge. Given the rarity of their child's condition, many parents felt that health care providers did not have sufficient experience in caring for someone with their child's diagnosis. This often put family members in the position of acting as experts on their child's illness.[23] Well-informed nurses can lighten this burden for families and become advocates for the patient's care.

Impact on family relationships. The sick child has a tremendous impact on family relationships, especially the relationship between the parents.[23] Acknowledging this potential issue enables nurses to identify tools that may help alleviate the stress of families with children who have Gaucher disease. Nurses can listen to patients and their family members, validate their concerns, and help them feel connected by informing them of resources such as support groups and conferences. And with the consent of all parties, they may help families connect with similarly affected families within their practice.

For more information on Gaucher disease, clinical trials, or LSDs, visit the following websites:

- National Gaucher Foundation (www.gaucherdisease.org)
- ICGG Gaucher Registry (https://clinicaltrials.gov/ct2/show/NCT00358943)
- NORD (https://rarediseases.org) ▼

For nine additional continuing nursing education activities on the topic of genetic diseases, go to www.nursingcenter.com/ce.

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