Clinical Practice Guidelines

Gaucher Disease

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INTRODUCTION

The AccordantCare™ program works with health plans to assess, monitor, and support those with certain complex, chronic conditions. The focus of the program is to improve health outcomes and prevent or limit disease-related complications. AccordantCare offers unique services at no additional charge to the patients, putting them in a strong position to adhere to their treatment plan.

There are several ways AccordantCare augments physicians' efforts. Through regular telephone contact, AccordantCare nurses:

- Keep patients informed about the disease process
- Coach patients in self-motivation and self-care skills
- Encourage patients to alert their physician when new symptoms arise
- Direct patients to resources that help pay for medication, transportation, home modifications, etc.
- Ensure preventive and screening measures are accomplished
- Provide emotional support to patients and caregivers
- Screen for depression
- Find local support groups

We invite physicians to make use of the services offered by AccordantCare and to suggest ways we can further patients' treatment goals. To offer feedback, get more information, ask questions, or voice concerns, call toll-free 1-800-948-2497 to speak with a program representative from 8 a.m. to 9 p.m., Monday through Thursday, and from 8 a.m. to 5 p.m. on Friday, Eastern Time. Messages left after hours will be returned the next business day.

Intent of Guidelines

The purpose of this Clinical Practice Guidelines is to describe current patterns of practice where there is no fully established national guideline for diagnosis and management. It is not meant to dictate care of patients. Decisions about care are made by the physician and the patient based on the individual needs of that patient.

A patient's healthcare plan may or may not pay for the all medicines, tests, equipment, or services mentioned in this document. Benefits should be checked with the individual's healthcare plan to assure payment.

DISEASE OVERVIEW

Definition of Gaucher Disease

Gaucher disease is the most prevalent disorder of a family of about 40 different genetic diseases called lysosomal storage disorders.[1] There is variability in the presentation of this inherited metabolic disorder, from being asymptomatic throughout life to being a rare perinatal lethal disorder.[2] [3] Prior to the initiation of

enzyme replacement therapy (ERT) in the 1990s, Gaucher disease was often progressive and debilitating, and occasionally life-threatening, but treatment has ameliorated the symptoms and reversed the progression.

Gaucher disease can result when an individual inherits an autosomal recessive mutation in the *GBA* gene that encodes the enzyme glucocerebrosidase, also known as acid β-glucosidase.[2 4] Glucocerebrosidase is a lysosomal enzyme that breaks down the substrate glucosylceramide.[2] In individuals with this mutated *GBA* gene, a deficiency of glucocerebrosidase leads to an accumulation of glucosylceramide in the lysosomal compartments of macrophages and other cells.[5] The enlarged cells containing undigested glucosylceramide are considered to be a hallmark of this disease and are commonly called Gaucher cells.[4,6]

Gaucher disease is a multisystem disease because Gaucher cells often infiltrate many body systems including the spleen, liver, bone marrow, and skeleton.[4] They may also collect in other tissues, including in the lungs, kidney, skin, eyes, lymphatic system, heart, and rarely in the nervous system and brain. Tissues and organs that contain large numbers of Gaucher cells become enlarged and stop functioning properly.[6]

Gaucher disease was the first lysosomal storage disorder for which a successful treatment was developed.[5] Currently, mainline treatments include enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). Supportive care may include:

- transfusion of blood products for severe anemia and bleeding;
- analgesics for bone pain;
- joint replacement surgery for restoration of function; and
- oral bisphosphonates and calcium for osteopenia.

When possible, management by a multidisciplinary team at a Comprehensive Gaucher Center is advised.[2]

Prevalence of Disease

The prevalence of Gaucher disease is about 1 in 40,000 worldwide,[7] with about over 10,000 people having the disease.[8]

The overall incidence of Gaucher disease in the general population is about 1 in 50,000 to 1 in 100,000.[9] Type 1 Gaucher disease is by far the most common,[10] accounting for 95% of cases.[11] The incidence of type 2 Gaucher disease is about 1 in 100,000 live births.[1,12] And the incidence of type 3 Gaucher disease is about 2 in 100,000 live births.[1,12]

Gaucher disease affects men and women equally.[6] About half the cases of Gaucher disease are diagnosed before the age of 10 years[13]; of these, about two-thirds are diagnosed before the age of five.[14]

Classification of Disease

Gaucher disease is one of 40 or so lysosomal storage disorders, a family of genetic diseases that involve an enzyme deficiency, impaired receptor, or other defect in lysosomal function.[15] Most of these diseases are rare, but as a group their incidence is about 1 in 1,500 to 1 in 7,000 live births.[16]

Traditional Classifications of Gaucher Disease

Traditionally, doctors have classified Gaucher disease into three main phenotypes based on the amount of CNS (central nervous system) involvement and the patient's age at disease onset.[5] The three main classifications of Gaucher disease are[17]:

Type 1: Nonneuronopathic disease
Type 2: Fulminant or acute neuronopathic disease that is fatal during infancy
Type 3: Chronic neuronopathic disease that usually results in death during adolesence or early adult life

Subtypes of Gaucher Disease

Additional phenotypic categories may be recognized within these three broad groups.[2,17] For example, a perinatal, lethal subtype of type 2 disease presents with pyramidal signs, fish-like or collodion skin changes, and nonimmune hydrops fetalis[2] (an abnormal accumulation of serous fluid in two or more fetal compartments).

Some doctors recognize three subtypes of type 3 disease[9]:

- Subtype 3a: progressive neurologic disease dominated by myoclonus and dementia;
- Subtype 3b: neurological manifestations largely limited to horizontal supranuclear gaze palsy and cognitive decline during adolescence, with aggressive visceral and skeletal disease, and commonly associated with lung involvement;
- Subtype 3c: neurological manifestations largely limited to horizontal supranuclear gaze palsy, with mild visceral involvement, and progressive calcification of the mitral and aortic valves.[2]

Since some of the distinctions between the types are not absolute, Gaucher disease is best understood as a broad, continuing spectrum of clinical presentations that extend from birth through the newborn period into adulthood.[18,19] However, its classification into three general types is still useful for prognosis and management.[2]

DIAGNOSIS OF DISEASE

Clinical History & Examination

Clinical findings alone are not diagnostic of Gaucher disease,[2] but its diagnosis by enzyme testing is unequivocal. However, the rarity of Gaucher disease and the nonspecific and heterogeneous nature of its symptoms may delay its consideration by the clinician.[17] Even though Gaucher disease may be challenging to diagnose, prompt diagnosis before the occurrence of irreversible complications is critical to the Gaucher disease management model.[17]

Because the early symptoms of type 1 Gaucher disease tend to reflect the hematological aspects of the disease, patients are most likely to be referred to hematologists for diagnosis and management. However, many patients with Gaucher disease do not present with the classical symptoms and are virtually asymptomatic.[9] Because Gaucher disease can be present with no (except for a deficiency of glucocerebrosidase) signs and symptoms, or with any of a spectrum of signs and symptoms,[19] the disorder may take extended time to diagnose. One study found that the average time taken to diagnose type 1 Gaucher disease was 48 months.[20]

Signs and Symptoms

Other than a deficiency of glucocerebrosidase, no one sign or symptom is obligatory at any time. In general, the clinical presentation of all three types of Gaucher disease can involve one or a combination of the following.[5]

- Enlarged spleen
- Enlarged liver
- Deformed and broken bones

The division of Gaucher disease into three clinical types based on the signs and symptoms of each[12] is straightforward based on a clinical finding of nonneuronopathic disease (type 1) or nervous system involvement (types 2 and 3).[21]

Tests for Disease

The most efficient and reliable[2] biochemical test to diagnose Gaucher disease measures the amount of glucocerebrosidase activity in peripheral blood leucocytes,[14,22] fibroblasts,[14] or other nucleated cells.[14] A typical adult with Gaucher disease will have 0% to 15% of the normal glucocerebrosidase activity.[2] Activity for other lysosomal enzymes will usually measure within the normal range.[12]

Since the results of testing for glucocerebrosidase activity are not reliable predictors of disease type, severity, or carrier status,[2] doctors frequently perform a targeted mutation analysis for the four common Gaucher mutations and for other rarer mutations.[2] While it should not be used for diagnosis in lieu of

biochemical testing,[2] identifying the genotype is an important part of confirming the diagnosis[12] and can be helpful in defining the class, severity, and prognosis of Gaucher disease.[22] In addition, doctors may perform a sequence analysis of the *GBA* coding region, bone marrow examination, serum protein tests for various biomarkers, and serum protein electrophoresis and an immunoglobulin profile.

For patients considering treatment with the SRT eliglustat (Cerdelga®), use an FDA-cleared test to determine the *CYP2D6* genotype, whether the patient is an CYP2D6

- ultra-rapid metabolizer;
- extensive metabolizer;
- intermediate metabolizer; or
- poor metabolizer.[23]

APPROACH TO MANAGEMENT OF PRIMARY CONDITION

Summary of General Management

Currently there are several treatment options available to patients with Gaucher disease including enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). Because of its variable and systemic symptoms, Gaucher disease requires an individualized approach to treatment.[4] Each individualized treatment plan should consider the patient's quality of life needs as well as his or her signs and symptoms of disease.[4]

Once a diagnosis of Gaucher disease is confirmed, the focus should be on performing a comprehensive evaluation of all the patient's specific body systems (e.g., blood, spleen, bone) to[17]

- establish baseline disease characteristics,
- determine the patient's treatment needs, and
- develop an individualized plan for treatment goals and monitoring.

Goals of Treatment

The aim of treating Gaucher disease is to achieve and maintain the specific goals for treating all the affected body systems using the most appropriate type and dose of therapy.[24] Treatment of Gaucher disease is usually a life-long process.[4] Thus, maintaining therapeutic goals requires ongoing patient cooperation and assessment.[4]

An important step involves regular, systematic monitoring of all aspects of the disease as recommended by the International Collaborative Gaucher Group.[24] This systematic checking allows doctors to determine whether the goals are achieved or not.[24] The treatment plan is considered successful only when all goals are achieved and maintained.[24]

Therapies for Treating Gaucher Disease

Three ERT products, which are all recombinant enzymes manufactured in a laboratory—

- imiglucerase (Cerezyme®),
- velalglucerase alfa (Vpriv®), and
- taliglucerase alfa (Elelyso™)

and two SRT products—

- miglustat (Zavesca®) and
- eliglustat (Cerdelga®)—

are currently FDA approved to treat patients with Gaucher disease.[25-29]

Many Gaucher patients also require adjunctive treatment for pain relief and osteopenia.[4] Others need physical therapy for skeletal complications.[4] Still others need specific therapy for pulmonary hypertension.[4]

PREVENTION AND MANAGEMENT OF COMPLICATIONS

Accordant helps patients prevent and manage complications by teaching them early warning signs, encouraging adherence to treatment plans, offering supportive care, and recommending physician contact when needed. The goals and cooperative interventions below do not represent a comprehensive list of complications but reflects some of the more common clinical situations specific to the disease. General health topics (e.g., age-appropriate cancer screening) are beyond the scope of this document.

Goal: Promote Healthy Behavior

Cooperative interventions

- Provide educational resources that promote proper nutrition and exercise programs that help to prevent obesity and comorbid conditions such as osteoporosis.
- Encourage patients not to smoke and provide information and education on resources that help patients to stop smoking.
- Encourage flu vaccination/pneumococcal vaccination, unless contraindicated, to high-risk patients with disease.

Goal: Promote Self-Management of Condition

Cooperative interventions:

- Inform patients that a program nurse is available for incoming calls 24 hours a day.
- Educate patients on their treatment options, benefits, risks, and side effects, to enhance adherence through informed decision making.
- Educate patients regarding the signs, symptoms and prevention of the complications of Gaucher disease.
- Educate and support the patient's family and/or caregiver.

- Provide information on national and community-based Gaucher disease foundations and resources.
- Provide an approved list of educational materials and website listings with assessments and on an as-needed basis.

Goal: Stabilize Disease and Prevent Exacerbations
Cooperative interventions:

- Educate patients on the signs and symptoms of Gaucher disease and the specific complications they may encounter.
- Educate the patient/caregiver on the importance of obtaining genetic counseling.
- Encourage patients to follow the physician-prescribed treatment regimen and report any increase or worsening of symptoms to their physician immediately.
- Reinforce any skills needed to manage the disease.
- Educate the patient/caregiver on the value of imaging studies in measuring disease severity and adjusting the physician treatment plan.
- Encourage the patient's adherence with ERT or SRT, followed yearly or every other year (annually for symptomatic children[30]) with MRI or other imaging or laboratory studies.
- Monitor patients regularly and communicate to their physician a summary of reasons for nonadherence, if any, with the prescribed treatment plan.
- Communicate with the physician when there has been a change in a patient's clinical or functional status.

Goal: Prevent Complications Related to Hepatomegaly / Splenomegaly
Cooperative interventions:

- Educate the patient/caregiver on signs and symptoms of liver and spleen involvement and when to notify the physician.
- Establish if the patient has had a splenectomy and educate regarding vaccinations for *pneumococcus*, *haemophilus influenza* (HIB), and *meningococcus*, ideally administered prior to splenectomy.

Goal: Prevent and/or Monitor Bone Complications
Cooperative interventions:

- Educate the patient/caregiver on signs and symptoms of bone involvement and when to see the physician.
- Establish if the patient has had any broken bones, bone crisis, or bone infections in the last three months and educate the patient/caregiver on the signs and symptoms associated with each; emphasize to patients the importance of reporting the signs and symptoms of bone disease to their physician immediately.
- Coordinate any patient needs for physical therapy/durable medical equipment and confer with the physician as needed.

Goal: Prevent Falls and Fractures
Cooperative interventions:

- Educate patients about the importance of treatment for osteoporosis, if indicated, and about the importance of adherence with medications for osteoporosis.
- Encourage adherence to any physician-approved weight-bearing exercise plan to promote bone strength and prevent osteoporosis and stress fractures.

Goal: Promote Behavior to Ensure Medication Safety
Cooperative interventions:

- Educate patients about their medication, its dosing, potential side effects and interactions.
- Monitor patients for drug-to-drug interactions and inform physician of any medication errors or unreported side effects.
- Monitor patient adherence with all appropriate laboratory evaluations.
- Encourage patients to carry all prescription and over-the-counter (OTC) medications to physician visits.

Goal: Promote Coping with Condition
Cooperative interventions:

- Evaluate the adequacy of the patients' support systems and work with physician, the patient, caregiver, family and health plan to correct any deficiencies.
- Assist the physician in detecting the patient's mood disturbances using a telephonic depression screening tool. Obtain the patient's consent to notify and provide his/her physician with screening results. Facilitate a corrective plan as approved by the patient and physician.
- Enhance the patient's access to support groups and encourage patient-physician communication.

PATIENT FOLLOW-UP

Ongoing follow-up with patients to evaluate their status is essential. For example, follow-up with the patient may be helpful after home safety evaluations, physical therapy, or the acquisition of new durable medical equipment. Accordant can work with the patient to coordinate referrals, community resources, and government services. We also can collaborate with other healthcare professionals on behalf of the patient.

Please inform Accordant of any issues that require monitoring or follow-up with your patient so that we may effectively communicate the specifics of the physician treatment plan.

Examples of ways that physicians can facilitate Accordant follow-up include:

- Encourage patients to work with Accordant for education, information, and self-care needs.
- Inform Accordant of the patient's unique educational needs or barriers to care so that we can supplement your activities.
- Communicate to Accordant the physician-driven treatment plan or referral needs so that we can optimally support your activities.
  - Apprise Accordant of any issues that require monitoring or follow-up.
  - Communicate to Accordant any strategies to prevent injury or disease complications.
- Inform Accordant that a member is considering becoming pregnant or is pregnant.
- Communicate with Accordant throughout a member's pregnancy regarding the physician treatment plan, member adherence, and needed patient education.
- Inform Accordant of medications prescribed to the patient that require monitoring so that we can maximize patient adherence with the necessary testing.
- Communicate to Accordant the physician treatment plan for bone involvement, comfort measures, pain relief, and weight-bearing activities of your patient so that we may effectively communicate the specifics of the physician treatment plan.
- Communicate to Accordant any other activities that we can facilitate: for example, social worker evaluation, adult daycare services, transportation needs, assistance with obtaining drugs and supplies, etc.

PATIENT EDUCATION

List of approved websites:

The National Gaucher Foundation
http://www.gaucherdisease.org/

The National Institute of Neurological Disorders and Stroke
http://www.ninds.nih.gov/disorders/gauchers/gauchers.htm

The ICGG Gaucher Registry
https://www.registrynxt.com/Gaucher/Pages/RegistryNXTHome.aspx

The Gauchers Association
http://www.gaucher.org.uk/

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