



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Gaucher Disease with Normocytic Normochrome Anemia Manifestation in a 13-Month-Old Baby: A Case Report

Nova Linda^{1*}, Nice Rachmawati Masnadi¹, Gustina Lubis¹, Amirah Zatil Izzah¹

¹Department of Pediatrics, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

ARTICLE INFO

Keywords:

Gaucher disease
Glucocerebrosidase enzyme
Deficiency enzyme
Enzyme replacement therapy

*Corresponding author:

Nova Linda

E-mail address:

novalinda.dr@gmail.com

All authors have reviewed and approved the final version of the manuscript.

<https://doi.org/10.37275/bsm.v6i9.578>

ABSTRACT

Background: Gaucher disease is a sphingolipidosis, an inherited disorder of metabolism resulting from glucocerebrosidase deficiency, causing the deposition of glucocerebrosidase and related compounds. This study aimed to describe Gaucher disease in one year old baby girl. **Case presentation:** A 13-month-old girl was referred from the district hospital with a diagnosis of hemolytic anemia. The Patient come with major complaints in the form of enlarged abdomen since 6 months ago. The patient looked pale and coughed since 7 days ago, accompanied by a cold. Ultrasound examination of the abdomen shows splenomegaly. Based on supporting examinations, the effect of normocytic normochrome anemia with reticulocytosis was obtained. The bone survey resulted in an Erlenmeyer flask image on both the humerus and femur suitable for Gaucher disease. The results of microscopic evaluation on bone marrow smear found large cells with Gaucher cell characteristics. Laboratory evaluation of glucocerebrosidase enzymes showed that there was a deficiency deficiency β -glucosidase. Patients get enzyme replacement therapy for 7 times, each therapy is carried out every 2 weeks. **Conclusion:** Enzyme replacement therapy is the definitive effective therapy in patients with Gaucher disease. Follow-up should, in principle, be individualized, as the heterogeneity of the disease and a number of associated conditions precludes strict protocolized follow-up.

1. Introduction

Inborn errors of metabolism are rare, and therefore their diagnosis requires a high index of suspicion. Timely diagnosis leads to early treatment and may help avoid acute and chronic complications, developmental compromise, and even death. Symptoms and signs tend to be nonspecific and are more often caused by something other than an inherited disorder of metabolism. These more likely causes should also be investigated.¹⁻³

Disorders manifesting in the neonatal period tend to be more serious; manifestations of many of the disorders typically include lethargy, poor feeding, vomiting, and seizures. Disorders that manifest later

tend to affect growth and development, but vomiting, seizures, and weakness may also appear. History and physical examination that can be found at inborn errors of metabolism are growth delay, developmental delay, neuromuscular symptoms, congenital brain malformation, autonomic symptoms, non-physiological jaundice, unusual odors in body fluids reflecting the accumulation of specific compounds, change in urine color on exposure to air, organomegaly and eye changes.⁴⁻⁶

Gaucher disease is a sphingolipidosis, an inherited disorder of metabolism resulting from glucocerebrosidase deficiency, causing the deposition

of glucocerebroside and related compounds. Symptoms and signs vary by type but are most commonly hepatosplenomegaly or central nervous system changes. Diagnosis is by DNA and enzyme analysis of white blood cells. Glucocerebrosidase normally hydrolyzes glucocerebroside to glucose and ceramide. Genetic defects of the enzyme cause glucocerebroside accumulation in tissue macrophages through phagocytosis, forming Gaucher cells. Accumulation of Gaucher cells in the perivascular spaces in the brain causes gliosis in neuronopathic forms.⁷

There are three types of Gaucher disease, which vary in epidemiology, enzyme activity, and manifestations. Diagnosis of Gaucher disease is by DNA analysis and/or enzyme analysis of white blood cells. Carriers are detected, and types are distinguished by mutation analysis. Although biopsy is unnecessary, Gaucher cells—lipid-laden tissue macrophages in the liver, spleen, lymph nodes, bone marrow, or brain that have a wrinkled tissue-paper appearance are diagnostic.⁷ Enzyme replacement therapy (ERT) has been used in the treatment of Gaucher disease - to reverse the symptoms and improve the quality of life. It must be taken throughout the life of the individual. Otherwise, the health problems from the gene defect return. Patients must be under the care of a physician to monitor the therapy for any adverse reactions and adjust dosages.⁷ This study aimed to describe Gaucher disease in year old baby girl.

2. Case Presentation

A 13-month-old girl was referred from Muaro Bungo district hospital with a diagnosis of hemolytic anemia. The patient had been hospitalized at Muaro Bungo District Hospital for 5 days. The patient come with major complaints in the form of an enlarged

abdomen 6 months ago. The patient looked pale and had coughed since 7 days ago, accompanied by a cold. There was no history of a decrease in body weight even though body weight was difficult to rise. Her highest body weight was 7.5 kg, the same as her body weight 2 months before. The patient has a normal appetite. She took breastfed on demand, formula milk 2-3x per day, about 75-100 cc per time, porridge 2-3x/day, and small portions. The patient could speak one word "ma-, pa-." Micturition was regular amounts and colors, and defecation was regular color and normal consistency. Family history showed that the patient's brother was diagnosed with Gaucher disease and died 3 years ago at the age of 2.5 years. Her parents' marriage is known to be a consanguineous marriage.

Physical examination revealed an enlarged abdomen, palpation of the abdomen was solid with an abdominal circumference of about 45 cm. The liver was found to have a 3/4-1/4 sharp edge, flat surface, and chewy consistency. The spleen was at Schoefner 5, sharp edge, flat surface, and chewy consistency. The percussion was tympani, and bowel sounds positive normal. Peripherally acral was warm and had good capillary refilling time.

Routine blood investigations showed hemoglobin 9 g/dl, white blood cell 9.680/mm³, platelet 177.000/mm³, erythrocyte 3.8 million, hematocrit 29%, Reticulocyte 3.7%, MCV 75 fl, MCH 24 pg, MCHC 31%. Abdominal ultrasound examination showed splenomegaly, homogeneous density, liver, and both kidneys, gall bladder, and urine bladder didn't perform abnormalities. Based on investigations, the impression was normocytic normochromic anemia with reticulocytosis. This patient was diagnosed with normocytic normochromic anemia due to suspected hemolytic anemia accompanied by suspect Gaucher disease.



Figure 1. Clinical appearance of the patient

The bone survey, bone marrow puncture, Comb's test, and glucocerebrosidase enzyme examinations were scheduled to confirm the diagnosis. The bone survey

resulted in an Erlenmeyer flask image on both the humerus and femur suitable for Gaucher disease.

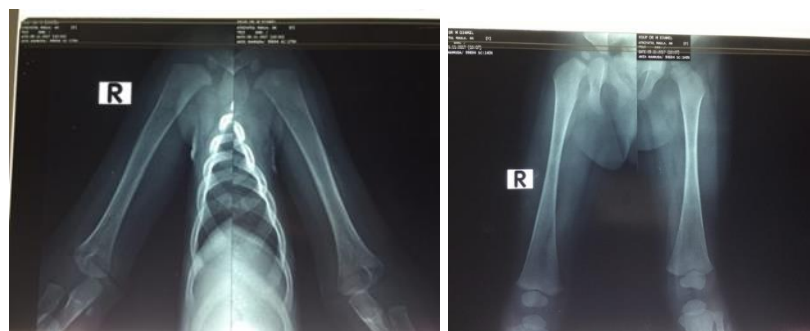


Figure 2. Bone survey

Bone marrow smear had resulted in normocellular hematopoietic activity within normal limits. The results of the microscopic evaluation of the bone marrow smear found large cells with Gaucher cell characteristics. The suggestion was a planned examination of the glucocerebrosidase enzyme.

Laboratory evaluation of the enzyme glucocerebrosidase showed a deficiency of β -glucosidase deficiency. This patient is planned to receive definitive enzyme replacement therapy at Cipto Mangunkusumo National Referral Hospital in Jakarta.

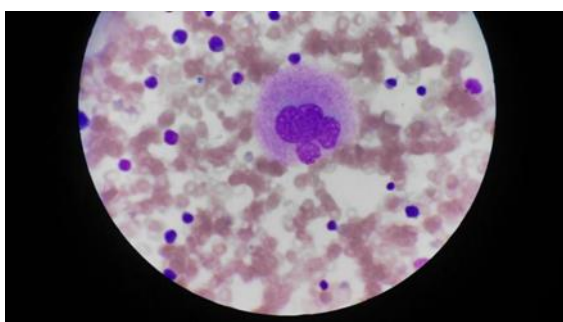


Figure 3. Bone marrow smear

The patient received enzyme replacement therapy 7 times. Each therapy was carried out every 2 weeks. The enzyme used was Cerezyme 800 U with 100 ml NaCl 0.9%. Enzyme administration was carried out for 1 hour. The patient was also treated with 8 mg methylprednisolone and 2.5 mg cetirizine 12 hours before enzyme replacement therapy (ERT). The patient was allowed outpatient after receiving seven sessions of enzyme replacement therapy. Follow-up of the condition after outpatient, the patient experienced improvements, including an increase in body weight to 8.5 kg, the height of 78 cm, upper arm circumference of 12 cm, liver size 4-5 cm below arcus costae, 4-5 cm below processus xypoides, lien size Schoeffner 7.

3. Discussion

Gaucher disease (GD) is the most prevalent lysosomal disorder caused by an autosomal recessive defect of the gene encoding β -glucocerebrosidase, the enzyme responsible for the accumulation of glucosylceramide into reticuloendothelial cells, rendering GD a multi-organ chronic disorder. A deficiency of β -glucocerebrosidase (β -glucosidase) results in storage of the lipid glucosylceramide, an intermediate in the catabolism of globoside and gangliosides. Gaucher disease can be somewhat artificially divided into three forms that can be differentiated by the relative degree of neurological involvement.^{7,8}

The lysosomal enzyme β -glucocerebrosidase (β -GCase) is involved in the degradation of the natural glycosphingolipid glucocerebroside (or glucosylceramide; GC) into glucose and ceramide. The deficient activity of this enzyme causes Gaucher disease. The enzyme β -GCase is activated by saposin C, which is derived from proteolytic cleavage of prosaposin. The deficiency of saposin C results in a decrease in β -GCase and gives rise to a clinical variant of Gaucher disease with neuronopathic features.⁹

Gaucher disease has first been described by Philippe Gaucher in 1882 and is now recognized as one of the most prevalent lysosomal storage disorders. Its inheritance is autosomal recessive, and the disease

is pan-ethnic, but there are some ethnic predilections. In Western countries, type I Gaucher disease or the non-neuronopathic variant is most common and has a high prevalence in the Ashkenazi Jewish population of 1 in 850, and the carrier frequency is 1:17.⁷⁻⁹ In general, the prevalence is believed to be around 1 in 75,000, but it is likely that this is an underestimation since milder variants remain undiagnosed. The neuronopathic variants are extremely rare, with variable ethnic backgrounds, although clusters of these patients have been described in Norrbotten (Sweden), Poland, and in the Jenin Arab population.⁹

All forms of Gaucher disease are inherited in an autosomal recessive fashion. Lipid-laden cells (Gaucher cells) derived from the monocyte-macrophage system containing cytoplasm with a "wrinkled tissue paper" or crumpled silk" appearance is characteristic. The liver, spleen, and brain (in neuronopathic forms) of affected individuals have shown markedly increased glucosylceramide content.⁸

In Gaucher disease type I, Gaucher cells and glucosylceramide accumulate in the vascular periadventitial areas of the Virchow-Robinow spaces. Gaucher cells are especially prominent on the spleen, liver sinusoids, hepatic Kupffer cells, bone marrow, lymph nodes and rarely lung. Storage in the liver and spleen can lead to massive hepatosplenomegaly. Another consequence of pancytopenia in a small number of patients is lung involvement with interstitial lung disease, and pulmonary hypertension can occur.⁷⁻⁹

Fibrosis in systemic organs and brain gliosis occurs. Progressive accumulation of Gaucher cells in bone marrow, vascular compromise, and infarction lead to skeletal complications, including osteopenia, osteosclerosis, osteonecrosis (e.g., avascular necrosis of the femoral head), painful bone crises, and remodeling abnormalities. Massive infiltration by Gaucher cells alone cannot explain the multifaceted characteristics of the disease. The accumulation leads to the secondary activation of macrophages, inducing the release of various cytokines and lysosomal proteins.⁷⁻⁹

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. In an animal model, inflammatory infiltration of several organ systems, B-cell stimulation, and expression of TNF- α and IL-1 β were observed. These observations may explain the increased occurrence of auto-antibodies, B-cell lymphomas, gammopathies, and multiple myeloma in Gaucher patients. Gaucher cells (GC) can coalesce to form a pseudotumors lesion (gaucheroma) that may resemble chondrosarcoma. In neuropathic forms of Gaucher disease, a significant amount of glucosylceramide and glucosyl sphingosine are present in the CNS. 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.

Three major forms of GD have been clinically described. The most prevalent is the so-called non-neuronopathic form (type 1) characterized by anemia, thrombocytopenia, enlargement of the spleen, skeletal abnormalities, and in a small number of patients, lung involvement with interstitial lung disease and pulmonary hypertension.¹⁰

Type 1 Gaucher disease has a wide phenotypic variability. In general, the build-up of undegraded GC in macrophages results in hepatosplenomegaly, bone marrow involvement, cytopenia, and skeletal disease. Most patients with this disorder present with unexplained thrombocytopenia and splenomegaly. Common presenting signs and symptoms include splenomegaly with associated hypersplenism, epistaxis, easy bruising, and hepatomegaly. Hypersplenism and bone marrow infiltration lead to pancytopenia. Although massive hepatomegaly may occur, hepatic failure or cirrhosis is rare. Growth Retardation is often present in children, but bone lesions usually occur later than visceral involvement.^{8,9}

More exceptionally, the first symptoms can be

related to skeletal involvement, such as painful bone crises or avascular necrosis. Although the majority are diagnosed during adolescence/adulthood, severe manifestations may already be present during early childhood. Spleens can become massively enlarged, which necessitated splenectomy before enzyme replacement therapy was available. After splenectomy, these patients are vulnerable to septicemia and progressive skeletal, liver, and pulmonary disease.⁷

Once extreme bone marrow infiltration has occurred, the risk for bone complications increases. This can be shown by a reduction in fat signal in the bone marrow on MRI. Skeletal complications include avascular necrosis, specifically of the femoral head, but also in other joints, pathological fractures, and bone crises. These crises resemble the acute bone pain seen in sickle cell disease and can only be managed by supportive measures such as morphinomimetics. Imaging of the skeleton shows characteristic, although not pathognomonic, features including osteopenia, sclerosis, Erlenmeyer flask deformities of the femurs, lytic lesions, and fractures. On MRI, a decrease in fat signal and sometimes areas with high water signal can be seen. This last feature does not always indicate acute disease. Early AVN and infarcts can also be recognized on MRI.⁷⁻⁹

While severe, progressive disease in children and young adults has been described, on the other end of the clinical spectrum, a diagnosis of Gaucher disease can be made as a coincidental finding in an otherwise healthy person. The very mild patients usually have little disease progression. Gaucher disease type 1 is also associated with other conditions, including a higher risk for malignancies, specifically multiple myeloma.

As a large proportion (up to 20 %) of adult Gaucher disease patients have a monoclonal protein, it is clear that there is an increased risk, and patients should be monitored for this. In addition, several cases of hepatocellular carcinoma have been reported, presumably associated with advanced liver involvement. Pulmonary Hypertension and renal and cardiac involvement have all been reported. The

increased risk for these conditions should be kept in mind during clinical follow-up. Individual factors that put patients at risk for these complications are currently under investigation.

Painful bone crises may occur, especially during childhood or adolescence. In children, acute hip involvement may sometimes be mistaken for Legg-Calve-Perthes disease. Gaucher disease Type 1 also has been misdiagnosed as lymphoma, leukemia, bleeding disorders, and osteomyelitis. Lung Infiltration by Gaucher cells may happen in children, but this is a rare finding. Pulmonary hypertension, portal hypertension, and renal involvement are encountered rarely. Cancer, especially hematological malignancies, appears to be slightly more common in individuals who have Gaucher Disease than in the general population.⁷

Type 2 and 3 Gaucher diseases are the neuronopathic Gaucher disease forms that are traditionally distinguished based upon the onset of neurological disease and the rate of deterioration. Type 2 patients always present with very early psychomotor developmental delay and a rapidly fatal course. However, an early diagnosis can also be made in type 3, the patient, and considerable overlap of disease manifestations between type 2 and 3 diseases exists. Therefore, neuronopathic forms are increasingly regarded as a phenotypic continuum. Since management decisions will be made primarily based upon the course of progression, Vellodi and co-workers have suggested using the terms "acute" and "chronic" instead of type 2 and type 3.⁷⁻⁹

The acute neuronopathic disease then refers to onset at <1 year of age with progressive neurological features including bulbar and pyramidal signs and cognitive impairment. Chronic neuronopathic disease encompasses all patients with neurological disease manifestations in the context of Gaucher disease who do not have the acute form. The chronic neuronopathic disease group harbors several variants: the subtype living in Northern Sweden (Norrbotten) with relatively mild neurological features, but the extensive visceral disease is sometimes referred to as

type 3a to distinguish these from patients with more prominent neurological features (type 3b). Another atypical variant of the chronic neuronopathic disease is referred to as type 3c and has first been reported in a group of Jenin Arab patients. Homozygosity for the D409H mutation in these patients is associated with valvular heart disease with cardiovascular calcifications in addition to oculomotor apraxia and mild visceromegaly.⁷⁻¹⁰

Gaucher disease type 2 is a severe, progressive disorder that presents in infancy or early childhood with massive hepatosplenomegaly, failure to thrive, and progressive neurological dysfunction with spasticity, cortical thumbs, and opisthotonus. Survival is limited to the first two or three years of life. Strabismus and oculomotor apraxia may be the first sign of fetal disease drops, and a congenital ichthyosis-like rash also has been described.⁷⁻⁹ Gaucher disease type 3 is an intermediate in severity between type 1 and 2. severe, early-onset massive organomegaly and slowly progressive neurological dysfunction are typical. Some affected individuals do not have massive organomegaly. This form is relatively common in the Norrbottnian region of Sweden.⁷⁻⁹ Diagnosis is performed with a decrease in β -glucosidase activity present in peripheral blood leucocytes and fibroblasts. Sometimes the diagnosis becomes evident when Gaucher cells are detected after a bone marrow biopsy is performed for suspected malignancy, or a liver biopsy is undertaken to investigate hepatomegaly.¹¹⁻¹³

Skeletal x-rays may reveal the characteristic "Erlenmeyer Flask" deformity of the distal femur in Gaucher disease type I. Because well-established genotype-phenotype correlations exist, the mutation is often performed. For example, the 1226 G (N370S) mutation is considered to be neuroprotective because it has never been detected in patients with the neuronopathic disease. On the other hand, the Homozygosity of the 1448C (L444P) mutation is associated with neuronopathic disease, although there may be exceptions. Prenatal diagnosis is possible by measuring β -glucosidase activity in amniocytes or

chorionic villi. If the mutations are known, DNA analysis is also possible.^{11,12}

Niemann-Pick disease type C (NPC) is a model for inborn errors of metabolism whose gene product mediates molecular trafficking rather than catabolizing macromolecules, as in classic lipidoses. We report the case of an infant who presented with hepatosplenomegaly without neurological abnormalities. Decreased activity of acid β -glucosidase and elevated serum chitotriosidase and tartrate-resistant acid phosphatase on repeated measurements led to the initial diagnosis of Gaucher disease (GD).¹³

Failure to respond to enzyme replacement therapy after one year, however, put the diagnosis in question. Cholesterol esterification assays in cultured skin fibroblasts and NPC gene analysis led to the correct diagnosis of NPC. The patient had markedly reduced cholesterol esterification and was a compound heterozygote for a known and novel mutation in the NPC gene (395delC and 2068insTCCC), which are both predicted to lead to protein truncation. Although the full phenotype of NPC involves hepatosplenomegaly and neurodegenerative disease, the initial presentation in a pediatric patient may be restricted to visceral disease.¹³

Before enzyme replacement therapy became available, the treatment of a Gaucher disease patient had been symptomatic. Splenectomy was usually performed in case of grossly enlarged spleens, leading to infarcts, abdominal discomfort, or severe cytopenia secondary to hypersplenism. After splenectomy, cytopenia is usually immediately resolved. However, the patient is at risk for further liver involvement, hepatopulmonary syndrome, and pulmonary hypertension.⁷⁻⁹

In addition, splenectomized patients more frequently develop bone crises and pathological fractures. Also, the absence of the spleen puts them at a higher risk of septicemia from pneumococci and other encapsulated bacteria. Thus, splenectomy should be avoided whenever possible. Bone crises usually present as acute, circumscribed, severe, persistent pain in a long bone, pelvis, or spine, often

with signs of inflammation. No other treatment than supportive care with bed rest and nonsteroidal anti-inflammatory drugs or morphine is available. Orthopedic procedures such as joint replacement in case of avascular necrosis are sometimes necessary. Bleeding has been a major problem related to thrombocytopenia, thrombocytopathy, and decreased clotting factors. Coagulation studies, including PT and aPTT, need to be performed around every surgical procedure or pregnancy.⁹

Enzyme replacement therapy (ERT) is the mainstay of treatment for type 1 disease. Therapy consists of a bimonthly intravenous infusion of human β -glucosidase manufactured using recombinant DNA techniques. ERT improves anemia, thrombocytopenia, hepatosplenomegaly, and bone crises. Prolonged treatment over 2 or 3 years may be required for any noticeable improvement in the skeletal disease. Severe skeletal manifestations can be prevented if ERT is begun before irreversible bone damage has occurred. Because presentation in childhood is indicative of moderate or severe disease, all children should be considered for ERT therapy, even those with isolated splenomegaly.⁷⁻¹⁰

Intravenous administration, usually once every two weeks, of recombinant β -GCase (Cerezyme, Genzyme Corp., MA) has proven to result in the reversal of most disease manifestations. In patients with advanced liver, lung, or bone disease, the effectiveness is more limited. But in those initiating therapy, before irreversible damage has occurred, the responses are very good. Many dosing regimens have been explored, with higher doses generally leading to more robust responses. However, individualization of dosing has become standard practice since doses between 15 and 60 U/kg now may all produce sustained responses. It needs to be emphasized that many patients do not need to be treated as they have very mild, nonprogressive disease manifestations.^{1,10}

The precise criteria to start ERT in type 1 Gaucher disease are not unequivocal. Some believe that most patients need ERT, while others tend to be more conservative. In general, children with symptoms are

always treated, while adults with stable disease and mild splenomegaly without severe platelet count (e.g., below $60 \times 10^9/l$) and without severe bone marrow infiltration may remain untreated. Currently, the risk factors for late complications, such as multiple myeloma, osteoporosis, or liver/lung disease, are unknown. Whether early initiation of ERT can prevent this is unclear and needs to be investigated. Patients with the acute neuronopathic form of Gaucher disease do not benefit from ERT, and it is now generally accepted that these should not be treated. In a very young patient with neurological symptoms, it may be difficult to decide whether this represents an acute or a chronic form. In such a case, it may be an option to discuss temporary treatment with the option to stop when the course of the disease is rapidly progressive.

7

In patients with the chronic neuronopathic form, ERT may certainly alleviate the symptoms related to hepatosplenomegaly and partially also skeletal disease. However, there is no evidence that ERT has reversed, stabilized, or slowed the progression of neurological involvement. Detailed recommendations for treatment are provided in the consensus paper by Vellodi et al. In type 3c, ERT is usually not indicated, as these patients do not have extensive visceral disease. Over the last years, new ERTs have been developed. Currently, velaglucerase (VPRIV, Shire HGT) has also received marketing authorization in the EU and the USA, whereas taliglucerase (Uplyso, Protalix/Pfizer) has been approved by the FDA only. All these enzymes have shown effectiveness, and choices for treatment will probably depend on whether there are any potential differences in effectiveness or safety, as well as reimbursement strategies and costs.^{8,9}

ERT also should be considered in those who have type 3 disease because of the relatively slow progression of neurological disease in these individuals. There is still debate about whether the enzyme may reach the brain. Although a few type 2 patients have received ERT, such treatment has no effect on the devastating neurodegenerative course in this subtype and generally is not recommended.¹⁰

An alternative approach is based on small molecules that inhibit substrate synthesis. The first and only authorized treatment is miglustat (*N*-butyl deoxyojirimycin, Zavesca, Actelion). This compound is an imino sugar, which inhibits the glucosyltransferase involved in the first step in the formation of complex glycosphingolipids. The rationale is that the reduction in the substrate is balanced against the residual β -G Case activity, which ultimately results in the degradation of stored glycolipids. Indeed, miglustat results in reductions in liver and spleen size and gradual improvements in hemoglobin and platelet count.⁹

The official use of miglustat is for patients with mild to moderate type 1 Gaucher disease who are unsuitable to receive ERT. Patients may prefer the convenience of oral treatment over lifelong intravenous infusions. Oral SRT with Miglustat improves hepatosplenomegaly and hematological parameters. Its effect on bone complications and the brain is unclear. Although SRT is not likely to replace ERT, it may prove to be a useful adjunctive therapy. Currently, in the United States, Miglustat is approved by the FDA for use only when ERT is not a therapeutic option.

However, ERT remains the first choice of therapy. Although direct head-to-head comparative trials have not been conducted, ERT is believed to be superior to SRT. In addition, many patients experience gastrointestinal side effects, which limits the use of miglustat. Newer SRTs are currently under development with a potentially better effectiveness/toxicity profile. SRT has been suggested to be used in neuronopathic Gaucher disease. However, one small trial failed to demonstrate effectiveness, and miglustat is not authorized for use in neuronopathic diseases. Some anecdotal reports suggest that miglustat may have some effect, and therefore combination therapy with ERT is sometimes tried. It is expected that the use of small molecules may further be explored as some act as chaperones by stabilizing the mutated β -GCase and hence increase its activity.¹⁰

For neuronopathic disease, a helpful scheme for the follow-up of neurological symptoms has been published. Some of the recommendations for follow-up in non- neuronopathic Gaucher disease refer to earlier-Defined therapeutic goals. It should be kept in mind that these goals are in fact, mean responses in blood counts, liver and spleen volumes, and skeletal parameters rather than clinically meaningful endpoints.^{9,12}

Dose adjustments should be made on an individual basis rather than on the achievement of these goals. For example, in patients with very large spleens, platelet responses will initially be very slow, and in the absence of clinically relevant bleeding episodes, there is no justification for a dose increase. In general, bleeding, severe anemia, and symptomatic organomegaly are alleviated within 12–24 months. Of importance is that good clinical responses are always accompanied by substantial decreases in chitotriosidase or, in deficient patients, in CCL18/PARC, ACE, or ferritin levels. The absence of a response in these parameters indicates failure of treatment.^{9,12}

Because of the increased risk for multiple myeloma, pulmonary Hypertension, Parkinson's disease, and perhaps other conditions such as diabetes, it may be wise to include relevant physical, laboratory, or imaging parameters in the follow-up. Skeletal imaging should preferably be performed with MRI, as this allows the assessment of the degree of bone marrow involvement. Serial follow-up with skeletal X-rays is unnecessary and exposes patients to high levels of radiation. DEXA scanning has difficulties in interpreting results in pediatric patients and in adults with sclerotic lesions may also give false outcomes. However, in those with milder diseases, regular follow-up to detect early osteopenia or osteoporosis is of importance.¹³⁻¹⁵

4. Conclusion

Enzyme replacement therapy is the definitive effective therapy in patients with Gaucher disease. Follow-up should in principle, be individualized, as the

heterogeneity of the disease and a number of associated conditions precludes strict protocolized follow-up.

5. References

1. Stirneman J, Belmatoug N, Camou F, Serratrice C, Froissart R, et al. A review of Gaucher disease pathophysiology, clinical presentation, and treatments. *Int J Mol Sci* 2017; 18(2): 441.
2. Campeau PM, Scriver CR, Mitchell JJ. A 25-year longitudinal analysis of treatment efficacy in inborn errors of metabolism. *Mol Genet Metab*. 2008; 95: 11-6.
3. Hruska KS, LaMarca ME, Scott CR, Sidransky E. Gaucher disease: Mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA). *Hum Mutat*. 2008; 29: 567-83.
4. Vaccaro AM, Motta M, Tatti M, Scarpa S, Masuelli L, et al. Saposin C mutations in Gaucher disease patients resulting in lysosomal lipid accumulation, saposin C deficiency, but normal prosaposin processing and sorting. *Hum Mol Genet*. 2010; 19: 2987–97.
5. Sidransky E. Gaucher disease: Insights from a rare Mendelian disorder. *Discov Med*. 2012; 14: 273-81.
6. Kinghorn KJ, Gronke S, Castillo-Quan JI, Woodling NS, Li L, et al. A *Drosophila* model of neuronopathic Gaucher disease demonstrates lysosomal-autophagic defects and altered mTOR signaling and is functionally rescued by rapamycin. *J Neurosci*. 2016; 36: 11654-70.
7. Lo SM, Mc Namara J, Seashore MR, Mistry PK. Misdiagnosis of Niemann-Pick disease Type C as Gaucher Disease, *J Inherit Metab Dis* 2010; 33(S3): S429.
8. Nagral A. Gaucher disease. *J Clin Exp Hepatol*. 2014; 4(1): 37-50.

9. Rolfs A, Giese AK, Grittner U, Mascher D, Elstein D, et al. Glucosylsphingosine is a highly sensitive and specific biomarker for primary diagnostic and follow-up monitoring in Gaucher disease in a non-Jewish, Caucasian cohort of Gaucher disease patients. *PLoS ONE*. 2013; 8: e79732.
10. Berger J, Lecourt S, Vanneaux V, Rapatel C, Boisgard S, et al. Glucocerebrosidase deficiency dramatically impairs human bone marrow haematopoiesis in an in vitro model of Gaucher disease. *Br J Haematol*. 2010; 150: 93-101
11. Jian J, Tian QY, Hettinghouse A, Zhao S, Liu H, et al. Progranulin recruits HSP70 to β -Glucocerebrosidase and is therapeutic against Gaucher disease. *EBioMedicine*. 2016; 13: 212-24.
12. Yap TL, Gruschus JM, Velayati A, Sidransky E, Lee JC. Saposin C protects glucocerebrosidase against α -synuclein inhibition. *Biochemistry*. 2013; 52:7 161–7163.
13. Arends M, van Dussen L, Biegstraaten M, Hollak CE. Malignancies and monoclonal gammopathy in Gaucher disease; a systematic review of the literature. *Br J Haematol*. 2013; 161: 832–842.
14. Astudillo L, Therville N, Colacios C, Segui B, Andrieu-Abadie N, et al. Glucosylceramidases and malignancies in mammals. *Biochimie*. 2015; 125: 267-80.
15. Braudeau C, Graveleau J, Rimbart M, Neel A, Hamidou M, et al. Altered innate function of plasmacytoid dendritic cells restored by enzyme replacement therapy in Gaucher disease. *Blood Cells Mol Dis*. 2013; 50: 281–288.