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Gaucher's Disease: A Case Report

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ABSTRACT

Gaucher disease is a rare genetic disorder in which a person lacks an enzyme called glucocerebrosidase (GBA). Gaucher disease is an autosomal recessive inherited disorder of metabolism where a type of fat (lipid) called glucocerebroside cannot be adequately degraded. The lack of GBA causes harmful substances to build up in the lung, liver, spleen, bones, bone marrow, brain, and eyes. These substances prevent cells and organs from working properly. There are three recognized Types of Gaucher disease and each has a wide range of symptoms. Type 1 is the most common, does not affect the nervous system, and may appear early in life or adulthood. Many people with Type 1 Gaucher disease have findings that are so mild that they never have any problems from the disorder. Type 2 and 3 do affect the nervous system. A man, 27th, goes to the hospital with pain at the upper of his left knee, swollen since 3 weeks ago, hypertension(-), DM (-), history of left knee operation. Traumatic history (-). HB: 14,9mmgr/dl, AL 7,6. AT 186, HMT 43,8%, GDS 95 mg/dl, APTT 34,4. PPT: 11,6, diff eosinophil: 3,2. From the symptoms dan clinical findings from this patient we can make a conclusion, the case is typical of Gaucher disease type 1.

INTRODUCTION

Gaucher diseases (GD) is named for the Frech dermatologist Philippe C.E. Gaucher who described a 23-year-old female patient in 1882 who had an enlarged spleen that he believed was due to an epithelioma.[1] This disease is a rare autosomal recessive metabolic disorder caused by mutation in GBA1.[2] The most prevalent lysosomal storage disorder, is an autosomal recessive, multiorgan disease with a variety of genotypic underpinnings and phenotypic expressions which encodes for the lysosomal hydrolase enzyme, β- glucocerebrosidase, which leads to an accumulation of its substrate in macrophages.[2,3] It results from the accumulation of undegraded glucosylceramides in the lysosomes of monocytes and macrophages in the reticuloendothelial system.[3] The affected leukocytes, known as Gaucher cells, preferentially accumulate in the bone marrow, liver, spleen, and lungs leads to hepatosplenomegaly and cytopenias.[3,4] Skeletal involvement may follow three processes: irreversible lesion such as osteonecrosis, reversible

changes such as long bone deformity, and generalized osteopenia or osteoporosis. Gaucher disease is most common in Jewish people of Eastern and Central European descent (Ashkenazi).[3] Patient with GD can display a spectrum of phenotypic heterogenicity, and are broadly classified into 3 subtype, depending on the absence or presence of neurological symptoms.[2,4] The diagnosis has to be confirmed by measuring the β- glucocerebrosidase activity in the peripheral leukocytes and by molecular analysis. Each patient needs an accurate initial multisystemic assessment, staging the damage of all the possible organs involved and the burden of the disease.[5] The option of therapy are enzyme replacement and gene therapy.[1]. The researcher is interested in reporting a patient with a Gaucher diagnosis given the scenario described above.

Case Presentation

The patient is a 27-year-old male with type 1 Gaucher disease. He went to the hospital with debilitating pain in the upper of his left knee, swollen since 3 weeks ago, hypertension (-), diabetes mellitus (-), history of a left knee operation. Traumatic history (-). From the x-ray appearance, an osteonecrosis appearance was found on the left knee. The medullary cavity was found along with the thinning of the cortex and endosteal scalloping, resulting in remodeling in the distal femurs resulting in the so-called Erlenmeyer flask deformity (Figure 1).

This patient's blood test showed that in normal values. HB: 14,9mmgr/dl, AL 7,6. AT 186, HMT 43,8%, GDS 95 mg/dl, APTT 34,4. PPT: 11,6, diff eosinophil: 3,2. This patient was treated with analgetic and calcium. No other treatment for this patient.

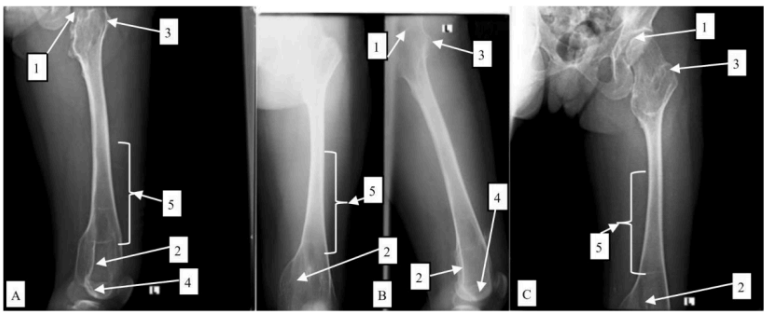

Figure 1. Left femur X-ray in AP (A), lateral (B), and oblique (C) positions. There is osteonecrosis of the left femoral head (1) and distal femur (2). There is a bulging of the left greater trochanter (3) and distal femur (4), which indicates an Erlenmeyer flask deformity (5)

DISCUSSION

Pathophysiology

The reticuloendothelial cells play a central role in the pathogenesis of the diseases. The so-called "Gaucher cells" are large macrophages loaded with glucosylceramide and characterized by the presence of surface macrophage markers, intense phagocytic activity, and characteristic cytoplasmic inclusions.[5] Irrespective of the mutation, glucosylceramide (GlcCer) is degraded much more slowly in cells from Gaucher patients than in normal cells and as a consequence, accumulates intracellularly, primarily in cells of mononuclear phagocyte origin.[1] Mutation in the GBA1 gene lead to a marked decrease in GCase activity. The consequences of this deficiency are generally attributed to the accumulation of the GCase substrate, GlcCer, in macrophages, inducing their transformation into Gaucher cells.[6] Most mutations in GlcCer appear to either partially or entirely decrease catalytic activity or to reduce ClcCer stability or both.[1]

Gaucher cells mainly infiltrate the bone marrow, the spleen, and the liver, but they also infiltrate other organs and are considered the main protagonist factors in the disease's symptoms. The monocyte/ macrophage lineage is preferentially altered because of their role in eliminating erythroid and leukocytes, which contain large amounts of glycosphingolipids, a source of GlcCer. GlcCer accumulation in Gaucher cells is considered the first step towards bone involvement, leading to vascular compression which is the source of necrotic complications. The pathophysiological mechanisms of neurological involvement remain poorly explained; GlcCer turnover in neurons is low and its accumulation is only significant when residual GCase activity is drastically decreased, on with some types of GBA1 mutation.[6]

In this case report, we reported a 27-year-old male with debilitating pain in the upper left knee three weeks prior to admission. He denied any history of trauma, diabetes mellitus, and neoplasm. From the x-ray appearance, an osteonecrosis appearance was found on the left knee. The medullary cavity was found along with the thinning of the cortex and endosteal scalloping, resulting in remodeling in the head and distal femurs resulting in the so-called Erlenmeyer flask deformity.

Recent observations indicate that Gaucher cells do not only result from the transformation of macrophage cells but correspond to a district M2 subpopulation from an alternative differentiation pathway. There are many functional states of macrophage polarization, and they can be fully polarized and acquire a specific phenotype like M1 (characteristic macrophage activation) or M2 (alternative macrophage activation).

Since GlcCer is an important constituent of biological membranes and is a key intermediate in the biosynthetic and degradative pathways of complex glycosphingolipids, its accumulation in Gaucher disease is likely to have severe pathological consequences.[1] GlcCer is also the substrate of an alternative pathway in which a ceramidase transforms it into glucosyl sphingosine, which

then diffuses into fluids due to its reduced hydrophobicity.[6] The accumulation of glucocerebroside leads to a secondary activation of macrophage, inducing the release of various cytokines and lysosomal proteins, that per se may be responsible for the different phenotypes.[5] Chitotriosidase is one of such markers, which can be increased by 1000 folds in Gaucher patients.[5] It is important to note that up to 6% of the general population has a deletion in the chitotriosidase gene, such that chitotriosidase activity is very low, causing the loss of any diagnostic power in such subjects.[5]

The cellular pathology of Gaucher disease begins in lysosomes, membrane-bound organelles that consist of a limiting, external membrane and intra-lysosomal vesicles. Endogenous and exogenous macromolecules, including GlcCer, are delivered to lysosomes by processes such as endocytosis, pinocytosis, phagocytosis, and auto phagocytosis. The lysosomal proteins themselves, at least the soluble hydrolases, are targeted to lysosomes mainly via the mannose-6-phosphate receptor. The mechanism by which GlcCer is targeted from its site of synthesis in the endoplasmic reticulum to lysosomes is not known. Gaucher-like cells are well described in various hematological malignancies unrelated to Gaucher's diseases, including Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma (MM), and chronic myelogenous leukemia (CML).[1]

Symptom

The most frequent phenotype is type 1 GD, which found in children and adults who have signs and symptoms that present mainly with hematologic, visceral, and skeletal manifestations, and without the central nervous system (CNS) but can produce chronic and progressive disease manifestations.[2,4] Clinical suspicion of GD1 is associated with signs sociated with and/or the presence of splenohepatomegaly and cytopenia, which have a 30 – 50 % incidence as the first or presenting symptom, and a 60 – 95 % incidence as the leading symptom at the time of diagnosis which is the widespread accumulation of tissue macrophage engorged with lysosomes that are laden with glucosylceramide.[1,4] The progressive nature of type 1 GD has been demonstrated in natural history studies in patient populations from Japan and The Netherland.[1] Diagnostic algorithms for Gaucher disease are based on the most frequently presenting signs of hematologists. However, 25 – 32 % have been found to present with bone signs and. Or symptoms as the only or main presenting sign of the disease.[4]

Most people who have Gaucher disease have varying degrees of the following problems:

- **Abdominal complaints.** Because the liver and especially the spleen can enlarge dramatically, the abdomen can become painfully distended.
- **Skeletal abnormalities.** Gaucher disease can weaken bone, increasing the risk of painful fractures. It can also interfere with the blood supply to your bones, which can cause portions of the bone to die.

- **Blood disorders.** A decrease in healthy red blood cells (anemia) can result in severe fatigue. The gaucher disease also affects the cells responsible for clotting, which can cause easy bruising and nosebleeds.

Type 1

The onset and the severity of the disease vary considerably.[5] Although the overall mean onset of patients in the Gaucher Registry is at 20 years 4 months.[6] There is an extreme variability in the initial clinical presentation and patients can be diagnosed at any age.[5,6] 56% of patients experienced onset before 20 years old. However, this Registry primarily includes symptomatic and treated patients, and thus the mean age is probably skewed. Two-thirds (68%) of this group were diagnosed before 10 years old and almost half (48%) before the age of 6.[6]

According to the literature, 80 – 95 % of patients with type 1 including asymptomatic patients, present with some form of bone involvement at the time of diagnosis.[4] Prevalence in Europe and North America 90 – 95 % with absence of neurological impairment.[6] Bone symptoms range from dull bone pain in the lower extremities (shaft and joints) and bone crises, to pathological fractures.[5] Presenting other signs may include Erlenmeyer flask (EM) deformity, decreased bone mineral density (BMD), bone infarcts (BI), osteosclerosis, avascular bone necrosis (AVN), osteolytic lesions, pathological fractures (Fx), bone pain, and bone crises.[1,4,5] Between 27 – 63 % of patients report a history of bone crises. This shows that failure to diagnose promptly allows the progression of bone involvement. The first symptoms in young or adult patients are typically a combination of adynamic, mild fatigue, thrombocytopenia, anemia, and bone complaints.[5,7]

The history and physical examination of a patient with advanced type 1 creates a lasting impression.[6] In patients as young adults or at an older age, hepatosplenomegaly is less striking compared to pediatric patients.[1] The history of chronic disability in these often highly accomplished individuals, massive organomegaly, cytopenia, and bone disease with additional rare complications are unmistakable hallmarks of the disease. The dramatic clinical phenotype underscores a single gene's power to alter the structure and function of a single cell type that triggers the development of a multisystem disease. Splenomegaly is observed in more than 90% of patients and is sometimes massive with a spleen weighing up to several kilograms and causing abdominal pain or distension.[6] An also always more pronounced compared to liver. If there is disproportionate hepatomegaly, the presence of primary hepatic comorbidity should be sought. It should be noted that even among apparently asymptomatic patients, osteoporosis, osteonecrosis, or lytic lesion may be found.[1,6] Fatigue is common (50% of patients) and often has an impact on school life or socio-professional activities.[6]

Type 2

Type 2 is the acute neuronopathic form.[1,6] This type is often difficult to distinguish from types 1 and 3 based solely on enzymatic activity or phenotype, although the total absence of glucocerebrosidase is associated with early lethality.[8] Neuronopathic Gaucher Disease (<5% of cases in most countries but up to 20% in some cohorts) usually refers to children who display neurological abnormalities before age 6 months and die by age 2 – 4 years despite enzyme replacement therapy with an average age of death of 9 months.[1,6] It is characterized by early and severe neurological impairment starting in infants (Figure 2) aged 3 – 6 months old and by systemic involvement with hepatosplenomegaly.[6] Type 2 is the rarest, most severe, and most progressive form which is characterized by a precocious and rapid neurological degeneration comprising a brainstem involvement associated with splenomegaly, pulmonary, and hematological signs.[7,9] The developmental mechanisms underlying type 2 remain poorly understood. Induced pluripotent stem cell (iPSC)-derived neurons can provide a useful cellular model to probe GD2 pathogenesis.[9]

Patients with type 2 invariably exhibit clinical signs in the first year of life although the type and severity of manifestations can vary widely and exhibit epidermal abnormalities regardless of whether ichthyosis is clinically evident.[8] The consistency of this phenotype was strengthened by the reports of many single cases worldwide and in scarce and old reviews.[7] On electron microscopy, the skin ultrastructure reveals immature partially-processed lamellar bilayers.[8] Type 2 has long been considered as a homogeneous clinical entity. However, several cases of a more severe, perinatally lethal form of neuronopathic GD were reported. Fetuses and newborns with perinatal-lethal GD are usually merged into the GD2 subtype, although specific signs accompany the earliest onset of the disease.[7]

First sign is hydrops fetalis characterized by an abnormal accumulation of fluid in multiple body areas and has been associated with several LSDs. Newborns with type 2 may present with congenital ichthyosis, an abnormal skin disorder resulting in shine. Hepatosplenomegaly enlargement of both the liver and spleen is one of the characteristic signs observed among patients with all three types of GD. Thrombocytopenia is observed among all forms of GD and occurs in approximately 40% of patients with type 2. Anemia is also frequently observed in these patients.

All patients with type 2 GD experience a rapid neurological decline but manifestations vary widely. Some patients present with arthrogryposis (joint contractures), microcephaly, or hypokinesia.[8] Apnea related to increasingly laryngeal spasms occurs after a few months. Fetal GD is the rarest (<1%) and most severe form of the disease. It usually manifests with hydrops fetalis, hepatosplenomegaly, ichthyosis, arthrogryposis, facial dysmorphia, and fetal thrombocytopenia.[6]

Type 3

Type 3 GD is characterized by progressive neurological features in addition to the typical systemic manifestations.[10] Currently, the minimum definition of type 3 requires the presence of supranuclear gaze palsy. This neurological abnormality consists of saccadic eye movement slowing affecting predominantly the horizontal eye movement, but vertical saccades are almost always slow as well.[1] Patients with type 3 disease develop a bedridden status or die at various ages from early childhood to young adulthood. This type is further classified into types 3a and 3b based on the extent of neurological involvement. Type 3 is characterized by relatively mild neurological symptoms (i.e. isolated supranuclear gaze palsy often manifesting as ocular motor apraxia) with severe visceral involvement like patients with type 1.[11]

In this case report, the only clinical symptom found was pain in the left knee. A medullary cavity enlargement was found on the x-ray examination. Any other manifestations were not found. Thus, it can be determined that the patient was suffering from Type 1 Gaucher Disease.

Skeletal Manifestation

Skeletal manifestations of Gaucher disease vary, ranging from asymptomatic Erlenmeyer flask deformity of the distal femora to pathologic fractures, vertebral collapse, and acute bone crises that can be confused with acute osteomyelitis. Painful bone crises result from episodes of bone infarction, leading to osteosclerosis analogous to that occurring in sickle cell disease. In children with Gaucher disease, acute hip lesions can be misinterpreted as Legg-Calvé-Perthes disease, and avascular necrosis of the hips is a common complication in individuals of all ages.[12]

This patient's x-ray examination showed osteonecrosis on the left head dan distal of the femur. The medullary cavity was found along with the thinning of the cortex and endosteal scalloping, resulting in remodeling in the distal femurs resulting in the so-called Erlenmeyer flask deformity (Figure 2).

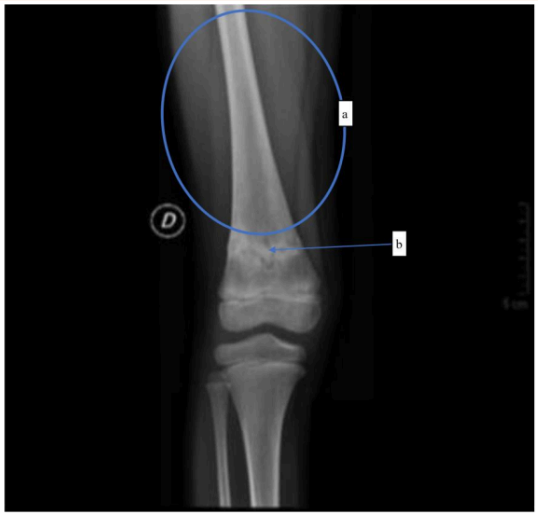

Figure 2. X-ray showing Erlenmeyer flask deformity in right femur (a) and femoral metaphysisi stress fracture in the healing phase (b).

Complication

1. Bone crises may occur sporadically, especially in times of growth, and may indicate infarcts. Avascular necrosis of the hip is not uncommon.
2. Splenic rupture can result from trauma.
3. Cirrhosis is a rare complication.
4. Rarely, pulmonary infiltration by Gaucher cells may manifest as overt lung disease, which may present as pulmonary infiltrates and lung consolidation; this pattern is especially common in patients with type 2 disease.
5. Parenchymal infiltration with fibrosis has been described in children with type 3 disease.
6. Intrapulmonary vascular dilatation in the presence or absence of portal hypertension has also been described in some patients with Gaucher disease, resulting in hypoxic lung disease.
7. Immunologic abnormalities, including hypergammaglobulinemia, T-lymphocyte deficiency in the spleen, and impaired neutrophil chemotaxis, are also common. The malignancy multiple myeloma is more common in individuals with Gaucher disease.[8,13]

Plain Radiographic

- Skeletal involvement is seen in 70-100% of patients and primarily involves long bones (tibia, humerus, femur) as well as vertebrae. Ribs, hands and wrists, ankles and feet, and mandible may also be involved [6]. Features of skeletal involvement include:
- osteopenia
- osteonecrosis
- pathological/crush fractures
- endosteal scalloping
- Erlenmeyer flask deformities
- H-shaped vertebrae

MRI is more accurate than ultrasonography in determining organ size and can be used for volumetric assessment. MRI may be useful in revealing early skeletal involvement, such as avascular necrosis and spinal degradation, as well as in delineating the degree of bone marrow infiltration. Skeletal radiography can be used to detect and evaluate skeletal manifestations of Gaucher disease. Perform chest radiography to evaluate pulmonary manifestations. Dual-energy x-ray absorptiometry (DEXA) is useful in evaluating osteopenia. Bone scans may be useful in diagnosing bone crises.[14]

Abdominal magnetic resonance imaging (MRI) is the most appropriate examination for assessing liver and spleen dimensions (organ volume) and morphology. The spleen sometimes presents nodules suggestive of lymphoma. Computed tomography (CT) has previously been used for estimating Gaucher organ volumes; nonetheless, MRI, because of justifiable concerns about CT radiation, is preferable because repeat assessments are routinely required.[6] Bone magnetic resonance imaging (MRI) is the test of choice for evaluating the effects of GD on bone. Bone marrow infiltration is predominant at the proximal and distal ends. T1 weighted sequences are recommended to detect and quantify bone marrow infiltration, while T2 weighted sequences are used to detect complications such as AVN or bone infarction. Hypointense signals are generally observed in T1 weighted sequences, reflecting the replacement of normal bone marrow fat by Gaucher cells. Infiltration may be quantified by means of the various scores used in reference centers, such as the Bone Marrow Burden score. Assessment of bone marrow infiltration is more difficult in children due to the presence of red bone marrow in the long bones. Magnetic resonance imaging is used to assess the extent of lesions and whether complications are recent (edema due to recent infarction) or longstanding.[6,15] Other types of MRI are used for semi-quantitative assessments of bone marrow infiltration (Quantitative Chemical Shift Imaging), but they are not available in all centers. Whole-body MRI makes it possible to reduce examination time,

particularly for disease monitoring purposes. The images must be carefully analyzed because additional images are sometimes required for the less visible sites, especially limb extremities (hands and feet).[15]

However, on this patient, we did not perform MRI or CT Scan due to this patient because we don't have MRI and CT Scan too expensive for this patient. Standard osseous radiographs were previously used to detect Erlenmeyer flask deformity of the femurs with the widening of the lower third. This can be accompanied by thinning of the cortical bone (which may appear scalloped), AVN and bone infarct sequelae (34% of cases), lytic lesions (18% of cases) that are generally well delineated without peripheral increased bone density, and the sequelae of traumatic or pathological fractures. The initial assessment should include radiological imaging of the pelvis, spine, femurs, tibiae, and humeri. Radiological imaging need not be systematically reused thereafter for monitoring purposes, except for specifically following the progression of AVN to osteoarthritis. The sensitivity of standard radiological imaging for the detection of abnormalities in GD is low and the use of multiple X-rays is no longer standard practice given the limited knowledge gained from them and risk of radiation exposure.[6] Echocardiography is used to screen for pulmonary arterial hypertension.[15]

Bone densitometry is used to diagnose osteopenia/osteoporosis, which is common in adults or children >5 years old, and to calculate lumbar spine and femoral bone mass. Osteopenia is defined as a T score between −1 and −2.5; osteoporosis is defined as a T score ≤ −2.5. The severity of osteopenia may be correlated with genotype, splenomegaly and hepatomegaly.[6]

Workups

1. X-Ray

   An x-ray fetects fracture and late bone problems. However, it is not the best way to asses changes in the bone marrow, strength of bones, or early signs of bone disease. An x-ray may also be taken to look for changes in bone such as Erlenmeyer flask deformity.[16]

2. MRI

   Magnetic resonance imaging uses magnets and radio waves to create images of parts of your body, It is a powerful and sensitive tool for ongoing monitoring of bone. An MRI may be used to assess the buildup of Gaucher cells in the bone marrow and to what extent they may have caused changes in the bone.[16]

3. DEXA

   A dual-energy x-ray absorptiometry scan is used to diagnose bone loss and assess your risk for developing bone fractures. It is the gold standard for measuring bone mineral density (BMD).[16]

A buildup of Gaucher cells can affect your bone marrow (where blood cells) are formed by interfering with the production of your blood cells. In Gaucher disease, the spleen becomes enlarged and overactive, breaking down too many red blood cells. Anemia can make you feel fatigued. People often describe feeling tired or weak, being breathless, or lacking energy. An overactive spleen can reduce blood plateles (PLATE-lets). This can make it harder for your blood to clot. For this reason, you might bruise and bleed easily. An overactive spleen decreses the number of avilable white blood cells. These cells help your body fight infection. Fewer white blood cells may lead to more infections.[13,17]

4. Hemoglobin Test

   This is a blood test to measure the total amount of hemoglobin in your blood. Hemoglobin, a part of redblood cells, caries oxygen. Low hemoglobin levels can be an indikator of anemia, which can lead to fatigue and other problems.[13,17]

5. Platelet Count

   This is a blood test to measure the number of platelets in your blood. Platelets are needd for normal blood clotting. Low platelet count (thrombocytopenia) may cause bruising and bleeding.[13,17]

6. Biochemical Evaluations

   These are blood tests that check substances called biomarkers that can monitor diseases progression and can help check your progress toward achieving the goals of your disease management plan. It msy check these biomarkers associated with Gaucher disease are chitotriosidase, angiotensin converting enzyme, and tartrate-resistant acid phosphatase.[13,16,17]

CONCLUSION

Although it is the most common of the lysosomal storage diseases, Gaucher disease remains rare and most cases present a gradual onset phenotype, which explains its delayed diagnosis. It is important to include GD in the diagnostic decision tree in cases of splenomegaly and/or thrombocytopenia, in order to avoid potentially harmful splenectomy.

Significant new insights into GD's pathophysiology show that GCase deficiency has a much broader impact than the simple macrophage load that transforms them into Gaucher cells. These insights will open new pathways for the development of innovative therapeutic strategies. Eventually, drugs that can modify the neurological phenotype are expected to be developed. It is likely that more complex molecular studies will ultimately contribute to customized patient management. The therapeutic advances of recent years, including the development of new enzymes and a new substrate inhibitor, represent significant progress, but research efforts must

be maintained. Patients with GD, including asymptomatic patients, must be monitored regularly to detect any complications in the disease's progression.

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