Clinical manifestations and management of Gaucher disease

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Summary

Gaucher disease is a rare multi-systemic metabolic disorder caused by the inherited deficiency of the lysosomal enzyme β-glucocerebrosidase, which leads to the accumulation of its normal substrate, glucocerebroside, in tissue macrophages with damage to haematological, visceral and bone systems. Anaemia, thrombocytopenia, enlargement of liver and/or spleen, skeletal abnormalities (osteopenia, lytic lesions, pathological fractures, chronic bone pain, bone crisis, bone infarcts, osteonecrosis and skeletal deformities) are typical manifestations of the most prevalent form of the disease, the so-called non-neuronopathic type 1. However, severity and coexistence of different symptoms are highly variable. The determination of deficient β-glucocerebrosidase activity in leukocytes or fibroblasts by enzymatic assay is the gold standard for the diagnosis of Gaucher disease. Comprehensive and reproducible evaluation and monitoring of all clinically relevant aspects are fundamental for the effective management of Gaucher disease patients. Enzyme replacement therapy has been shown to be effective in reducing glucocerebroside storage burden and diminishing the deleterious effects caused by its accumulation. Tailored treatment plan for each patient should be directed to symptom relief, general improvement of quality of life, and prevention of irreversible damage.

KEY WORDS: Gaucher disease; glucocerebroside; storage burden; activated macrophage; enzyme replacement therapy.

Etiology and pathogenesis

Gaucher disease (GD) is an inherited lysosomal storage disease caused by an autosomal recessive defect of the gene encoding β-glucocerebrosidase, enzyme responsible for the accumulation of glucosylceramide into reticuloendothelial cells, rendering GD a multi-organ chronic disorder (1, 2). These lipid-laden cells are called Gaucher cells and are predominantly found in the spleen, liver, bone marrow and rarely lung. As a consequence, hepatosplenomegaly, pancytopenia, bone complications and, in a small number of patients, lung involvement with interstitial lung disease and pulmonary hypertension can occur (2, 3). Massive infiltration by Gaucher cells alone cannot explain the multifaceted characteristics of the disease. The accumulation leads to a secondary activation of macrophages, inducing the release of various cytokines and lysosomal proteins (4). The most striking seems to be the increased expression of chitotriosidase, which can be raised 1000-fold in Gaucher patients and is produced in Gaucher cells. The plasma concentration strongly correlates with the accumulation of Gaucher cells in the body (5). In an animal model, an inflammatory infiltration of several organ systems, B-cell stimulation and expression of TNF-α and IL-1β were observed (6). These observations may explain the increased occurrence of auto-antibodies, B-cell lymphomas, gammopathies and multiple myeloma in Gaucher patients (7, 8). Similarly, most of the Gaucher changes in the long bones can be explained by the release of cytokines by storage cells in the bone marrow. To date, the pathogenic etiology of neurological involvement in GD is still incomplete (9).

Diagnosis of GD

Residual levels of glucocerebrosidase in patients with GD have been variously estimated at 5-25% of normal activity. The measurement of β-glucocerebrosidase activity in leukocytes or in cultured fibroblasts obtained by skin biopsy is the gold standard for the diagnosis of GD (10). As for many other lysosomal enzymes, recently screening methods using dry blood spots have been developed also for β-glucocerebrosidase (11). The finding of a reduced β-glucocerebrosidase activity can be supplemented by detection of the genetic defect. The glucocerebrosidase gene (GBA) is located on chromosome 1q21; it contains 11 exons and 10 introns, covering 7.6 kilobases (kb) of sequence. There is a highly homologous pseudogene (psGBA), spanning 5.7 kb with the same exon and intron number as the GBA, located 16 kb downstream, sharing approximately 96% of the sequence in coding regions. Almost 300 mutations and polymorphisms in GBA have been identified. Most are point mutations, but insertions or deletions, splice site alterations, and recombinating alleles, also with the nearby pseudogene, have also been described (12). Recently mutations in gene of saposin C, that is the β-glucocerebrosidase activator, have been also reported in association with GD (13). Four mutations account for over 90% of disease alleles in Ashkenazi Jewish patients: N370S, 84GG, L444P and IVS2+1G (14). Non-Jewish pa-

tients exhibit a much wider range of genotypes, although two mutations (N370S and L444P) are common in both populations. Of note, homozygosis for L444P normally results in neuronopathic disease whereas the presence of a single mutant N370S allele usually prevents neurological involvement. However, genotype-phenotype correlations are of limited clinical value and the clinical diversity of this single gene disorder suggests that modifier genes and environmental factors must play an important role (15).

Genetic diagnosis can be performed during pregnancy using amniocentesis or chorionic villi sampling, but this test is only useful in populations with a high gene frequency or in families already known to be affected (16).

The detection of Gaucher cells in bioptic samples is not required for diagnostic purpose, even if it often represents the step triggering the diagnostic suspicion in adult patients. In fact, approximately 60% of all new GD diagnoses are still made by a bone marrow biopsy or histology of a surgically removed spleen.

Epidemiology

GD is pan-ethnic, but it has a particular high prevalence among Ashkenazi Jews (17). Within this population, non-neuronopathic forms of GD occur with a frequency of approximately 1:850 and carrier frequency is 1:17. Based on epidemiological investigations in Italy a prevalence of 1:40,000-1:86,000 is assumed in the general population. Acute neurological forms occur even less frequently. A prevalence estimate of 1:500000 may however be too low, as cases with fetal or neonatal manifestations (fetal hydrops, congenital ichthyosis) are not always properly diagnosed.

Clinical classification

Three major forms of GD have been clinically described. The most prevalent is the so-called non-neuronopathic form (type 1) characterized by anaemia, thrombocytopenia, enlargement of the spleen, skeletal abnormalities (18), and in a small number of patients, by lung involvement with interstitial lung disease (18) and pulmonary hypertension (19, 20). Type 1 is essentially a macrophage disorder, lacking primary central nervous system involvement. Patients with type 1 GD display a large variety of symptoms, ranging from asymptomatic subjects to those who display child-onset disease. Type 2 GD is an acute neuronopathic form with severe prognosis and survival limited to the first two or three years of life; it is characterized by neurological impairment in addition to visceral symptoms. The neurological symptoms start with oculomotor abnormalities followed by brainstem involvement. Type 3 GD is also characterized by neurological involvement but neurological symptoms generally appear later in life than in type 2 disease, and include abnormal eye movements, ataxia, seizures, and dementia, with patients surviving until their third or fourth decade (21). Recently, a clinical association has been reported between the presence of mutations in the β-glucocerebrosidase gene and Parkinsonism (22, 23).

The identification of new phenotypes and appreciation that even patients with type 1 may develop some late-onset neurologic manifestations, may suggest is to consider GD as a continuum of disease states (Table 1) (24).

Finally, a significant increased risk of haematological malignancies has been reported in GD. GD is frequently associated with immunologic abnormalities: polyclonal hypergammaglobulinemia may occur at diagnosis in 14-41% of adults (25-27); an increased prevalence of the pre-malignant condition mono-

Table 1 - Clinical classification of the forms of GD. Recently the classic categories of types 1, 2 and 3 have blurry edges along a phenotypic continuum. Patients with GD can have a spectrum of symptoms, ranging from mild to severe neurological effects (24).

	Non-neuronopathic GD	Acute neuronopathic GD	Chronic neuronopathic GD
Incidence	1:40000-1:60000 1:850 in Ashkenazi Jews	<1:100000	<1:50000 to <1:100000
Ethnic group	Panethnic, more common in Ashkenazi Jews	Panethnic	Panethnic
Age at onset of disease	Any age	Infancy	Childhood
CNS symptoms	-	+++	+ → +++ (progressive)
Hepatosplenomegaly	+ → +++	++	+ → +++
Hematological symptoms	+ → +++	+++	+ → +++
Bone symptoms	- → +++	-	++ → +++

Gaucher Disease - a phenotypic continuum
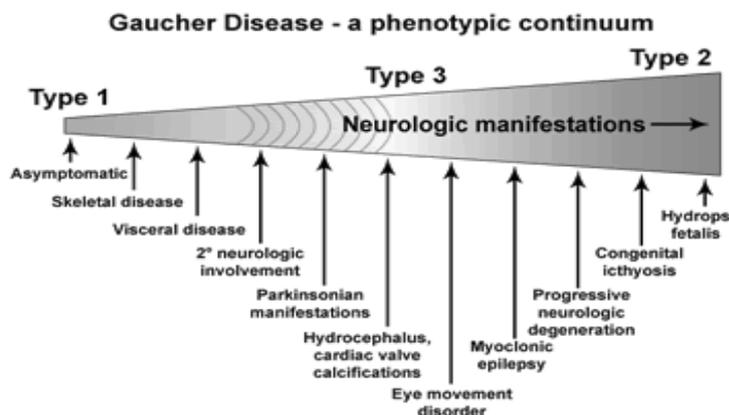
clonal gammopathy of undetermined significance (MGUS), up to 25%, has been described. In GD the increased risk of MM is reported as ranging from 5.9 (28) to 51.1 times that of normal population. An increased risk of other hematological malignancies, such as amyloidosis or B-cell non-Hodgkin Lymphoma (NHL), has also been reported (29-31).

Association between GD and solid organ malignancies is less clear but an increased incidence of hepatocellular carcinoma (HCC) has been described (29).

Bone manifestations in GD

Skeletal involvement has a high prevalence in adult type 1 GD patients and represents actually the major morbidity for its frequent association with considerable pain, limitations in mobility and an extremely negative impact on the quality of life. The bone manifestations of GD are multifaceted and can include bone marrow infiltration, severe acute "bone crises", chronic intermittent bone pain, bone infarction, lytic lesions, Erlenmeyer flask deformity of the distal femur, osteopenia, osteoporosis, osteonecrosis, subchondral joint collapse, pathologic fractures of long bones and vertebrae, and growth retardation in children (2, 9, 32, 33).

Bone disease has a very high prevalence in type 1 GD, with a radiological evidence described in 93% of patients. Data from the International Collaborative Gaucher Group (ICGG) Registry show that at diagnosis bone pain is present in 50% of type 1 GD patients, bone marrow infiltration in 82%, Erlenmeyer flask deformity in 60%, osteonecrosis in 30%, localized or generalized decrease of bone mineral density (BMD) in 49% and in 36%, respectively (34).

The underlying pathology of bone disease is related to the accumulation of Gaucher cells that infiltrate the bone marrow compartment and lead directly or indirectly to localized bone defects, including cortical thinning, osteonecrosis and lytic lesions. The pattern and the progression of the bone marrow infiltration vary from patient to patient, but in general the infiltration seems to begin in the lumbar spine, before entering the metaphysis and diaphysis of the femur, and then being seen in the epiphysis in the later stages. Magnetic resonance imaging (MRI) is the most sensitive diagnostic procedure for the detection of bone marrow changes. Affected bone areas have pathologically reduced signal using T1-weighted spin echo sequences. The reduced signal is caused by displacement of the signal-rich yellow bone marrow (Figure 1) (35). Bone marrow infiltration has also been connected with abnormal bone remodeling. The Erlenmeyer flask deformity is a common remodeling disorder, which occurs in over 60% of the patients. This manifests as a deformity of the distal long bones and generally affects the distal femur (Figure 2) or proximal tibia (36). The metaphyseal regions are expanded and show incorrect bone remodeling, which seems to be connected with a relative failure of osteoclast activity. Another pathological skeletal change seen in GD patients with progressive bone disease is osteonecrosis, also known as avascular necrosis. Osteonecrosis is ischaemic death of bone tissue due to chronic bone infarction. The patient has often suffered many bone crises prior to the onset of the necrotic process. However, vascular obstruction is not necessarily the primary pathological mechanism. Gaucher cells can also damage the vessel wall through the release of lysosomal contents, with localized osteonecrosis that may be extensive. Osteonecrosis usually occurs bilaterally in the head of the fe-
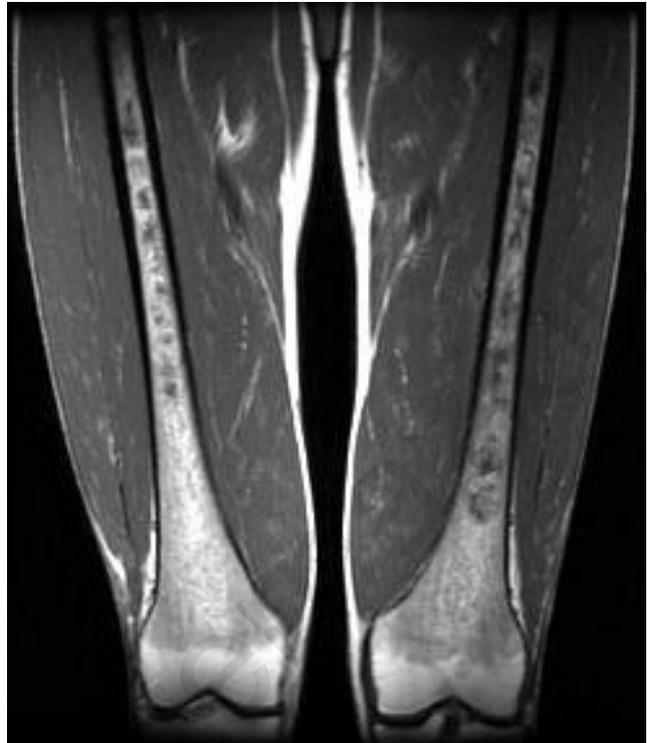

Figure 1 - Coronal T1-weighted sequence of the femurs showing severe bone marrow infiltration with some focal areas.

Figure 2 - A-P X-ray image of the distal femurs showing the Erlenmeyer flask deformity in the distal diametaphyseal transition zone.

mur, but some patients have repeated episodes in the same hip. Involvement of the femoral neck can precede the pathological changes in the head of the femur (37). Osteonecrosis can affect medullary as well as cortical bone. Medullary osteonecrosis may also be entirely asymptomatic. These lesions may cause major disability from pathological fractures

and collapse of osseous endplates with joint disintegration and its replacement is often necessary to relieve pain and restore mobility. In children, the disorder is sometimes misdiagnosed as Legg-Calve-Perthes disease. One third of adult GD patients have a history of osteonecrosis (18); while specific genotypes, prior splenectomy, trauma, strenuous physical exertion, and pregnancies appear to be predisposing factors for the development of osteonecrosis, it is not possible to accurately predict in individual patients the future risk for its development. Bone crises can be a manifestation of the osteonecrotic process, when a sufficient proportion of the bone is affected. Extensive osteonecrosis can cause generalized systemic disease characterized by severe pain (due to edema in the bone cavity), high fever, shivering, complete disability, a high leukocyte count and an increased erythrocyte sedimentation rate. When a bone crisis occurs, it is the most incapacitating manifestation of GD, frequently requiring opiate analgesic. Differential diagnosis from septic osteomyelitis may be difficult. Patients with Gaucher crises have a negative blood culture. The best diagnostic option is a technetium-99m bone scan within 2-3 days of onset of bone crises. It is "cold" in Gaucher bone crises and "hot" in septic osteomyelitis (38). Although bone pain usually occurs in GD, there are not always specific radiological findings. The nature of the bone pain differs, in fact this symptom may be dull, sharp, non-specific or severe and localized, like joint pain. Patients with GD are highly likely to suffer fractures, which relates to the increased prevalence of osteopenia, osteonecrosis, infarction and bone crises. Fractures can occur anywhere in the skeleton. Delayed skeletal growth is very common in children with GD, particularly in those with severe type 1.

Gaucher cells can alternatively damage bone tissue since they are also activated macrophages which secrete several cytokines (TNFα, IL6, IL10, IL4 and monocyte chemo-attractant proteins) and/or interact with cells in their environment. The locally increased cytokines in bone stimulate production of osteoclast precursors, resulting in imbalances in bone remodeling to favour resorption over formation, leading to osteopenia or osteoporosis. A decreased bone mineralization can occur locally or diffusely and widespread, and can affect trabecular bone, as well as cortical bone (39). The lumbar spine represents an ideal location for the assessment of localized bone disease, as well as generalized osteoporosis. In fact, marrow infiltration is thought to begin in the lumbar vertebrae and then progress to the pelvis and the appendicular skeleton; moreover, the lumbar spine has a higher percentage of trabecular bone and may be more sensitive to changes in systemic bone mass than other sites where cortical bone predominates.

Evaluations and monitoring for type 1 GD

Challenges to patient care posed by clinical heterogeneity, variables progression rates, and potential permanent disability that can result from untreated or sub-optimally treated haematological, skeletal and visceral involvement dictate a need for comprehensive, serial monitoring. A consensus on minimum recommendations for effective monitoring of adult patients with type 1 GD had been developed by the ICGG Registry coordinators, with reproducible initial baseline and annual follow-up evaluations of all clinically relevant aspects of the disease. Assessment of disease severity includes blood tests, biochemical biomarkers, MRI or ultrasound for measurement of spleen and liver volume, a combination of modalities to evaluate trabecular and compact bone disease, including radiographs, bone densitometry by dual energy X-ray absorptiometry and MRI to assess the severity of bone marrow infiltration. Doppler echocardiogram, chest X-ray and electrocardiogram are useful to exclude pulmonary hypertension (Table 2) (40).

Different biochemical biomarkers are evaluated to quantify dynamic changes in the clinical course over the years: ferritin, immunoglobulin, angiotensin-converting enzyme (ACE), tartrate resistant acid phosphatase (TRAP) (41). At the present time plasma levels of the hydrolase chitotriosidase and the CC-chemokine ligand 18/pulmonary activated-related chemokine (CCL18/PARC) are considered useful tools. Both parameters correlate well with the body burden of Gaucher cells. Chitotriosidase activity in serum can increase up to 100-4000-fold over the normal values in GD, and is reduced by treatment. However, 5-6% of the general population is homozygous for the chitotriosidase gene mutation causing complete deficiency of the enzyme activity (42). Chitotriosidase measurement is unreliable in these situations. Serum CCL18/PARC, which is not affected by any known genetic abnormality, is increased 10-40 fold over the normal levels in GD and decreases during therapy with a pattern similar to chitotriosidase (43).

Disease management

GD is a multi-organ, chronic, heterogeneous disorder, requiring an individualized approach towards treatment. Many variables such as severity and rate of disease progression, concomitant pathological conditions, the impact of disease manifestations on quality of life and the phenotype/genotype relationship should be considered prior to the initiation of treatment in a patient with GD (10, 40, 44). At the present time, the therapeutic options for adult GD patients are enzyme replacement therapy (ERT) and substrate reduction therapy (SRT), although bone marrow transplantation and gene therapy have been applied in rare cases. It is generally accepted that a GD patient must be treated in the presence of complications such as anaemia, thrombocytopenia, bleeding tendency, skeletal disease, liver or lung involvement or organomegaly. Type 1 GD was the first lysosomal storage disorders for which an effective ERT was developed and it has become a prototype for treatments for related orphan diseases.

After its introduction, in 1991, ERT has emerged as the standard of care for type 1 GD (45, 46). In order to establish the severity of disease and to tailor the initial and maintenance ERT dose, a classification in high- and low-risk type 1 GD patients has been suggested by a panel of experts (Tables 3, 4) (47).

Over two decades since the introduction of therapy, it has become definitely clear that many of the symptoms and signs of visceral GD such as hepatosplenomegaly, as well as anaemia and thrombocytopenia, and often, skeletal or lung involvement, will respond adequately to ERT (48). Three different human recombinant enzymes have been approved; two of them are available in EU and USA: Imiglucerase (Cerezyme, Genzyme Corporation, Cambridge MA, USA) since 1994, and Velaglucerase alfa (VPRIV, Shire HGT, Cambridge MA, USA) since 2010. An additional preparation,

Table 2 - Minimum recommendations for monitoring patients with non-neuronopathic GD (40).

	Patients not on ERT		Patients on ERT Not achieved therapeutic goals		Patients on ERT achieved therapeutic goals	Patients on ERT At time of dose change or significant clinical complications
Frequency (every X months)	12	12-24	3	12	12-24	
Comprehensive physical examination	X			X	X (annual)	
SF-36 (QoL) survey	X			X	X (annual)	X
Blood tests						
Hemoglobin	X		X		X	X
Platelet count	X		X		X	X
Biochemical markers	X		X		X	X
Visceral						
Spleen volume (volumetric MRI or CT)		X		X	X	X
Liver volume (volumetric MRI or CT)		X		X	X	X
Skeletal						
MRI of entire femora (coronal; T1 and T2 weighted)		X		X	X	X
DEXA (lumbar spine and femoral neck)		X		X	X	X

Table 3 - Type 1 GD Highest Risk Patients- One or More of the following symptoms (47).

Symptomatic skeletal disease
Moderate to severe osteopenia
Avascular necrosis
Chronic bone pain
Pathological fractures
Bone crises
Joint replacement(s)
Impaired quality of life due to GD
Cardiopulmonary disease, including pulmonary hypertension
Platelet count <60,000mm³ or abnormal bleedings
Symptomatic anaemia or haemoglobin < 8g/dl
Transfusion dependency
Significant liver disease
Severe hepatomegaly (>2.5xnormal)
Infarcts
Varices
Portal hypertension
Hepatitis
Significant spleen disease
Severe splenomegaly (>15xnormal)
Infarcts
Significant renal disease

Table 4 - Type 1 GD Lower Risk Patients (47).

Normal liver, cardiac, lung and renal function

Minimal impairment of quality of life due to GD

No obvious and recently rapid progression of disease manifestations

Skeletal disease limited to mild osteopenia and Erlenmeyer flask deformity

Haemoglobin>10.5 g/dl for females and >11.5 g/dl for males

(or not more than 2 g/dl below lower limit of normal for age and sex)

Platelet count >60,000mm³ on three determinations

Liver volume <2.5 x normal

Spleen volume < 15 x normal

Taliglucerase alfa (Elelyso, ProtalixBiotherapeutics, Carmiel, Israel) is available only in USA. The ICGG Registry has monitored the responses of a thousand patients world-wide to Imiglucerase (45). Decreased spleen and liver volumes and

increased haemoglobin levels and platelet counts usually occur within 6 months of advent of therapy with every-other-week doses of 15-60 units/kg body weight. Platelet count in patients with massively enlarged spleens may require longer periods to respond, but dramatic improvements usually continue within the first 2-4 years of therapy (46, 49). Normalization or near-normalization of haemoglobin and platelet count as well as liver and spleen volume, with reduction in bone pains and prevention of irreversible skeletal complications are the ultimate end-points. Improvement in bone marrow and in

the osseous skeleton in response to ERT has been observed to occur more slowly than the visceral and haematological responses. Increase of bone mineral density in response to ERT could take up to 8 years (50), and ERT is effective in ameliorating bone marrow infiltration only after years (Table 5) (51). Besides, pathological damage such as osteonecrosis, bone infarcts and fracture, once it has occurred, is irreversible, so the maximal benefit derived from ERT in terms of eliciting a response in the skeletal system may occur with early enzyme administration and preventive approaches. The use of biphosphonates can be an effective and safe mean to increase bone density and prevent complications (52). Supportive management for bone pains or bone crises is frequently required, and orthopedic surgery may be necessary in cases of pathologic fractures or osteonecrosis (53).

Substrate synthesis inhibition therapy is an alternative oral approach, based on reduced synthesis of glucosylceramide by inhibiting the appropriate synthetic enzyme (i.e. glucosyl-ceramide synthase), resultanting in decreased production of this dangerous lipid and the ability of the residual enzyme activity to restablish a new steady state. This approach was first tried with the iminosugar N-butyldeoxynojirimycin, Miglustat (Zavesca, Actelion Corp) (54), approved by EMA in 2002 for patients with mild-to-moderate GD who are unsuitable for ERT and by FDA in 2003 for patients in whom ERT is not a therapeutic option. Clinical trials demonstrated effects on the visceral organs in type 1 GD with some shrinking of hepatosplenomegaly and improvement of haematologic findings. However, the substantial adverse events related to the use of miglustat, in particular significant diarrhea, and controversial tremor and paresthesias, limited drug's acceptance. Ceramide analog of the substrate, Eliglustat (Genz-112638; Genzyme Corp) (55) is a novel agent with a better safety profile and higher potency than miglustat. Eliglustat was approved by FDA in August 2014 and approval procedures by EMA in January 2015.

Table 5 - Therapeutic goals for ERT in GD patients (49).

Therapeutic goals for anemia
Increase hemoglobin levels within 12 to 24 months to
≥11g/dl for women and children
12g/dl for men
Eliminate blood transfusion dependency and reduce fatigue, dyspnoea and angina
Maintain improved hemoglobin values achieved after 12 to 24 months of therapy

Therapeutic goals for thrombocytopenia
Increase platelet count during the first year of therapy sufficiently, to prevent surgical, obstetrical and spontaneous bleeding
Patients with splenectomy - normalization of platelet count by one year of treatment
Moderate baseline thrombocytopenia - the platelet count should increase by 1.5- to 2-fold by year one and approach normal levels by year two
Severe thrombocytopenia - the platelet count should increase by 1.5-fold by year one and continue to increase slightly during years two to five, but normalization is not expected
Avoid splenectomy
Maintain stable platelet counts to eliminate risk of bleeding

Therapeutic goals for hepatomegaly and splenomegaly
Reduce and maintain the liver volume to 1.0 to 1.5 times normal
Reduce the liver volume by 20 to 30% within years one to two by 30 to 40% by years three to five
Reduce and maintain spleen volume to less than two to eight times normal
Reduce the spleen volume by reduce and maintain the 30 to 50% by year one and by 50 to 60% by years two to five
Alleviate symptoms due to splenomegaly
Eliminate hypersplenism

Therapeutic goals for skeletal pathology
Lessen or eliminate pain within one to two years
Prevent bone crisis
Prevent osteonecrosis and subchondral joint collapse
Improve bone mineral density
Increase trabecular bone mineral density by three to five years
Pediatric patients:
  • Attain normal or ideal peak skeletal mass
  • Increase cortical and bone mineral density (BMD) by two years

Therapeutic goals for growth in pediatric patients
Normalise growth and achieve normal onset of puberty

Therapeutic goals for pulmonary involvement
Reverse hepatopulmonary syndrome and dependency on oxygen
Ameliorate pulmonary hypertension (ERT+ adjuvant therapies)
Improve functional status and quality of life
Prevent sudden death
Prevent pulmonary disease by timely initiation of ERT and avoidance of splenectomy

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Conclusion

Gaucher is a rare disease with heterogeneous multisystem involvement. The non-neuronopathic GD may show different symptoms at any age. Related to the predominant manifestation, GD patient can refer to different specialists (pediatrician, internist, hematologist for hematological changes, gastroenterologist for hepatosplenomegaly, rheumatologist or orthopedic for bone disease), but the rarity of the disease and nonspecific and heterogeneous nature of GD symptoms may impede its consideration in the differential diagnosis. Since diagnosis of GD by enzyme testing is unequivocal, performing the test may be convenient in patients with dubious pathological signs. A delay in diagnosis can cause the occurrence of irreversible complications, such as avascular necrosis or MM, in a rare disease for which an effective treatment is available. Different aspects of pathophysiology and in particular determination of disease severity remains incompletely understood, and the precise relationship between GD and certain co-morbidities, especially cancer, remains unclear. Moreover, bone disease and its pathophysiology are yet to be fully understood to aid diagnosis, monitoring and treatment of GD.

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