Laporan Kasus

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GAUCHER'S DISEASE

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ABSTRACT

Background : Gaucher ((go-SHAY)disease is a rare genetic disorder in which a person lacks an enzyme called glucocerebrosidase (GBA).[1] Gaucher disease is an autosomal recessive inherited disorder of metabolism where a type of fat (lipid) called glucocerebroside cannot be adequately degraded. Genome. The lack of the GBA causes harmful substances to build up in the lung, liver, spleen, bones, and 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.[1,2]

Case Presentation : A man, 27th go to the hospital with pain at upper of left knee, swollen since 3 week ago, hipertension (-), DM (-), history of left knee operation. Traumatic hystory(-)**.** 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

Conclusion : From the symptoms dan clinical finding from this patient we can make conclusion, the case is typical gaucher disease type 1

CASE PRESENTATION

Introduction

Gaucher diseases (GD) is named for the Frech dematologist Philippe C.E. Guacher who described a 23-year-old female patient in 1882 who had an enlarged spleen that he believed was duet o an epithelioma.[3] This disease is a rare autosomal recessive metabolic disorder caused by mutation in GBA1.[4] The most prevalent lysosomal storage disosrder, 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.[4,5] It results from the accumulation of undegraded glucosyceramide in the lysosomes of monocytes and macrophages in the reticuloendothelial system.[5] The affected leukocytes, known as Gaucher cells, prefentially accumulate in the bone marrow, liver, spleen, and lungs leads to hepatosplenomegaly and cytopenias.[5,6] 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 an Central European descent (Ashkenazi).[5] Patient with GD can display a spectrum of phenotypic heterogenecity, and are broadly classified into 3 subtype, depending on the absence or presence of neurological symptoms.[4,6] The diagnosis has to be confirmed 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 organ involved and the burden of the disease.[7] The option of therapy are enzyme replacement and gene therapy.[3]

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.[7] 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 mononucleae phagocyte origin.[3] 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.[8] Most mutation in GlcCer appear to either partially or entirely decrease catalytic activity or to reduce ClcCer stability or both.[3]

Gaucher cells mainly infiltrate bone marrow, the speeln, and liver, but they also infiltrate other argans 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 amount of glycosphingolipids, a source of GlcCer. GlcCer accumulation in Gaucher cells is considered the first step towards bone involvement, leading to the 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.[8]

Recent observations indicate that Gaucher cells do not only result from the transformation macrophage cells, but correspond to a distrinct 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 constutient of biological membranes and is a key intermediate in the biosynthetic and degradative pathways of complex glycophingolipids, its accumulation in Gaucher disease is likely to have severe pathological consequences.[3]

GlcCer is also the substrate of an alternative pathway in which a ceramidase transforms it into glucosylsohingisine, which then diffuses into fluids due to its reduced hydrophobicity.[8] 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 of the different phenotypes.[7] Chitotriosidase is one of such markers, which can be increased by 1000 folds in Gaucher patient.[7] It is important to note that up to 6% of the general population has a deletion in chitotriosidase gene, such that chitotriodase activity is very low, causing the loss of any diagnostic power in such subjects.[7]

The cellular pathology of Gaucher disease begins in lysosomes, membranebound organelles that consist of a limiting, external membrane and intra-lysosomal vesicles. Endogenous and exogenous macromolecules, including GlcCer, are deliverd to lysosomes by processes such as endocytosis, pinocytosis, phagocytosis, and autophagocytosis. 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 varius haematological malignancies unrelated to Guacher diseases, including Hodgkin's desease, non-Hodgkin's lymphoma, multiple myeloma (MM) and chronic myelogenous leukemia (CML).[3]

Symptom

The most frequent phenotype is type 1 GD, which found in children and adults who have signs and symptoms that presenting mainly with hematologic, visceral, skeletal manifestations, and without the central nervous system (CNS) but can produce chronic and progressive diseases manifestations.[4,6] Clinical suspicion of GD1 is associated with sign sociated with and/or the presence of spleno-hepatomegaly and cytopenia, which have a 30 – 50 % incidence as first or presenting symptom, an a 60 – 95 % incidence as

the leading symptom at the time of diagnosis which is widespread accumulation of tissue macrophage engorged with lysosomes that are laden with glucosylceramide.[3,6] The progressive nature of type 1 GD has been demonstrated in natural history studies in patient population from Japan and The Netherland.[3] Diagnostoc algorithms for Gucher disease are based in 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.[6]

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. Gaucher disease also affects the cells responsible for clotting, which can cause easy bruising and nosebleeds.

Type 1

The onset and the severity of disease vary considerably.[7] Although the overall mean onset of patients in the Gaucher Registry is at 20 years 4 months.[8] There is an extreme variability in the initial clinical presentation and patients can be diagnosed at any age.[7,8] 56% 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.[8]

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.[6] Prevalence in Europe and North

America 90 – 95 % with absence of neurological impairment.[8] Bone symptoms range from dull bone pain in the lower extremities (shaft and joints) and bone crises, to pathological fractures.[7] 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.[3,6,7] Between 27 – 63 % patients report a history of bone crises. This shows that failure to diagnose promptly allows progression of bone involvement. The first symptoms in young or adult patients are typically a combination of adynamia, mild fatigue, thrombocytopenia, anemia, and bone complaints.[7,9]

The history and physical examination of patient with advanced tupe 1 creates a lasting impression.[8] In patients as young adults or at an older age, hepatosplenomegaly is less striking compared to pediatric patients.[3] The history of chronic disability in these often highly accomplished individuals, massive organomegaly, cytopenia, 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 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.[8] An also always more pronounced compared to liver. If there is disproportionate hepatomegaly, presence of a primary hepatic comorbidity shold be sought. It should be noted that even among apparently asymptomatic patients, osteoporosis, osteonecrosis, or lytic lesion may be found.[3,8] Fatigue is common (50% of patients) and often has an impact on school life or socioprofessional activities.[8]

Type 2

Type 2 is the acute neuronopathic form.[3,8] This type often difficult to distinguish from type 1 and 3 based solely on enzymatic activity or fenotype,

although total absence of glucocerebrosidase is associated with early lethality.[10] Neuronopathic Gaucher Disease (<5% of cases in most countries but up to 20% in some cohort) 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.[3,8] It is characterized by early and severe neurological impairment starting infants aged 3 – 6 months old and by systermic involvement with hepatosplenomegaly.[8] Type 2 is the rarest, most severe, and most progressive form which characterized by a precocious and rapid neurological degeneration comprising a brainstem involvement associated with splenomegaly, pulmonary, and hematological signs.[9,11] 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.[11]

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.[10] The consistency of this phenotype was strengthened by the reports of many single cases worldwide and in scarce and old reviews.[9] On electron microscopy, the skin ultrastructure reveals immature partially-processed lamellar bilayers.[10] 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.[9]

First sign is hydrops fetalis characterized by an abnormal accumulation of fluid in multiple body areas has been associated with several LSDs. Newborns with type 2 may present with congenital ichthyosis, an abnormal skin disorder resulting in shinny. Hepatosplenomegaly enlargement of both the liver and spleen is one of the characteristic sings observed among patients with all three type 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 arythrogryphosis (joint contractures), microcephaly, or hypokinesia.[10] 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.[8]

Figure 1. The patient show the first infant at age 6 months and post tracheotomy at 16 months.

Type 3

Type 3 GD is characterized by progressive neurological features in addition to the typical systemic manifestations.[12] Currently, the minimum definition of type 3 requires the presence of supranuclear gaze palsy. This neurological abnormality consist of saccadic eye movement slowing affecting predominantly the horizontal eye movement, but vertical saccades are almost always slow as well.[3] 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.[13]

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.[14]

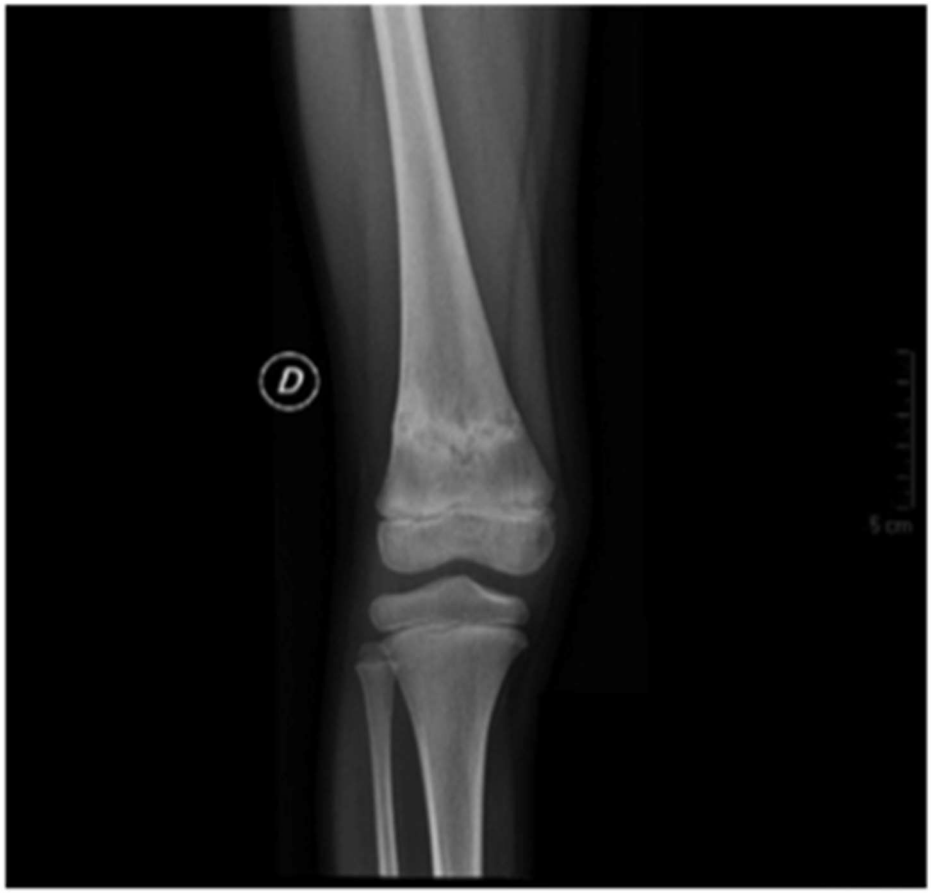


Figure 2. X-ray showing Erlenmeyer flask deformity in right femur and femoral metaphysisi stress fracture in the healing phase.

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.

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.[15]

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.[8] 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.[8,16] 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).[16]

Standard osseous radiographs were previously used to detect Erlenmeyer flask deformity of the femurs with 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.[8]

Echocardiography is used to screen for pulmonary arterial hypertension.[16]

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.[8]

Exam and Tests

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.

2. MRI

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

3. DEXA

   A dual-energi x-ray absorptiometry scan used to diagnose bone loss and asess your risk for developing bone fractures. It is the gold standard for measuring bone mineral density (BMD).[17]

A buildup of Gaucher cell can affect your bone marrow (where

blood cells) are formedly by interfering with with the production of your blood cells. In Gaucher disease, the spleen becomes enlarged and overactive, breaking down too many red blood cells. This leads to anemia (uh-NEEWM-ee-ya). 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.

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.

5. Platelet Count

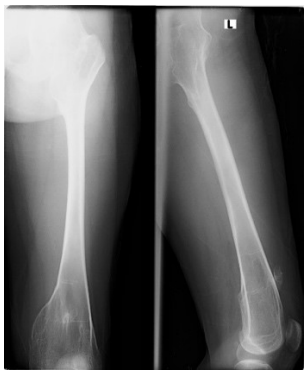
   This is a blood test to measure the number of platelets in your blood. Platelets are needd for normal blood clotting. Low platelet count (thrombocytopenia) may cause bruising and bleeding.

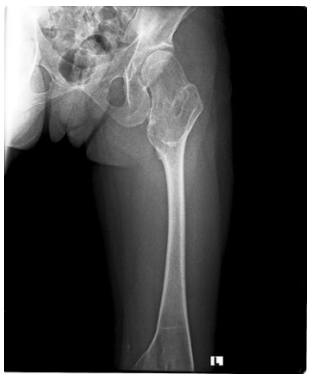
6. Biochemical Evaluations

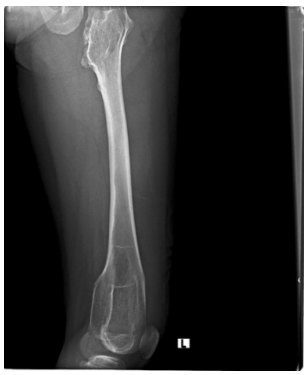
   These are blood tests that check substances called biomarkers that can monitor diseases progression and can help check your progress toward achieving the goals of your disease management plan. It msy check these biomarkers associated with Gaucher disease are chitotriosidase, angiotensin converting enzyme,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

Case Report

Patient is 27-year-old male with type 1 Gaucher disease. He went to the hospital with pain at upper of left knee, swollen since 3 weeks ago, hipertension (-), diabetes mellitus (-), history of left knee opration. Traumatic hystory (-).







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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