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TOPIC HIGHLIGHT

Yusuf Bayraktar, Professor, *Series Editor*

Gaucher disease: New developments in treatment and etiology

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Abstract

Gaucher disease (GD) is an autosomal recessive disease which if undiagnosed or diagnosed late results in devastating complications. Because of the heterozygous nature of GD, there is a wide spectrum of clinical presentation. Clinicians should be aware of this rare but potentially treatable disease in patients who present with unexplained organomegaly, anemia, massive splenomegaly, ascites and even cirrhosis of unknown origin. The treatment options for adult type GD include enzyme replacement treatment (ERT) and substrate reduction treatment (SRT) depending on the status of the patient. Future treatment options are gene therapy and "smart molecules" which provide specific cure and additional treatment options. In this review, we present the key issues about GD and new developments that gastroenterologists should be aware of.

Key words: Gaucher disease; Enzyme replacement treatment; Substrate reduction treatment; Gene therapy; Liver fibrosis

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INTRODUCTION

Gaucher disease (GD) is a storage disease in which macrophage sphingolipidosis accumulation occurs. This progressive disease results from deficiency of glucocerebrosidase (acid-β-glucosidase) in lysosomes. This enzyme is responsible for cleaving β-glycoside into β-glucose and ceramide subunits[1]. GD is inherited in an autosomal recessive fashion. The OMIM (Online Mendelian Inheritance in Man: http://www.ncbi.nlm.nih.gov/Omim) code for adult type GD is 230800.

It has 2 major forms: non-neuropathic (type 1, most commonly observed type in adulthood) and neuropathic (type 2 and 3). The disease is characterized by massive splenomegaly due to excessive accumulation of glucosylceramide in splenic macrophages. Other than spleen, so called "Gaucher cells" are the lipid-laden macrophages and can be observed in liver and bone marrow. Therefore GD causes organ damage where macrophages are densely present. Clinical alterations in bone, liver and spleen resulting in splenomegaly, hepatomegaly, hematological changes and orthopedic complications are the most predominant ones. Rarely kidney, skin, heart and central nervous system may be involved.

Recent advances in genetic technology have made it possible to manage the GD patients with enzyme replacement treatment (ERT). Substrate reduction treatment (SRT) is also currently available. In this review, we will discuss new developments in adult type GD disease in terms of its etiology and treatment from a gastroenterologists' point of view.

ETIOLOGY AND PATHOGENESIS

The gene coding for the enzyme responsible for GD is located on chromosome 21. In this single gene, about 200 mutations are defined up to date[1]. Most commonly observed mutations are N370S, L444P, RecNciI, 84GG, R463C, recTL and 84 GG is a null mutation in which there is no capacity to synthesize enzyme. However, N370S mutation is almost always related with type 1

Table 1 Worldwide most common mutations in GD

Population	Most frequently observed mutations	Frequency of mutations (%)
Turkish[3]	N370S L444P	61.80
Japanese[4]	L444P F2131	55
Taiwanese[5]	L444P RecNciI	78.50
Czech and Slovak[6]	N370S L444P RecNciI	76
Ashkenazi Jews[7]	N370S, c.84-85insG IVS2 + 1G-->A L444P	93
Hungarian[8]	N370S L444P RecNciI	70.30
Spanish[9]	N370S L444P	68.70

disease and milder forms of disease. Very rarely, deficiency of sphingolipid activator protein (Gaucher factor, SAP-2, saposin C) may result in GD. This rare condition is due to congenital absence of carrier protein involved in sphingolipid catabolism[2].

Worldwide differences in genetic mutations are shown in Table 1. Therefore, genetic heterogeneity results in phenotypic heterogeneity. The phenotypic presentation of the same mutation may vary in a wide spectrum. This difference is most possibly related with ethnicity, genetic background, environmental and nutritional factors. But most important of all, the exact pathophysiological mechanisms of GD are not clear yet. Since the total accumulation of glycosphingolipid in a massively enlarged spleen constitutes only about 2%, there must be other unknown pathways that result in splenic proliferation, activation and enlargement[10]. One of the most important changes occurs in macrophages. The accumulation of glycosphingolipid in the lysosomes of macrophages results in some expected consequences by unknown mechanisms. One important pathway is the activation of macrophages. The great majority of evidence of macrophage activation stems from the fact that patients with GD have increased levels of macrophage-derived inflammation related molecules such as interleukin-1β, interleukin-6, interleukin-10 and TNF-α[11,12]. With regard to macrophage activation, these cytokines might be responsible for some consequences like increased osteoclastic activity in bones resulting in osteopenia, osteoporosis and fractures.

Activated macrophages also secrete some other molecules that can be used as a marker of disease activity and surveillance. The enzyme chitotriosidase (CT) and CC chemokine ligand 18 (CCL8) are examples of these markers. CT is originally a chitinase which is responsible for degradation of chitin. In humans, CT playas a role during the remodeling phase of the tissue healing process and in immune-chemotaxis[13,14]. Previous studies reported that screening of increased CT activity can be used as a GD marker[15,16]. But the null allele in the general population, which is expressed at a mean frequency of 4%, causes deficiency of the enzyme[17]. The levels of the enzyme may also increase in elderly people[18] and in other granulomatous diseases such as sarcoidosis[19]. In addition, other macrophage markers such as macrophage inflammatory protein (MIP)-1α, MIP-1β[20] and soluble CD163[21] can also be used for surveillance of the disease.

CLINICAL MANIFESTATIONS

In general, GD patients present initially with hematological abnormalities due to hypersplenism. Gastroenterologists can be consulted because of anemia, massive splenomegaly or hepatomegaly of unknown cause. Although rare, patients presenting with hepatosplenomegaly and ascites are reported[22]. As mentioned previously, GD involvement changes in severity according to the density of macrophages in the particular organ and partially depends on the phenotypically heterozygous nature of the disease itself.

The most common mutation, N370S, could result in subtle symptoms and silent disease due to presence of some degree of enzymatic activity resulting in delays in diagnosis. The delays in diagnosis eventually results in irreversible complications. A recent study by Mistry *et al* showed that in adult patients with type 1 disease the average time from first appearance of symptoms of GD to final diagnosis was 48 mo. In addition, hematology-oncology specialists who were managing two-thirds of the patients considered diagnosis of GD only in 20% for the classical symptoms (bone pain, organomegaly and low blood counts)[23].

The diagnosis of GD is straightforward. The demonstration of genetically miscoded or absent enzyme levels is diagnostic. For this purpose, direct analysis of glucocerebrosidase in peripheral blood leukocytes is utilized. The activity of glucocerebrosidase is variable in white cell type[24], enzyme activity usually increases from granulocytes to lymphocytes to monocytes. Type 1 GD patients have 10 to 15 percent of the normal enzyme activity whereas type 2 and 3 patients usually have lower activity. Due to considerable overlap of enzymatic activity between heterozygote carriers and normal individuals, enzyme analysis cannot distinguish GD carriers from non-GD-carriers. In order to differentiate the carrier state, the genetic analysis which was mentioned previously should be applied for definitive diagnosis.

After diagnosis, GD patients should be classified according to clinical severity scores. The modified scoring system developed by Zimran (Zimran severity score index, ZSSI)[25] should be used during initial evaluation and during follow up of patients taking treatment (Table 2).

Gastrointestinal system involvement in GD

In the type 1 GD, gastrointestinal complications such as hepatomegaly, splenomegaly, cirrhosis, ascites, and esophageal variceal hemorrhage predominate and

are well known. However, other associations such as increased risk of hepatic carcinogenesis and cholelithiasis are not taken into consideration.

In the literature, there are reports of increased risk GD associated hepatocellular carcinoma (HCC)[26-28]. In a recent survey, the risk of development of HCC in GD patients is found to be 141 times more than normal controls[29]. The overall risk of malignancy (especially hematological malignancies such as multiple myeloma) development is known to be increased. However, some studies suggest that this risk is not different from the normal population in early and middle age[30].

Patients with GD, especially females over age of forty are found to be increased in risk of cholelithiasis. This increased risk is usually attributed to factors like anemia, prior splenectomy, hepatic involvement and an increased biliary excretion of glucosylceramide[31,32]. The management of cholelithiasis is not different from non-GD patients.

The portal hypertension observed in GD has 2 causes. The first is the overflow in the portal system secondary to splenomegaly which usually resolves after splenectomy. The second is observed in patients who already had a splenectomy. In these patients, massive infiltration of Gaucher cells in the liver parenchyma results in intrahepatic portal hypertension. The accumulation of excessive sphingolipid in liver macrophages (Kupffer cells) might result in activation of some unknown mechanisms or cell-to-cell interactions might ensue which eventually results in hepatic fibrosis. Hepatic fibrosis and eventual cirrhosis is the most feared complication of GD for liver involvement[33,34]. Although ERT results in reversal of hepatomegaly to normal, hepatic fibrosis still remains a challenge. The exact pathophysiological pathways of progressive hepatic fibrosis are unknown, but progressive fibrosis is observed mostly in pediatric patients. In initial presentation, hepatic transaminase levels are found to be elevated in nearly 50% of patients[25].

Other non-specific findings of GD involvement of the liver are hepatomegaly (detected in 100% of patients with splenomegaly but detectable only in 87% of patients with splenectomy), non-specific mass like lesions in liver, peri-portal and retroperitoneal lymph nodes[35].

Liver transplantation is rarely necessary compared to a few decades ago because of the introduction of ERT. However, development of features of progressive liver fibrosis such as elevated liver transaminase levels and no normalization in hepatomegaly despite adequate enzyme treatment should alert for rapidly developing fibrosis in a given patient. Liver transplantation should always be an option in patients with GD. Theoretically, there is a risk of recurrence of liver disease due to excessive burden of glycosphingolipid influx more than transplanted liver can handle. This risk is higher in patients with a spleen; therefore a splenectomy (if not performed until time of transplantation) should also be performed when transplantation is decided.

Despite its rarity, GD may involve other sites of the gastrointestinal system other than the liver and spleen. GD may result in "Gaucher cell pseudotumors" in the abdomen resulting in mass like lesions[36,37]. This phenomenon is very important because GD is related with increased incidence of cancer but currently, GD pseudotumors are rare due to ERT. Association of GD with colonic infiltration of "Gaucher cells"[38], massive gastrointestinal bleeding due to ileal involvement[39] and Menetrier disease of the stomach[40] are also reported.

Table 2 Zimran severity score index, 1992 (SSI scores of 0-10: Mild disease; 11-25: Moderate disease; > 25: Severe disease)

Feature	Detail	Score
Cytopenia	Non-splenectomized	1
	Splenectomized	
	Leukopenia	1
	Anemia	1
	Thrombocytopenia	1
Splenomegaly	None	0
	Mild	1
	Moderate	2
	Massive	3
Splenectomy		3
Hepatomegaly	None	0
	Mild	1
	Moderate	2
	Massive	3
Liver enzymes (aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, lactate dehydrogenase)	Normal	0
	Some abnormal	1
	All abnormal	2
Signs of clinical liver disease		4
CNS involvement		20
Other organ involvement (kidney, lungs or any other)		4
Bone disease-objective findings	No signs	0
	X-ray or nuclear scan abnormality	1
Bone disease-objective findings	No pain	0
	Mild pain	2
	Chronic pain unrelated with fractures	3
Bone fractures	No fracture	0
	Post-traumatic fracture	1
	Pathologic fracture or aseptic necrosis	5

TREATMENT STRATEGIES IN GD

Pre-treatment evaluation in GD

Since adult GD patients come to attention after development of symptomatic anemia, organomegaly or complications such as fractures, indications for specific treatment of GD are beyond the presence of these symptoms. The available ERT and SRT options are expensive (annual cost of ERT is around 1 billion US dollars[41]) and individual responses for these treatments are highly variable so that some patients may report no improvement. Therefore, with parallel to variability in phenotypic presentation, decision for treatment

must be individualized. In our personal practice, severe organomegaly, high degree of cytopenia, event of minor bleeding due to thrombocytopenia, bone disease, liver enzyme elevations with severe organomegaly and presence of any organ involvement other than liver-spleen-bone triad are indications of treatment. The aims of treatment are reversal of organomegaly, prevention of complications and increase in quality of life.

ERT

Alglucerase (extracted from human placenta) is the first enzyme treatment modality for GD patients to provide specific treatment. Major limitations of this product were its low degree of reproducibility (because of low number of available placenta), risk of blood borne infections, very short half-life (about 4.7 min in blood and 2 h in visceral organs including liver and spleen)[42,43]. These limitations had resulted in new research and development of a recombinant enzyme; imiglucerase. Imiglucerase is obtained from genetically manipulated ovary cells of Chinese hamsters. This enzyme has a longer half life and lack of blood borne infection risk. Despite the clinical results, imiglucerase looks excellent; there is only one randomized controlled trial with imiglucerase up to date. In this study by Schiffmann *et al*[44], the primary end-point was the improvement in bone mineral density of the lumbar spine. ERT (combination of alglucerase and imiglucerase) was compared with vitamin D and calcitriol in three patient arms. The total number of randomized patients was 29. The authors concluded that "ERT alone, or in combination with calcitriol, cannot repair the bone composition in splenectomized adult Gaucher patients. They also stated that the ERT significantly improved hemoglobin, platelet counts, and liver volume. There are two other randomized trials. The first one was designed to compare the effectiveness of imiglucerase vs. alglucerase (15 patients per treatment arm) which found no significant difference in the two molecules[45]. The second randomized controlled trial is a recent study by deFost *et al*[46] who showed that "low frequency administration of ERT in adult Gaucher type I patients maintains stable disease in most patients".

Although the number of randomized controlled trials in ERT does not satisfy clinicians as compared with other conditions, this currently available treatment option remains unique. The other option of treatment is substrate reduction therapy (SRT) and has a limited field of clinical use.

SRT

The idea underlying SRT is the inhibition of formation of sphingolipids that accumulate during GD. N-alkylated imino sugars are the prototype of this treatment. N-butyl-deoxynojirimycin (NB-DNJ) or miglustat is used on GD to reduce the formation of glucosylceramide by inhibiting the glucosylceramide synthase enzyme[47]. There are various studies related to efficacy of SRT, which showed improved blood counts, decrease in volumes of liver and spleen and increased quality of life[48,49]. One recent study showed comparable results with ERT[50]. The most important advantages of SRT are its oral administration (ERT is given as intravenous administration over several hours and must be repeated in 2-3 wk intervals), low costs and availability. Major drawbacks of SRT are safety issues. Theoretically, long term inhibition of glycosphingolipid inhibition may result in detrimental results but no major adverse reaction is reported up-to-date. Minor adverse reactions are weight loss, mild tremor, diarrhea, and gastrointestinal upset. In patients who received previous ERT, switch to SRT is well tolerated[51]. SRT is currently limited only to adult type 1 patients who can not tolerate ERT.

"THE FUTURE" OF GD THERAPY

Gene therapy

The administration and incorporation of a healthy genome replacing a deficient genome appears to be the cure for GD. There are a few studies in the literature investigating this possibility. In early animal models of gene therapy the vectors responsible for "infecting" a healthy genome were viruses (adeno-associated virus, lentivirus and retrovirus). These studies showed promising results for the future[52-54]. Neither ERT nor SRT have achieved excellent results in terms of neurological and pulmonary involvement due to problems such as inability to pass through the blood-brain barrier. The advantage of gene therapy is its widespread infection of specific targeted cells in the body substantially increasing the enzyme levels to a considerable level.

Chaperone treatment

The ability of imino sugars to increase the strength of the target enzyme (glucocerebrosidase) is shown previously by Sawkar *et al* in a study[55]. These chemicals increase the half life of the enzyme by inhibiting its degradation and by providing stabilization. Although this option currently does not seem to offer a monotherapy option, chaperones might be an option for combination treatment strategies.

CONCLUSION

Adult type GD is a heterozygous disease. Because of vulnerability to delayed diagnosis, timely diagnosis and early initiation of appropriate therapy are crucial and prevent detrimental complications and stops the progression of disease to some extent. In the future, it might be possible to "cure" this genetic disease by gene-vaccines. Therefore, we require more investment on investigations for gene therapy. ERT and SRT have undeniable therapeutic effects, but there seems to be need for more evidence before putting them into "gold-standard" therapy for all patients.

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