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A Review of Gaucher Disease in Korea

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Gaucher disease (GD, OMIM #230800 OMIM#230800) is a rare, autosomal recessive inherited metabolic disorder caused by mutation in *GBA1* encoding the lysosomal enzyme, glucocerebrosidase. The deficiency of glucocerebrosidase leads to an accumulation of its substrate, glucosylceramide in macrophages of various tissues. Common clinical manifestations include cytopenia, splenomegaly, hepatomegaly, and bone lesions. The phenotype of GD is classified into three clinical categories: Type 1 (non-neuronopathic) is characterized by involvements on the viscera, whereas types 2 and 3 (neuronopathic) are associated with not only visceral symptoms but also neurological impairment, either severe in type 2 or variable in type 3. A diagnosis of GD can be confirmed by demonstrating the deficiency of acid glucocerebrosidase activity in leukocytes. Mutations in the *GBA1* should be identified as they may be of prognostic value in some cases. Biomarkers including Chitotriosidase, CCL18, and glucosylsphingosine (lyso-GL1) are useful in diagnosis and treatment monitoring. Currently available disease-specific treatment in Korea consists of intravenous enzyme replacement therapy and substrate reduction therapy. For enhancing long-term prognosis, the onset of Parkinson's disease and Lewy body dementia, or the occurrence of a blood disease or cancer (hepatocellular carcinoma) should be monitored in older patients. The development of new strategies that can modify the neurological phenotype are expected, especially in Asia including Korea, where the prevalence of neuronopathic GD is relatively higher than that in western countries.

Keywords: Gaucher disease, Glucocerebrosidase, *GBA1*, Biomarkers, Enzyme replacement therapy, Substrate reduction therapy

Introduction

Gaucher disease (GD, OMIM #230800) is a rare autosomal recessive inherited metabolic disease caused by mutations in the *GBA1*. This leads to a deficiency of the lysosomal enzyme, glucocerebrosidase (GCase, also called glucosylceramidase or acid β-glucosidase, EC: 4.2.1.25), which hydrolyzes glucosylceramide (GlcCer) into ceramide and glucose. The phenotype is variable but can be categorized into three clinical forms: type 1 typically presented with visceral symptoms including cytopenia, hepatosplenomegaly, and bone lesions cytopenia, splenomegaly, hepatomegaly, and bone lesions without neurological impairment, whereas types 2 and 3 are characterized by neurological damages. However, these distinctions are not absolute, and it is increasingly recognized that neuropathic GD represents a phenotypic continuum, ranging from extrapyramidal syndrome in type 1, at the mild end, to hydrops fetalis at the severe end of type 2. In Europe and North America, the incidence is reported around 1/40,000 to 1/60,000 births in the general population, but it can reach 1/800 births in the Ashkenazi Jewish population[1] and most of the patients (>90%) are type 1. In Korea, although the incidence has not been reported, it seems much lower than that of western countries, given that under 100 unrelated families with GD have been diagnosed and treated to date. Furthermore, approximately half of the patients are type 2 or 3[2].

Pathophysiology

A deficiency of GCase that attribute to the accumulation of the substrate, GlcCer in macrophages. The consequences of GlcCer accumulation in macrophage is inducing the transformation into Gaucher cells with called "crumpled tissue paper" appearance which is resulted from the presence of GlcCer aggregates in the macrophages under microscopic exam[3]. The monocyte/

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macrophage lineage is preferentially altered because of their role in eliminating erythroid and leukocytes, which contain large amounts of glycosphingolipids, a source of GlcCer[4]. However, the pathophysiological mechanisms of neurological involvement remain poorly understood. In addition to the role of substrate accumulation, inflammatory processes are also attribute the disease pathophysiology. Various cytokines and chemokines including IL-1β, IL-6, IL-8, TNFα (Tumor Necrosis Factor), M-CSF (Macrophage-Colony Stimulating Factor), MIP-1β, IL-18, IL-10, TGFβ, CCL-18, chitotriosidase, CD14s, and CD163s are present in increased amounts in Gaucher patients' plasma and could be implicated in hematological and bone complications[4-6]. Osteoporosis may be linked to IL-10, which inhibits osteoblast activity, but also to IL-1β, IL-6 and M-CSF, MIP-1α and MIP-1β, which stimulate bone resorption by increasing osteoclast activity[6]. Recently, Mystry et al.[7] reported another pathophysiologic mechanism by demonstrating alternative metabolic pathway of accumulated GlcCer in which a ceramidase transforms it into glucosylsphingosine (or lyso-glucosylceramide, lyso-GL1), which then diffuses into fluids due to its reduced hydrophobicity. This pathway is favored in cases of GCase deficiency. In the cytoplasm, glucosylsphingosine is metabolized by a second GCase that is active at a neutral pH (*GBA2* gene), producing sphingosine and then sphingosine-1-phosphate[8,9]. Glucosylsphingosine is normally absent from the human brain, but it is detectable in the brains of patients with GD-related neurological lesions, even if Gaucher cells are not observed in their nervous system. In addition, abnormalities in the intracellular trafficking of glucocerebrosidase are also been demonstrated[10,11].

Clinical Manifestations

1. Type 1 Gaucher disease

Type 1 GD (GD1), usually distinguished by the absence of neurological impairment, is the most common form in Europe and North America (90–95% of the GD patients). Its clinical presentation is variable, ranging from asymptomatic throughout life to early-onset forms presenting in childhood. Indeed, the majority of the patients are diagnosed before 20 years old[4]. Splenomegaly observed most commonly, in more than 90% of patients and hepatomegaly is noted in 60%–80% of patients[4]. Fatigue is common (50% of patients) and often has an impact on school life or social activities. In children, growth retardation and delayed puberty are common[12]. Up to 40% of GD1 patients have a focal lesion in the liver and/or spleen. A gaucheroma is the most likely diagnosis, but a hepatocellular carcinoma or a lymphoma of the spleen are other possible diagnoses. Gaucheromas have varied imaging characteristics and it is therefore difficult to distinguish a gaucheroma from another lesion[13]. The prevalence of gallstones in GD1 is 32%, much higher than in the general population[14]. Bile analyses reveal cholesterol stones and GlcCer. Pulmonary involvement may be related to infiltration of the lungs by Gaucher cells, creating an interstitial disease that can lead to pulmonary fibrosis, restrictive lung disease[4]. Bone involvement causes acute pain manifested as very painful bone crises, predominantly in the pelvis and lower limbs (more rarely in the upper limbs), and/or chronic pain[15]. There are several explanations of the bone crisis including ischemic vaso-occlusion, spontaneous of trabecular microfractures, alterations in the bone marrow or immune cells, inflammation, macrophage-derived factors, cytokines, and hormones[16,17]. Acute painful bone crises are more common in children (30% of children with GD1). They usually progress over 7–10 days and are associated with local inflammation, mild fever, polynuclear leukocytosis and a moderate inflammatory syndrome. These symptoms are similar to osteomyelitis, thus sometimes delaying diagnosis[15,18]. AVN is observed in 15% of cases, most often at the femoral or humeral heads. The prevalence of osteopenia or osteoporosis is higher than that of in normal population and accompanied in earlier age. Contrary to the conventional definition of GD1, certain neurological manifestations associated with this phenotype have been described in recent years. Patients with GD1 have an increased risk of developing Parkinson's disease (4–20 times greater), often at an earlier age than in normal PD[19-22]. The prevalence of minimally symptomatic peripheral neuropathies and small fiber neuropathies is 14% and therefore higher than in the general population[23].

2. Type 2 Gaucher disease

Type 2 GD is characterized by early and severe neurological impairment starting in 3–6 months old and by systemic involvement with hepatosplenomegaly. The triad consisting of opisthotonus, bulbar signs (particularly severe swallowing disorders), and oculomotor paralysis (or bilateral fixed strabismus) is very suggestive of the disease[4]. Apnea related to increasingly frequent and lengthy laryngeal spasms occurs after a few months. Seizures occurring later manifest as myoclonic epilepsy that is resistant to antiepileptic drugs. Splenomegaly is almost always present, associated with thrombocytopenia in 60% of cases. Death occurs before the third year of life, following massive aspiration or prolonged apnea[24]. The mean survival age of GD2 is 11.7 months

(range 2–25 months). Fetal GD is the rarest (<1%) and the most severe form of the disease. It usually manifests with hydrops fetalis, hepatosplenomegaly, ichthyosis, arthrogryposis, facial dysmorphia and fetal thrombocytopenia. Death often occurs in utero or soon after birth[25].

3. Type 3 Gaucher disease

Type 3 is also known as subacute or chronic form, and approximately up to 40% of GD is type 3 in Korea[2] whereas usually 5–10% of cases in western countries. The patients have visceral manifestations described in GD1, usually combined with oculomotor neurological involvement, which appears before 20 years of age in most cases. The severity of clinical symptoms is heterogeneous, particularly with regard to neurological involvement. Some patients present moderate systemic involvement with horizontal ophthalmoplegia as the only neurological symptom, whereas others present more severe forms with varying neurological signs including progressive myoclonus epilepsy (16% of patients), cerebellar ataxia or spasticity (20%–50% of patients), and dementia in some cases[26]. Neurological signs may occur several years after the visceral manifestations, even in patients initially identified and treated as having GD1. Disease onset is more common in young children, with neurological symptoms appearing before 2 years of age in half the cases[26]. Cardiac involvement with valve calcification are reported mainly in patients with GD3 of the c.1342G>C (D409H) genotype[27].

Diagnosis

1. Enzyme assay

The diagnosis of GD often takes several years after the onset of the first clinical and laboratory signs due to the rarity of the disease. The diagnosis of GD must be confirmed by establishing deficient GCase activity in leukocytes, or cultured fibroblasts. The residual enzyme activity is usually approximately 10%–15% of the normal value[28]. Dried blood spots can also be used for the enzymatic assay, but any potential deficiency should be confirmed using the previous method.

2. Genetics analysis

The molecular analysis of *GBA1* can be necessary for the definite diagnosis. The interpretation of genetic analysis needs high precaution because of the presence of a highly homologous pseudogene (*GBAP*) at the same locus (16 kb downstream) which is responsible for recombination events between *GBAP* and *GBA1* (e.g., RecNciI allele)[29]. More than 400 mutations have been described in the *GBA1*, some of them (c.1226A>G (N370S), c.84dup, c.1448T>C and c.115+1G>A), are more common in Ashkenazi Jewish GD1 patients. However, these mutations are rarely observed in Asian populations. There are some known genotype-phenotype correlations. Patients homozygous for the N370S mutation can remain asymptomatic for a long time, whereas those homozygous for the L444P mutation are at a high risk of developing neurological impairment (GD2 or GD3). In Korean population, G46E is a unique mutation with founder effect[2,30] and has been reported as neuroprotective allele[30].

3. Biomarkers

Tartrate-resistant acid phosphatase (TRAP) and angiotensin converting enzyme (ACE) was the traditional biomarkers. Their lack of specificity and the availability of more specific biomarkers have rendered them less useful nowadays[31]. Ferritinemia is higher than normal in most GD patients (>85%), while serum iron, transferrin saturation and soluble transferrin receptor concentrations remain normal[32].

Chitotriosidase, produced in large amount by Gaucher cells, is generally very high without treatment, so it can be used to monitor treatment efficacy and is considered to have some prognostic value[33]. However, chitotriosidase levels can vary considerably among patients; indeed, a mutation (24-bp duplication) in the *CHIT1* gene leads to total deficiency (homozygosity for the mutation) in 6% of the general population and chitotriosidase activity is low and difficult to interpret in a third of patients with a heterozygous mutation[34]. Increased chitotriosidase levels are also observed, but to a lesser extent, in other diseases (e.g., Niemann–Pick diseases, sarcoidosis, β-thalassemia, multiple sclerosis, Alzheimer's disease, or visceral leishmaniasis[4]. CCL18, a chemokine produced by macrophages (Gaucher cells), are 10–50 times higher in plasma of GD patients than those of controls[35,36]. Glucosylsphingosine (lyso-GL1) is a novel biomarker whose sensitivity and specificity are superior to those of chitotriosidase and CCL18[8,37]. It was recently shown to be valuable for patient monitoring, but has yet to be assessed on a larger scale. chitotriosidase, CCL18, and glucosylsphingosine are closely related within the context of GD: they vary in the same direction and are generally correlated[38].

Management

Currently enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) are available for treating GD patients. The goal is to treat patients before the onset of complications, the sequelae of which are disabling or not improved by further treatment, including massive fibrous splenomegaly, AVN, secondary osteoarthritis, vertebral compression and other fractures, hepatic fibrosis and lung fibrosis. Bone marrow transplantation could cure patients with GD, but this treatment is no longer offered given its low benefit/risk ratio and the current availability of effective, well-tolerated therapies[4].

1. Enzyme replacement therapy

ERT is to supply the GCase lacking in the cells. After using an enzyme extracted from human placenta in the early 1990s, recombinant GCase has been developed and used. Enzymes are deglycosylated, exposing their mannose residues in order to allow their uptake by macrophage receptors and their transfer to lysosomes. Generally, for children and "at risk adults", a starting dose of 60 U/kg every other week (EOW) has been recommended[39]. After the achievement of therapeutic goals this may be reduced to not less than 30 U/kg EOW to prevent worsening skeletal involvement during long-term maintenance therapy[39]. ERT improves hematological abnormalities and quality of life within a few months[40]. Hepatosplenomegaly decreases more slowly, usually over a period of two years. Improvement of bone abnormalities is usually observed after 2–4 years of treatment, but some abnormalities remain irreversible (hepatic or splenic fibrosis, AVN and bone infarction sequelae, etc.). ERT is not indicated for GD2 as treatment has no impact on the rapid progression of its severe neurological symptoms[24]. There is no evidence that ERT has reversed, stabilized, or slowed the progression of neurological involvement. The drugs are generally tolerable with 2–14% of patients develop antibodies against the enzyme, usually without clinical signs. Allergic reactions are rare (<1.5% of patients) and include urticaria, diarrhea, hypotension or laryngeal discomfort. During pregnancy, ERT may be required, firstly to control the disease, since GD can worsen during pregnancy, and secondly to limit thrombocytopenia which can be harmful during pregnancy or childbirth and contraindicates epidural anesthesia[4]. Monitoring during treatment includes regular clinical, laboratory (including hematologic and biomarkers), and radiological evaluations every six month. GD3 patients require additional neurological monitoring.

2. Substrate reduction therapy

The aim of SRT is to reduce excess cell GlcCer by decreasing its production. Miglustat is a second-line treatment to be used when ERT is no longer accepted by the patient or cannot be used due to intolerance. It is strictly contraindicated during pregnancy and contraceptive methods must be used by both male and female patients. To date, miglustat has not been found to have any effect on neurological symptoms in GD3, despite the fact that it crosses the blood–brain barrier. Another substrate inhibitor, eliglustat was granted a marketing authorization in 2015 and available 2018 in Korea. It is also an orally administered GlcCer synthase inhibitor which is more specific and more potent than miglustat. It was evaluated in phase 1, 2 and 3 clinical studies comprising nearly 400 patients overall whose follow-up results were published after four years[41-43]. This drug is suggested as first-line treatment for patients with GD1. Due to potential drug–drug interactions, its use with CYP2D6 inhibitors calls for special caution, depending on the patient's metabolizer status (CYP2D6 genotyping required before any prescription). Eliglustat is not recommended in patients with pre-existing cardiac disease (e.g., congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia, long QT syndrome), and in concomitant use with Class 1A and Class III antiarrhythmics. Adverse effects are uncommon and usually mild, including headache and pain in limb extremities in less than 10% of cases. Eliglustat offers eligible patients a daily oral therapy alternative to biweekly infusions of ERT[44].

3. Supportive treatments

In the era of ERT, splenectomy should be avoided in GD patients. The potential consequences of splenectomy include the usual risks of infection, thrombosis or neoplasia[45] as well as a risk of worsening the GD[46] due to an increased risk of skeletal-related events, hepatic fibrosis, cirrhosis, hepatic carcinoma and pulmonary hypertension. Painful bone crises often require temporary immobilization and use of analgesics. The use of bisphosphonates is controversial in GD because the pathophysiology of bone mass decline remains poorly understood. Bisphosphonates are nonetheless often indicated in cases of persistent osteoporosis, especially in postmenopausal women[46]. Orthopedic surgery may be required for bone complications including AVN and pathological fractures. To prevent bleeding, GD patients should be evaluated for coagulation abnormalities, especially prior to surgery, dental and obstetric procedures.

Therapies Under Investigation

A preliminary gene therapy protocol to introduce the *GBA1* gene into hematopoietic cells was used on GD3 patients[47]. However, the results were disappointing as the GCase levels proved too low for any clinical effect. Lentiviral vector gene transfer techniques have been used in mouse models of GD with promising results, but this approach is still at the basic research stage[48]. Molecular chaperone approach that enables proteins to take on the specific configuration and helps the production of functional enzymes has been tried[49]. The effect is thought to be responsible for the positive results of pilot studies with ambroxol[50].

Conclusion

Although the disease awareness and the rate of diagnosis is increasing, GD 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. Currently, available treatments enable to improve cytopenias, organomegalies, bone manifestations, and patients' quality of life. However, outcomes may be unfavorable due to progressive, irreversible neurologic impairment (in GD2 and GD3) and disabling bone disease despite specific treatment. For enhancing long-term prognosis, the onset of Parkinson's disease and Lewy body dementia, or the occurrence of a blood disease or cancer (hepatocellular carcinoma) should be monitored. The therapeutic advances of developing new strategies that can modify the neurological phenotype are expected to be developed, especially in Asia including Korea, where the prevalence of neuronopathic GD is relatively high.

References

1. Grabowski GA. Phenotype, diagnosis, and treatment of Gaucher's disease. Lancet 2008;372:1263-71.
2. Jeong SY, Park SJ, Kim HJ. Clinical and genetic characteristics of Korean patients with Gaucher disease. Blood Cells Mol Dis 2011;46:11-4.
3. Lee RE. The fine structure of the cerebroside occurring in Gaucher's disease. Proc Natl Acad Sci U S A 1968;61:484-9.
4. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. Int J Mol Sci 2017;18:441-71.
5. Hollak CE, Evers L, Aerts JM, van Oers MH. Elevated levels of M-CSF, sCD14 and IL8 in type 1 Gaucher disease. Blood Cells Mol Dis 1997;23:201-12.
6. van Breemen MJ, de Fost M, Voerman JS, et al. Increased plasma macrophage inflammatory protein (MIP)-1alpha and MIP-1beta levels in type 1 Gaucher disease. Biochim Biophys Acta 2007;1772:788-96.
7. Mistry PK, Liu J, Yang M, et al. Glucocerebrosidase gene-deficient mouse recapitulates Gaucher disease displaying cellular and molecular dysregulation beyond the macrophage. Proc Natl Acad Sci U S A 2010;107:19473-8.
8. Dekker N, van Dussen L, Hollak CE, et al. Elevated plasma glucosylsphingosine in Gaucher disease: relation to phenotype, storage cell markers, and therapeutic response. Blood 2011;118:e118-27.
9. Mistry PK, Liu J, Sun L, et al. Glucocerebrosidase 2 gene deletion rescues type 1 Gaucher disease. Proc Natl Acad Sci U S A 2014;111:4934-9.
10. Ron I, Horowitz M. ER retention and degradation as the molecular basis underlying Gaucher disease heterogeneity. Hum Mol Genet 2005;14:2387-98.
11. Yang C, Wang H, Zhu D, et al. Mutant glucocerebrosidase in Gaucher disease recruits Hsp27 to the Hsp90 chaperone complex for proteasomal degradation. Proc Natl Acad Sci U S A 2015;112:1137-42.
12. Kaplan P, Andersson HC, Kacena KA, Yee JD. The clinical and demographic characteristics of nonneuronopathic Gaucher disease in 887 children at diagnosis. Arch Pediatr Adolesc Med 2006;160:603-8.
13. Regenboog M, Bohte AE, Somers I, van Delden OM, Maas M, Hollak CE. Imaging characteristics of focal splenic and hepatic lesions in type 1 Gaucher disease. Blood Cells Mol Dis 2016;60:49-57.
14. Taddei TH, Dziura J, Chen S, et al. High incidence of cholesterol gallstone disease in type 1 Gaucher disease: characterizing the biliary phenotype of type 1 Gaucher disease. J Inherit Metab Dis 2010;33:291-300.
15. Wenstrup RJ, Roca-Espiau M, Weinreb NJ, Bembi B. Skeletal aspects of Gaucher disease: a review. Br J Radiol 2002;75 Suppl 1:A2-12.
16. Clarke LA, Hollak CE. The clinical spectrum and pathophysiology of skeletal complications in lysosomal storage disorders. Best Pract Res Clin Endocrinol Metab 2015;29:219-35.
17. Marcucci G, Zimran A, Bembi B, et al. Gaucher disease and bone manifestations. Calcif Tissue Int 2014;95:477-94.
18. Yossipovitch ZH, Herman G, Makin M. Aseptic osteomyelitis in Gaucher's disease. Isr J Med Sci 1965;1:531-6.

19. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med 2009;361:1651-61.
20. Mazzulli JR, Xu YH, Sun Y, et al. Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell 2011;146:37-52.
21. Alcalay RN, Dinur T, Quinn T, et al. Comparison of Parkinson risk in Ashkenazi Jewish patients with Gaucher disease and GBA heterozygotes. JAMA Neurol 2014;71:752-7.
22. Bultron G, Kacena K, Pearson D, et al. The risk of Parkinson's disease in type 1 Gaucher disease. J Inherit Metab Dis 2010;33:167-73.
23. Biegstraaten M, Mengel E, Maródi L, et al. Peripheral neuropathy in adult type 1 Gaucher disease: a 2-year prospective observational study. Brain 2010;133:2909-19.
24. Mignot C, Doummar D, Maire I, De Villemeur TB. Type 2 Gaucher disease: 15 new cases and review of the literature. Brain Dev 2006;28:39-48.
25. Mignot C, Gelot A, Bessières B, et al. Perinatal-lethal Gaucher disease. Am J Med Genet A 2003;120a:338-44.
26. Tylki-Szymańska A, Vellodi A, El-Beshlawy A, Cole JA, Kolodny E. Neuronopathic Gaucher disease: demographic and clinical features of 131 patients enrolled in the International Collaborative Gaucher Group Neurological Outcomes Subregistry. J Inherit Metab Dis 2010;33:339-46.
27. George R, McMahon J, Lytle B, Clark B, Lichtin A. Severe valvular and aortic arch calcification in a patient with Gaucher's disease homozygous for the D409H mutation. Clin Genet 2001;59:360-3.
28. Neufeld EF. Lysosomal storage diseases. Annu Rev Biochem 1991;60:257-80.
29. Horowitz M, Wilder S, Horowitz Z, Reiner O, Gelbart T, Beutler E. The human glucocerebrosidase gene and pseudogene: structure and evolution. Genomics 1989;4:87-96.
30. Kim YM, Choi JH, Kim GH, et al. The GBA p.G85E mutation in Korean patients with non-neuronopathic Gaucher disease: founder and neuroprotective effects. Orphanet J Rare Dis 2020;15:318.
31. Aerts JM, Kallemeijn WW, Wegdam W, et al. Biomarkers in the diagnosis of lysosomal storage disorders: proteins, lipids, and inhibodies. J Inherit Metab Dis 2011;34:605-19.
32. Mekinian A, Stirnemann J, Belmatoug N, et al. Ferritinemia during type 1 Gaucher disease: mechanisms and progression under treatment. Blood Cells Mol Dis 2012;49:53-7.
33. van Dussen L, Hendriks EJ, Groener JE, Boot RG, Hollak CE, Aerts JM. Value of plasma chitotriosidase to assess non-neuronopathic Gaucher disease severity and progression in the era of enzyme replacement therapy. J Inherit Metab Dis 2014;37:991-1001.
34. Bussink AP, Verhoek M, Vreede J, et al. Common G102S polymorphism in chitotriosidase differentially affects activity towards 4-methylumbelliferyl substrates. Febs J 2009;276:5678-88.
35. Deegan PB, Moran MT, McFarlane I, et al. Clinical evaluation of chemokine and enzymatic biomarkers of Gaucher disease. Blood Cells Mol Dis 2005;35:259-67.
36. Boven LA, van Meurs M, Boot RG, et al. Gaucher cells demonstrate a distinct macrophage phenotype and resemble alternatively activated macrophages. Am J Clin Pathol 2004;122:359-69.
37. Rolfs A, Giese AK, Grittner U, 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.
38. Murugesan V, Chuang WL, Liu J, et al. Glucosylsphingosine is a key biomarker of Gaucher disease. Am J Hematol 2016;91:1082-9.
39. Andersson HC, Charrow J, Kaplan P, et al. Individualization of long-term enzyme replacement therapy for Gaucher disease. Genet Med 2005;7:105-10.
40. Barton NW, Brady RO, Dambrosia JM, et al. Replacement therapy for inherited enzyme deficiency--macrophage-targeted glucocerebrosidase for Gaucher's disease. N Engl J Med 1991;324:1464-70.
41. Lukina E, Watman N, Arreguin EA, et al. A phase 2 study of eliglustat tartrate (Genz-112638), an oral substrate reduction therapy for Gaucher disease type 1. Blood 2010;116:893-9.
42. Lukina E, Watman N, Dragosky M, et al. Eliglustat, an investigational oral therapy for Gaucher disease type 1: Phase 2 trial results after 4 years of treatment. Blood Cells Mol Dis 2014;53:274-6.
43. Mistry PK, Lukina E, Ben Turkia H, et al. Effect of oral eliglustat on splenomegaly in patients with Gaucher disease type 1: the ENGAGE randomized clinical trial. Jama 2015;313:695-706.
44. Belmatoug N, Di Rocco M, Fraga C, et al. Management and monitoring recommendations for the use of eliglustat in adults with type 1 Gaucher disease in Europe. Eur J Intern Med 2017;37:25-32.
45. Kristinsson SY, Gridley G, Hoover RN, Check D, Landgren O. Long-term risks after splenectomy among 8,149 cancer-

free American veterans: a cohort study with up to 27 years follow-up. Haematologica 2014;99:392-8.
46. Cox TM, Aerts JM, Belmatoug N, et al. Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring. J Inherit Metab Dis 2008;31:319-36.
47. Dunbar CE, Kohn DB, Schiffmann R, et al. Retroviral transfer of the glucocerebrosidase gene into CD34+ cells from patients with Gaucher disease: in vivo detection of transduced cells without myeloablation. Hum Gene Ther 1998;9:2629-40.
48. Dahl M, Doyle A, Olsson K, et al. Lentiviral gene therapy using cellular promoters cures type 1 Gaucher disease in mice. Mol Ther 2015;23:835-844.
49. Sanchez-Martinez A, Beavan M, Gegg ME, Chau KY, Whitworth AJ, Schapira AH. Parkinson disease-linked GBA mutation effects reversed by molecular chaperones in human cell and fly models. Sci Rep 2016;6:31380.
50. McNeill A, Magalhaes J, Shen C, et al. Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells. Brain 2014;137(Pt 5):1481-95.