Gaucher disease: Initial assessment, monitoring, and clinical course

INTRODUCTION — Gaucher disease (GD) is an inborn error of metabolism that affects the recycling of cellular glycolipids. GD is the most common lysosomal storage disease. Glucocerebroside (also called glucosylceramide) and several related compounds that ordinarily are degraded to glucose and lipid components accumulate within the lysosomes of cells. GD is categorized into three clinical types. The disease involves the visceral organs, bone marrow, and bone in all affected patients. Type 1 (MIM #230800) is the most common. It is distinguished from type 2 (MIM #230900) and type 3 (MIM #231000) by the lack of characteristic involvement of the central nervous system.

Additional resources for information about GD for patients and families are listed in the table (table 1). Guidelines for the evaluation and monitoring of children and adults with GD, based upon data from the International Collaborative Gaucher Group (ICGG) Registry, and published data from international consensus panels are incorporated into the discussion in this topic [1-3].

The initial assessment and routine monitoring of patients with GD will be discussed here. The pathogenesis, genetics, clinical manifestations, diagnosis, and treatment are discussed separately. (See "Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis" and "Gaucher disease: Treatment").

INITIAL ASSESSMENT — Treatment must be tailored to the individual patient, because of the variability in the manifestations, severity, and progression of GD. Thus, each patient should undergo a comprehensive initial assessment of all potentially affected organ systems [3]. A decision is made regarding whether enzyme replacement therapy is indicated after the extent of symptoms and rate of progression are established. Treatment is then individualized to achieve specific therapeutic goals (table 2A-8) [9]. (See "Gaucher disease: Treatment").

The initial assessment involves confirmation of deficiency of glucocerebrosidase (also known as glucosylceramidase or acid beta-glucosidase, GBA), genotyping, and a complete family medical history if these were not part of the diagnostic process [3]. (See "Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis", section on 'Diagnosis').

Other aspects of the initial assessment that should be repeated at regular intervals throughout life include (table 3A-B) [8]:

- Complete physical examination
- Measurement of hemoglobin and platelet count
- Measurement of biomarkers
- Radiologic assessment of visceral and skeletal involvement
- Assessment of pain and patient-reported quality of life

The frequency with which this assessment should be repeated depends upon the treatment status and whether therapeutic goals have been achieved (table 3A-B). In addition, reassessment should be performed when the dose of enzyme therapy is changed if significant complications develop [3]. (See "Gaucher disease: Treatment").

Family history — The family history should include [1,2,3]:

- Information about ethnicity and consanguinity
- Information about disease severity in parents and/or affected siblings
- Information regarding a history of blood transfusions, splenectomy, pathologic fractures, bone pain, dyspnea, and/or recurrent chest infections (which may indicate undiagnosed GD)
- A family history of pulmonary hypertension (increases the risk of severe pulmonary hypertension)
- Parental heights (for prediction of adult height in skeletally immature patients)

Examination — Physical examination can provide important information regarding the severity, rate of progression, and response to therapy [8]. Important aspects of the examination include [1,2,10]:

- General appearance, demeanor, mood, and affect
- Weight, height, and head circumference percentiles, plotted on growth charts standardized for age and sex (see "Measurement of growth in children")
- Examination of the skin for bruising, petechiae, pallor, and pigmentation
- Eye examination for pingueculae (small soft brownish patches of tissue on the sclerae, just beyond the iris) that are nonspecific findings, but commonly seen in adult GD patients

The eye examination should also include evaluation for strabismus and/or abnormal extracocular movements. Additional ophthalmologic evaluation for patients who lack an N370S allele and are at risk for neuropathic disease is discussed separately (see "Neurologic" below)

- Palpation of the abdomen for enlarged liver and/or spleen; measurement of abdominal girth (the abdominal examination is supplemental to the radiologic evaluation) (see Radiology evaluation below)
- Gait, range of motion, muscle strength, and bone tenderness
- Assessment of pubertal status (see "Normal puberty")
- Evaluation for developmental delay (in children)
- Examination of the spine for kyphosis (including gibbus deformity, a particular form of kyphosis with a sharp angulation) and scoliosis (image 1)

Neurologic — The presence of neurologic complications has important implications for prognosis and treatment and should be determined as soon as possible after diagnosis [1,2]. Thoracic neurologic examination is critical for detecting evidence of neuropathic disease in patients with suspect genotypes (ie, without an N370S allele) [10], neurologic symptoms, a sibling with proven neuropathic GD, and/or onset of severe systemic GD before two years of age [4].

Children should undergo a thorough neurologic examination at baseline (table 4) [4]. This should include:

- Neurologic examination, performed by a neurologist, preferably a pediatric neurologist
• Eye movement examination, preferably by an ophthalmologist since the signs of ocular involvement can be difficult to detect in young children

• Additional neuroophthalmologic investigation, including direct ophthalmoscopy or electrocoagulography

• Measurement of hearing (by otoacoustic emission audiometry [OAE]) in young children and pure tone-audiometry in older patients (see "Hearing impairment in children: Evaluation")

• Brain imaging, preferably with magnetic resonance imaging (MRI), electroencephalography, and diagnostic brainstem-evoked responses

• Neurocognitive testing, with widely available protocols (eg, Wechsler Intelligence Scale for Children-III), ideally performed when the patient is sufficiently healthy to permit meaningful assessment

Psychosocial — Assessment of the child's social and educational development may require the involvement of the child's school and teachers [Ⅱ]. Detailed psychometric assessments (eg, IQ testing) should be conducted for patients at risk for developing neuropathic disease. In addition, signs of depression should be noted.

Cardiopulmonary — Cardiopulmonary involvement is rare in children with type 1 GD, but should be excluded at baseline in symptomatic patients [Ⅲ]. Risk factors for severe pulmonary hypertension in patients with GD include mutations other than N370S, a family history of pulmonary hypertension, angiotensin converting enzyme I gene polymorphism, asplenia, and female sex [Ⅲ].

Evaluation in children may include chest radiograph, high-resolution CT thoracic imaging, echocardiogram, echoscopy, and pulmonary function tests (forced vital capacity and peak expiratory flow rates). In adults, pulmonary evaluation should include a Doppler echocardiogram to estimate right ventricular systolic pressure [Ⅱ,Ⅸ]. (See "Overview of pulmonary function testing in children", and "Overview of pulmonary hypertension in adults").

Laboratory evaluation — The initial laboratory evaluation should include measurement of hemoglobin concentration, platelet count, and biochemical markers (ie, chitotriosidase, angiotensin converting enzyme [ACE], tartrate-resistant acid phosphatase [TRAP], and/or high density lipoprotein [HDL]) (table 3A-B) [Ⅱ,12-15]. These biochemical markers can be used in monitoring disease progression. The absolute concentrations of these enzymes are not helpful, but serial increases may be an early indicator of clinical release and should prompt investigation of disease status and compliance with therapy [Ⅸ]. Other biomarkers are under investigation for use in diagnosis and prediction of severity. (See "Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis", section on "Laboratory findings").

Examples of biomarkers that may be of clinical use include the following:

• Chitotriosidase, a chitinase, is a marker of "alternative" type macrophage activation that is overexpressed by the Gaucher cell. Its activity is increased in patients with GD and decreases in response to enzyme replacement therapy in conjunction with other indicators of clinical response [Ⅱ,12,17]. Measurement of chitotriosidase is recommended at baseline and periodically during therapy [Ⅷ]. Activity of chitotriosidase is absent in six to eight percent of patients who have a mutation in the chitotriosidase gene [Ⅲ]; in such patients assessment of ACE or tartrate-resistant acid phosphatase (TRAP) can be substituted [Ⅲ].

• The chemokine CCL18 (pulmonary and activation-regulated chemokine, PARC) is another marker of alternatively activated macrophages that is elevated in Gaucher disease [Ⅸ,ⅱ]. Concentrations of this protein correlate with several aspects of visceral and bony disease severity and respond to enzyme treatment in a similar manner to chitotriosidase [Ⅱ,ⅹ].

• An increased ratio of 16:0-glucosylceramide to 16:0-faetocysylceramide and elevated plasma concentrations of lysosomal-associated membrane protein-1 (LAMP-1) and saposin C appear to be correlated with patient phenotype, but are generally used not clinically [Ⅲ].

Measurement of glucocerebrosidase and genotyping should be performed if these were not part of the diagnostic process. Serum electrophoresis should be obtained at baseline and every 12 to 25 months, particularly in patients who are older than 50 years (because of an increased risk of multiple myeloma) [Ⅲ]. Clonal gammopathies are frequent among GD patients and should be monitored [Ⅲ]. Additional studies are recommended to monitor for other associated features, including B12 and vitamin D deficiency, iron overload, autoimmune disease, and platelet dysfunction (table 3A-B). (See Additional evaluation below.)

Radiology evaluation—The initial radiology assessment should include various examinations to evaluate liver and spleen volume and the extent and severity of skeletal disease (see "Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis", section on "Radiologic findings") [Ⅰ,ⅱ,ⅳ]. These studies may be helpful in determining whether enzyme replacement therapy is indicated and include:

• Volumetric computed tomography (CT) or magnetic resonance imaging (MRI) of the liver and spleen to help determine severity of hepatosplenomegaly, evaluate for cirrhosis or hepatic or splenic fibrosis, and assess response to therapy. Some centers use abdominal sonography to measure organomegaly [Ⅲ]. CT should only be used if the other modalities are unavailable or contraindicated to minimize radiation exposure [Ⅲ,ⅹ].

• MRI of the femoral head and lumbar spine to detect bone marrow infiltration, bone infarction, bone crises, and osteonecrosis (coronal T1- and T2-weighted scan) [Ⅲ,ⅹ,ⅳ]. T1-weighted MRI is the most sensitive means of assessing marrow infiltration and T2-weighted MRI is the most sensitive method of detecting active bone infarcts. There are several systems to grade marrow infiltration in GD, among which the Bone Marrow Burden Score is most widely used [Ⅹ]. Bone marrow infiltration varies considerably from site to site within a patient [Ⅹ]. A nonhomogeneous pattern of bone marrow involvement (type B marrow morphology) and extensive marrow packing were associated with avascular necrosis of the femoral head in one study, suggesting that MRI may be a useful tool for identifying patients at high risk of this outcome [Ⅹ].

• Ischemia can be detected by technetium bisphosphonate bone scintigraphy early in the course of bone pain crises [Ⅹ].

• Assessment of the skeletal age in children (according to the method of Greulich and Pyle) to assess growth retardation [ⅰ,ⅱ].

• Antero-posterior view of the entire femora and lateral view of the spine [ⅳ]: skeletal disease can occur without symptoms, particularly compression fractures of the spine and femoral head [ⅳ]. These radiographs will provide information regarding old fracture—"transtrophic bone changes, osteopenia, and other bone changes, such as the Erlenmeyer flask deformity of long bones.

• Radiographs of other skeletal sites to which the patient refers symptoms.

• Dual energy X-ray absorptiometry (DEXA) of the lumbar spine and nondominant !—renal neck may be used to measure generalized osteopenia [ⅱ,ⅳ,ⅰⅳ], although age-specific normative data for children are limited [ⅳ].

Sedation may be necessary for younger children during MRI or CT scanning. The risk of sedation in these settings appears to be acceptably low when performed in accordance with published guidelines. As an example, in a series of 960 instances of pediatric sedation, there were no deaths or serious injuries when recommended procedures for conscious or deep sedation were followed [ⅲ]. Nevertheless, the requirement for sedation limits the general applicability of MRI for routine follow-up assessment.

Functional health and well-being — Children with GD are subject to the same psychosocial problems as any child with a chronic disease (anger, fear, insecurity, isolation) [ⅱ]. Visceromegaly, growth abnormalities, and delayed puberty may affect their body image and self-esteem. These feelings may be exacerbated by fatigue and restrictions on physical activity. Chronic pain, fatigue, and missed school may affect school performance [ⅳ]. (See "Psychosocial" above.)

Functional health and well-being can be assessed through a survey instrument such as the short form 36 Health Survey (SF-36), which is validated for individuals ≥14 years of age [ⅱ]. Higher scores are preferable. In adults, pulmonary evaluation should include a Doppler echocardiogram to estimate right ventricular systolic pressure [Ⅱ,Ⅸ]. (See "Overview of pulmonary function testing in children", and "Overview of pulmonary hypertension in adults").

The occurrence and severity of pain (using a recognized pain assessment tool) should be monitored at each visit [ⅳ]. The use of a recognized pain assessment tool is recommended [ⅳ]. In young children, pain severity may be assessed with a visual analogue scale, such as the faces pain scales [ⅲ,ⅳ]. (See "Evaluation and management of pain in children"; and "Evaluation of chronic pain in adults").
Information about GD for patients and families is available through the Gaucher Registry and other resources (Table 1).

ROUTINE MONITORING — Routine monitoring of disease activity should be performed in all patients. Consensus minimum recommendations for effective monitoring of patients are provided by the ICSSG [8]. Laboratory and imaging studies are performed at baseline and then at recommended intervals [1,38]. The schedule is individualized according to the patient’s clinical course, whether the patient is receiving treatment, and, if so, the response to therapy (Table 3A-B). In addition, reassessment is performed when the dose of enzyme therapy is changed or if significant complications develop [3]. (See "Gaucher disease: Treatment" and "Laboratory evaluation" above and "Radiology evaluation" above.)

Neurologic monitoring — Close neurologic monitoring is necessary for at-risk patients (ie, children without a c.1226A>G mutation or with an allele associated with neuropathic disease) [1,39]. Neurologic involvement is insidious in some patients, manifesting in late childhood or beyond [4].

Neurologic monitoring is reviewed in the table (Table 5) [1,4,40].

ADDITIONAL EVALUATION — Additional evaluation may be indicated in some patients at the time of the initial assessment and/or during the clinical course if they fail to achieve their therapeutic goals. Patients who are unable to achieve their therapeutic goals should undergo evaluation for confounding factors (eg, poor compliance with therapy, development of comorbid conditions, or development of neutralizing antibody). The additional evaluation varies depending upon the manifestation of interest or the goal that is not achieved.

Anemia — Additional evaluation for anemia may include measurement of iron, iron-binding capacity, vitamin B12, white blood cell count, and serum immunoelectrophoresis. The incidence of vitamin B12 deficiency is increased among Ashkenazi Jews in Israel [41]. In addition, a decline in hemoglobin concentration, whether acute or gradual, should prompt evaluation for blood loss [3]. (See "Approach to the child with anemia" and "Approach to the adult patient with anemia".)

Bleeding — Patients with a history of bleeding tendency at the time of diagnosis may require evaluation for a bleeding diathesis. Abnormalities of various coagulation factors and qualitative platelet deficits have been reported in Gaucher disease [5,42,43], and it may be useful to look for these abnormalities of coagulation at baseline [1,38]. Evaluation may include measure of prothrombin time (PT) and activated partial thromboplastin time (PTT). (See "Approach to the child with bleeding symptoms" and "Approach to the adult patient with a bleeding diathesis".)

Hepatomegaly — Evaluation of liver function is indicated in patients with marked hepatomegaly or portal hypertension. This evaluation may include assessment of exposure to alcohol, hepatotoxic medications, blood products, sexually transmitted viral pathogens, and intravenous drug use. Measurement of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), alkaline phosphatase, albumin, total protein, and total and direct bilirubin are routine in most clinical settings. Liver imaging by ultrasound (including Doppler assessment of portal blood flow) will determine whether gross scarring and/or portal hypertension is present. Additional CT and MR imaging and liver biopsy may be necessary to reveal evidence of fibrosis or iron overload [44].

Testing for viral hepatitis should be performed in patients who have a history of blood transfusion, intravenous or other parenteral illicit drug use, or who live in areas where infectious hepatitis is endemic [9]. (See "Epidemiology, transmission, and prevention of hepatitis B virus infection" and "Epidemiology and transmission of hepatitis C virus infection".)

Skeletal disease — Measurement of serum calcium, phosphorous, alkaline phosphatase, and concentrations of vitamin D and parathyroid hormone may be indicated to exclude other causes of bone disease. (See "Overview of rickets in children".)

Growth retardation — Most children with GD who have severe stunting of stature also have severe visceral involvement [45]. Thus, other causes of growth retardation should be evaluated in otherwise mildly affected children [46]. (See "Causes of short stature".)

CLINICAL COURSE — The clinical course and life expectancy of GD type 1 is variable [3]. Severity may vary among siblings, even identical twins [47]. The spectrum ranges from asymptomatic disease, discovered incidentally in elderly adults, to fulminant disease presenting in early childhood. The disease is usually progressive, but at different rates [48]. In general, the disease has rapid progression in severely affected children, but has a more insidious course in more mildly affected adults. Thus, any rapid deterioration in adults requires evaluation for other causes. Stabilization of GD complications over time has been reported in untreated adults [49], as has spontaneous regression of disease manifestations [50]. (See "Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis", section on "Type 1 (GD1)."

The estimated average life expectancy at birth for a patient with GD type 1 was 68 years, based upon data from the Gaucher Registry, compared with 77 years in the standard United States population. Splenectomized and non-splenectomized patients had a life expectancy of 64 years and 72 years, respectively [51].

Symptomatic patients may die prematurely from sequelae of splenomegaly, severe bone disease, bleeding complications, infection, liver failure, or severe pulmonary disease [52]. In addition, patients with GD appear to have an increased risk of hematologic malignancy and multiple myeloma [24,53,54]. Review of data from 2742 patients in the International Gaucher Registry (92 percent with type 1, 81 percent treated with enzyme replacement therapy (ERT), median age in the third decade) indicates that the overall risk of cancer, including general hematologic malignancies, is not increased compared with the expected rate of individuals of the same age and sex in the United States population (relative risk [RR] 0.79, 95% CI 0.7-0.96) [24]. However, the risk of multiple myeloma was increased (RR 5.9, 95% CI 2.9-10.8). All but one patient with multiple myeloma were older than 60 years. Multiple myeloma was reported in patients who had and had not been treated with ERT. (See "Clinical features, laboratory manifestations, and diagnosis of multiple myeloma".)

GD types 2 and 3 are the neuropathic forms. GD2 has the poorest prognosis of all types of GD. Patients have rapidly progressive neurologic deterioration and death usually occurs before the child reaches two years of age. The average age of death was 11.7 months in one review of 15 original cases along with published data on 104 patients [59]. GD type 3 usually is more severe and aggressive than GD1, but has a more variable course than GD2. (See "Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis", section on "Type 2 (GD2)" and "Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis", section on "Type 3 (GD3)."

PREGNANCY — Pregnancy can exacerbate the symptoms of Gaucher disease, particularly in women whose disease is not controlled by enzyme replacement therapy (ERT) [18]. The risks of bone crises peri-partum and hemorrhage postpartum are increased. There is an emerging consensus that there are benefits to continuation of ERT in pregnancy [1,4,40]. Women with GD can generally expect a good pregnancy outcome. A literature review found 24 citations between 1952 and 2001 describing 302 pregnancies in 190 untreated women [1,38]. The live birth rate was 87 percent. Postpartum bleeding was the most common serious complication (4 of 23 ERT treated patients and 4 of 43 untreated patients). Thus, these women should be considered at high risk, and blood and fresh frozen plasma should be available at delivery. (See "Overview of postpartum hemorrhage".)

SUMMARY

- Gaucher disease (GD) is caused by deficiency of glucocerebrosidase, which results in abnormal accumulation of glycolipids within cellular lysosomes. (See "Introduction" above.)
- Treatment must be tailored to the individual patient, because of the variability in the manifestations, severity, and progression of GD. Thus, each patient should undergo a comprehensive initial assessment of all potentially affected organ systems (Table 2A-B) [8]. (See "Initial assessment" above.)
- The presence of neurologic complications has important implications for prognosis and treatment and should be determined as soon as possible after diagnosis. Neuropathic disease can be excluded at the time of diagnosis through objective assessment of eye movements and audiologic testing. However, children should undergo a thorough neurologic evaluation at baseline if these specialized tests are not available. (See "Neurologic" above.)
- Routine monitoring of disease activity should be performed in all patients. The schedule is individualized according to the patient’s clinical course, whether the patient is receiving treatment, and, if so, the response to therapy (Table 3A-B). In addition, reassessment should be performed when the dose of enzyme therapy is changed or if significant complications develop [3]. (See "Routine monitoring" above and "Gaucher disease: Treatment".)
- Additional evaluation may be indicated in some patients at the time of the initial assessment and/or during the clinical course if they fail to achieve their therapeutic goals (Table 2A-B). The additional evaluation varies depending upon the manifestation of interest or the goal that is not achieved. (See "Additional evaluation" above.)
- The clinical course and life expectancy of GD type 1 (GD1) is variable. The estimated average life expectancy at birth for a patient with GD1 is around 68 years. In contrast, most patients with type 2 GD (GD2) die within the first two years of life. GD type 3 (GD3) usually is more severe and aggressive than GD1, but has a more variable course than GD2. (See "Overview of rickets in children".)
Pregnancy can exacerbate the symptoms of Gaucher disease, particularly in women whose disease is not controlled by enzyme replacement therapy (ERT) [18]. The risks of bone crises peripartum and hemorrhage postpartum are increased. (See Pregnancy, above.)

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REFERENCES


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