Gaucher disease: an update

Dan L. Dumitrascu

2nd Department of Internal Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Abstract

Gaucher disease is a lysosomal storage disease affecting the bone marrow, spleen, liver, and nervous system. In Romania we follow up over 70 adult patients with Gaucher disease, who benefit from fully covered therapy. There is a need to screen for Gaucher disease, to diagnose early the condition and to use the best available therapy. This is a review of recent studies on Gaucher disease and is dedicated to trainees in medicine.

Keywords: Gaucher disease, enzyme replacing therapy, lysosomal disease, substrate reducing therapy, storage disease

Introduction

Gaucher disease (GD) is a rare disease with rather an average prevalence. In Romania we have more than 70 adult patients in evidence for GD and except two who refused therapy, all are under approved specific therapy.

It represents a hereditary condition of the metabolism of glucorerebrosides. It is caused by a genetic mutation, more frequently seen in Ashkenazi Jewish population, however encountered everywhere in the world. The mutation resides on chromosome 1 and is recessive. The gene codifying the synthesis of acid beta-glucosidase is localized on the long arm of the first chromosome (1q.21). Here there is an active gene including 11 exons and one pseudogene. The gene called GBA has several hundred described mutations including insertions, deletions or complex alleles. Two are the most common mutations: N370S and L444P.

The defect consists in a deficit of an enzyme called glucocerebrosidase or beta-glucosidase. When glucocerebrosidase is insufficient or inactive, the glucocerebrosides supposed to be catabolized by this enzyme accumulate in human cells. The accumulations, causing a so-called storage disease, are in the liver, spleen, bone marrow, kidneys, lungs and bone marrow (with implications in hematogenesis). The accumulating glucocerebrosides are nothing else than sugar containing cerebrosides (monosacharides) [1].

The storage of glycosphingolipids which are linked to cell (lysosomal) membranes are the cause of the lysosomal storage diseases. The insufficient or missing enzyme is in GD the β-glucocerebrosidase (acid β-glucosidase), which has an activity of glucosylceramidase, i.e. it produces the hydrolise of glucocerebrosides (a glycolipid). It has 497 aminoacids and a weight of 700 D.

Biomarkers for the diagnosis of GD

The diagnosis of GD has its gold standard by aspirative biopsy of the bone marrow. In this way we can evidence the existence of the typical accumulation cells. Unfortunately this method is rarely accepted and we rely therefore of biomarkers for GD.

Therefore we prefer to measure the enzymatic activity of the cerebrosidase from the dried blood spot [2-4]. The main biomarkers are presented in table I.

In GD, the ACE produced by activated splenic macrophages differs from that in liver macrophages, or in dendritic cells. This differences in structure of ACE is useful for the diagnosis of GD. PARC/CCL18 stands for Pulmonary and

DOI: 10.15386/mpr-2231

Address for correspondence:
ddumitrascu@umfcluj.ro

Activation-regulated Chemokine (PARC)/CCL18, first described in childhood lymphoblastic leukemia [5] and with minor importance now for GD.

Table I. Biomarkers for Gaucher disease.

Name	Observation
ACE	Influenced by common use of ACEI
Ferritin	Nonspecific
Tartrate-resistant acid phosphate	Methodological difficulties
Chitotriosidase	Not specific
PARC/CCL18	Also in autoimmune diseases
LysoGL1	For the moment the best biomarker

On the other hand, LysoGB1 is very useful [6]. The abbreviation stands for the substance glucosylsphingosine (lyso-Gb1), which represents a downstream result from the catabolism of glucosylceramid. This is an appropriated marker for diagnosis and also for evolution.

The therapy of GD

The field is quite poor for the moment although several drugs are filling the field. It is important that patients with GD have now the possibility to use expensive therapies even lifelong. The best choice is marrow transplantation but this therapy is not so easily available. Therefore we rely now on two established approaches: the enzyme substitution therapy (EST) and the substrate reduction therapy [7-11] (Table II).

Table II. Therapeutic alternatives in GD.

- **ERT: parenteral**
- Cerezyme® (imiglucerase)
- VPRIV® (velaglucerase alfa)
- Elelyso® (taliglucerase alfa)
- **SRT: enteral**
- Cerdelga® (eliglustat)
- Zavesca® (miglustat)

New therapies are expected, which should soon become available: use of Chaperons (small molecules), like in another lysosomal disease, Fabry disease; genetic therapy which would represent a major step forwards; and the oral administration of EST (for the moment available only as parenteral administration).

Association of GD with Parkinson disease

This is really the new kid on the block. Several papers were published recently about this topic [12-14]. The common link is represented by the gene GBA. It has indeed been observed that the mutations of the GBA gene, present also in GD and which encodes glucocerebrosidase are associated with Parkinson disease. But these mutations are not very specific, they can occur in other conditions not only in GD and Parkinson disease. They are also found in some forms of dementia and sleep disorders [12,15,16]. However the association of the GBA gene mutations with both GD and Parkinson open new research pathways for better diagnose and better to prevent Parkinson disease in GD.

Conclusions

Gaucher disease (GD) is a lysosomal storage disease which requires a good training of healthcare providers in order to early diagnose and correctly treat this condition with invalidating outcome. There are sufficient biomarkers for the diagnosis. Screening for suspicious cases should be undertaken. Therapy relies either on ERT or SRT according to specific indications and also preferences of the patient or its social ability to follow the therapy at home or in medical centers. The association of GD with Parkinson disease has been widely researched in the recent years. Both conditions have in common the association with GBA gene mutations.

References

1. Aerts JMFG, Kuo CL, Lelieveld LT, Boer DEC, van der Lienden MCJ, Overkleeft HS, et al. Glycosphingolipids and lysosomal storage disorders as illustrated by gaucher disease. Curr Opin Chem Biol. 2019;53:204-215.
2. Camassa JA, Diogo CC, Bordelo JPA, Bonelli MA, Viegas CA, Azevedo JT, et al. Tartrate-resistant acid phosphate as biomarker of bone turnover over the lifespan and different physiologic stages in sheep. BMC Vet Res. 2017;13:239.
3. Gaucher Disease: Biomarker Panel (ACE, CHITO, TRAP) Enzyme Activities, Serum. Available from: https://www.egl-eurofins.com/tests/?testid=BM
4. Danilov SM, Tikhomirova VE, Metzger R, Naperova IA, Bukina TM, Goker-Alpan O, et al. ACE phenotyping in Gaucher disease. Mol Genet Metab. 2018;123:501–510.
5. Struyf S, Schutyser E, Gouwy M, Gijsbers K, Proost P, Benoit Y, et al. PARC/CCL18 is a plasma CC chemokine with increased levels in childhood acute lymphoblastic leukemia. Am J Pathol. 2003;163:2065-2075.
6. Hurvitz N, Dinur T, Becker-Cohen M, Cozma C, Hovakimyan M, Oppermann S, et al. Glucosylsphingosine (lyso-Gb1) as a Biomarker for Monitoring Treated and Untreated Children with Gaucher Disease. Int J Mol Sci. 2019;20:3033.
7. Bennett LL, Mohan D. Gaucher disease and its treatment options. Ann Pharmacother. 2013;47:1182-1193.
8. Bennett LL, Turcotte K. Eliglustat tartrate for the treatment of adults with type 1 Gaucher disease. Drug Des Devel Ther. 2015;9:4639-4647.
9. Morales LE. Gaucher's disease: a review. Ann Pharmacother. 1996;30:381-388.
10. Morris JL. Velaglucerase alfa for the management of type 1 Gaucher disease. Clin Ther. 2012;34:259-271.

11. Grabowski GA, Golembo M, Shaaltiel Y. Taliglucerase alfa: an enzyme replacement therapy using plant cell expression technology. Mol Genet Metab. 2014;112:1-8.
12. Riboldi GM, Di Fonzo AB. GBA, Gaucher Disease, and Parkinson's Disease: From Genetic to Clinic to New Therapeutic Approaches. Cells. 2019;8:364.
13. Creese B, Bell E, Johar I, Francis P, Ballard C, Aarsland D. Glucocerebrosidase mutations and neuropsychiatric phenotypes in Parkinson's disease and Lewy body dementias: Review and meta-analyses. Am J Med Genet B Neuropsychiatr Genet. 2018;177:232-241.
14. Neumann J, Bras J, Deas E, O'Sullivan SS, Parkkinen L, Lachmann RH, et al. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. Brain. 2009;132(Pt 7):1783-1794.
15. Li Y, Sekine T, Funayama M, Li L, Yoshino H, Nishioka K, et al. Clinicogenetic study of GBA mutations in patients with familial Parkinson's disease. Neurobiol Aging. 2014;35:935.e3-e8.
16. Lesage S, Anheim M, Condroyer C, Pollak P, Durif F, Dupuits C, et al. Large-scale screening of the Gaucher's disease-related glucocerebrosidase gene in Europeans with Parkinson's disease. Hum Mol Genet. 2011;20:202-210.