HHS Public Access

Author manuscript

J Clin Neurosci. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

J Clin Neurosci. 2016 June ; 28: 185–186. doi:10.1016/j.jocn.2015.12.004.

Glucocerebrosidase Enzyme Activity in *GBA* Mutation Parkinson Disease

Roberto A. Ortega, MS[1], **Paola A. Torres, BS**[2], **Matthew Swan, MD**[1], **William Nichols, PhD**[3], **Sarah Boschung, BSN**[1], **Deborah Raymond, MS**[1], **Matthew J. Barrett, MD, MS**[1], **Brooke A. Johannes, MS, MSc**[1], **Lawrence Severt, MD, PhD**[1], **Vicki Shanker, MD**[1], **Ann L. Hunt, DO**[1], **Susan Bressman, MD**[1,4], **Gregory M. Pastores, MD**[2,5], and **Rachel Saunders-Pullman, MD, MPH**[1,4,*]

[1]Department of Neurology, Mount Sinai Beth Israel Medical Center, New York, NY, USA

[2]Department of Neurology, NYU Langone Medical Center, New York, NY, USA

[3] Division of Human Genetics, Cincinnati Children's Hospital Medical Center, and Department of Pediatrics; University of Cincinnati College of Medicine, Ohio

[4]Department of Neurology, Mount Sinai School of Medicine, NY, USA

Abstract

Mutations in the glucocerebrosidase (*GBA1*) gene, the most common genetic contributor to Parkinson's disease (PD), are associated with an increased risk of PD in heterozygous and homozygous carriers. While glucocerebrosidase enzyme (GCase) activity is consistently low in Gaucher disease, there is a range of leukocyte GCase activity in healthy heterozygous *GBA1* mutation carriers. To determine whether GCase activity may be a marker for PD with heterozygous *GBA1* mutations (*GBA1* mutation PD, *GBA* PD), *GBA* PD patients (n=15) were compared to PD patients without heterozygous *GBA1* mutations (idiopathic PD; n=8), heterozygous *GBA1* carriers without PD (asymptomatic carriers; n=4), and biallelic mutation carriers with PD (Gaucher disease with PD, GD1 PD; n=3) in a pilot study. GCase activity (nmol/mg protein/hour) in GD1 PD (median [interquartile range]; minimum–maximum: 6.4 [5.7]; 5.3–11) was lower than that of *GBA* PD (p=0.01), while GCase activity in *GBA* PD (16.0 [7.0]; 11–40) was lower than idiopathic PD (28.5 [15.0]; 16–56) (p=0.01) and asymptomatic carriers (25.5 [2.5]; 23–27) (p=0.04). Therefore, GCase activity appears to be a possible marker of

[*]**Corresponding author**: Rachel Saunders-Pullman, MD, MPH, The Alan and Barbara Mirken Department of Neurology, Mount Sinai Beth Israel Medical Center, 10 Union Square East, Suite 5J, New York, NY 10003 Phone: 212-844-8719 Fax: 212-844-8461, rsaunder@bethisraelny.org.

[5]Current address: Mater Misericordiae University Hospital, Dublin, Ireland

Conflicts of Interest/Disclosures

Dr. Severt has received personal compensation for activities with Teva Neuroscience, Allergan Inc., Merz Pharma, and UCB Pharma. Dr. Severt has received research support from Teva Neuroscience and Merz Pharma. Susan Bressman has received a royalty, license fee or contractual rights payment from Athena Diagnostics. The other authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

heterozygous *GBA1* mutation PD, and larger studies are warranted. Prospective studies are also necessary to determine whether lower GCase activity precedes development of PD.

Keywords

Biomarker; Gaucher; GBA; GBA1; GBA enzyme activity; Glucocerebrosidase; Parkinson's disease

1. Introduction

Heterozygous glucocerebrosidase enzyme (GCase) mutations (from the glucocerebrosidase gene [*GBA1*]) encode lysosomal GCase and increase the risk of Parkinson's disease (PD) and dementia with Lewy bodies [1,2]. However the penetrance of *GBA1* mutations is low [1,2]. While GCase activity is consistently decreased in type 1 Gaucher disease (GD1), a range of GCase activity in heterozygous *GBA1* mutation carriers exists [3,4]. To address the relationship between GCase activity and PD, this pilot study assesses GCase activity in *GBA1* mutation carriers, with and without PD, and non-carriers with PD (idiopathic PD).

2. Methods

Participants were recruited from a genetics study of PD in Ashkenazi Jews [6]. GCase activity from fresh blood was assayed using 4-methylumbelliferyl-β-D-glucopyranoside leukocyte assay [4] for 15 PD patients with heterozygous mutations (*GBA* PD) (12 N370S, one of each 84GG, R496H, and E326), eight idiopathic PD patients, four asymptomatic *GBA1* carriers (N370S, 84GG, R496H, and E326K) and three GD1 patients with PD (GD1 PD) (two previously reported; N370S/N370S, N370S/R496H, and N370S/A456P) [6]. Groups were compared using Mann–Whitney and Fisher's exact tests with Bonferroni correction. The internal review board approved this study.

3. Results

GCase activity (nmol/mg protein/hour) in *GBA* PD patients (median, interquartile range: 16.0, 7.0) was lower than idiopathic PD (28.5, 15.0) ($p=0.01$) and asymptomatic carriers (25.5, 2.5) ($p=0.04$), although the latter difference was not significant using a correction of $p<0.017$ (Fig. 1, Table 1). GCase activity in GD1 PD patients (6.4, 5.7) was lower than *GBA* PD patients ($p=0.01$).

4. Discussion

Lower peripheral GCase activity is associated with *GBA* PD, suggesting that reduced peripheral GCase activity has potential as a marker of *GBA* PD. While the causal mechanism for GCase to produce synucleinopathies has not been fully explicated, a bi-directional loop has been reported, where deficiency of GCase promotes α-synuclein via excess substrate, resulting in stabilization of α-synuclein into oligomers, and greater GCase dysfunction [5]. This is supported by our finding of decreased GCase activity in *GBA* PD. Gain of function has also been proposed, as GCase co-localizes with α-synuclein in Lewy

bodies in *GBA* PD [7]. Alternatively, gain and loss of function mechanisms may co-exist. Additional study including a larger sample, a greater distribution of mutation types and asymptomatic carriers, and assessment of sphingolipid substrate and products may lend insight into leukocyte GCase activity as a marker and its mechanism.

Acknowledgements

This study was supported by the Bigglesworth Family Foundation, Empire State Clinical Research Training Program, the Marcled Foundation, and NIH-NINDS NS073836.We are grateful to the study participants, who donated their time and energy for this study, as well as to Mariel Pullman and Amanda Glickman for their work. Funding: Bigglesworth Family Foundation, Empire State Clinical Research Training Program, Marcled Foundation, NIH- NINDS NS073836.

Sources of Support: the Bigglesworth Family Foundation, Empire State Clinical Research Training Program, the Marcled Foundation, and NIH-NINDS NS073836.

References

[1]. Sidransky E, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med. 2009; 361:1651–61. doi: 10. 1056/NEJMoa0901281. [PubMed: 19846850]

[2]. Nalls MA, et al. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. JAMA Neurol. 2013; 70:727–35. doi: 10.1001/jamaneurol.2013.1925. [PubMed: 23588557]

[3]. McNeill A, et al. Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells. Brain. 2014; 137:1481–1495. doi:10.1093/brain/awu020. [PubMed: 24574503]

[4]. Raghavan SS, et al. Leukocyte β-glucosidase in homozygotes and heterozygotes for Gaucher disease. American Journal of Human Genetics. 1980; 32:158–173. [PubMed: 6770675]

[5]. Mazzulli JR, et al. Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell. 2011 doi: 146(1):37-52. doi: 10.1016/j.cell. 2011.06.001.

[6]. Saunders-Pullman R, et al. Gaucher disease ascertained through a Parkinson's center: imaging and clinical characterization. Mov Disord. 2010; 25:1364–1372. doi: 10.1002/mds.23046. [PubMed: 20629126]

[7]. Westbroek W, Gustafson AM, Sidransky E. Exploring the link between glucocerebrosidase mutations and parkinsonism. Trends in Molecular Medicine. 2011; 17(9):485–493. doi:10.1016/j.molmed.2011.05.003. [PubMed: 21723784]

Highlights

1. 1. As glucocerebrosidase mutations increase the risk of Parkinson Disease (PD), glucocerebrosidase enzyme activity in different groups was evaluated.
2. The primary focus of this pilot study was on PD patients with and without *GBA1* mutations.
3. Glucocerebrosidase enzyme activity was lower in *GBA1* heterozygous mutation carriers with PD when compared to non-*GBA1* mutation PD.
4. Larger prospective studies are warranted determine whether enzyme activity is associated with the development of PD.

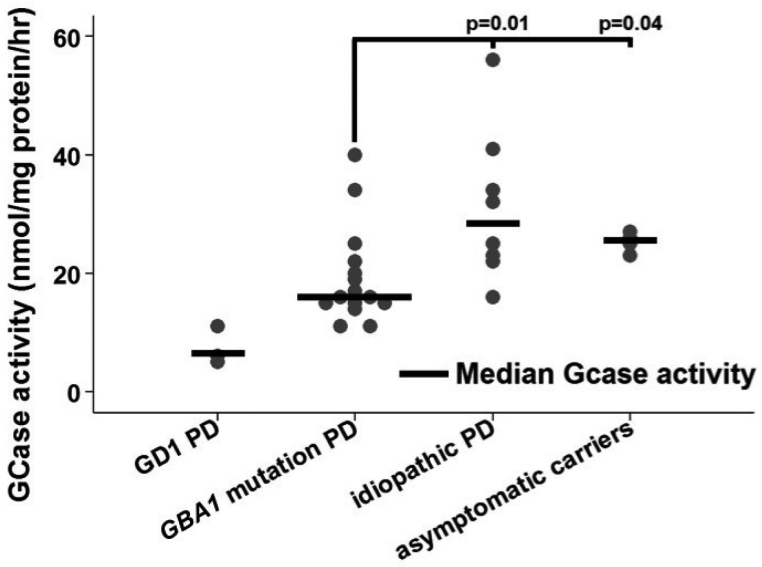

Fig. 1. Glucocerebrosidase enzyme (GCase) activity

Asymptomatic carriers = *GBA1* mutation carriers without Parkinson's disease, *GBA1* mutation PD = monoallelic *GBA1* mutation carriers with Parkinson's disease, GD1 PD = biallelic *GBA1* mutation carriers with Parkinson's disease, idiopathic PD = Parkinson's disease participants without *GBA1* mutations.

** GCase activity in GD1 PD (median 6.4, interquartile range 5.7) was lower than *GBA1* mutation PD (p=0.01). Each point represents the GCase activity measured for an individual.

Table 1

Summary of clinical features and glucocerebrosidase enzyme activity in Parkinson's disease and GBA1 mutation groups

					p value		
	GD1 PD (n=3)	***GBA1* PD (n=15)**	**IPD (n=8)**	**Non-PD carriers (n=4)**	***GBA1* PD *vs.* IPD**	***GBA1* PD *vs.* non-PD carriers**	**IPD *vs.* non-PD carriers**
Women, % (n)	66.7 (2)	40.0 (6)	25.0 (2)	50.0 (2)	0.66	0.57	0.55
Age, years	58.0 (7.0)	67.0 (10.0)	63.5 (11.5)	64.0 (4.5)	0.92	0.76	0.67
Onset age, years	53.0 (10.0)	59.0 (17.0)	57.5 (5.5)	---	0.90	---	---
Duration, years	5.0 (3.0)	10.5 (8.0)	5.0 (8.0)	---	0.67	---	---
H&Y stage	2.0 (1.5)	2.0 (1.0)	2.0 (0.0)	---	0.17	---	---
Activity [a]	6.4 (5.7)	16.0 (7.0)	28.5 (15.0)	25.5 (2.5)	0.01	0.04	0.73

Data are presented as median (interquartile range) unless otherwise indicated. *GBA1* PD = monoallelic GBA1 mutation carriers with Parkinson's disease, GD1 PD = biallelic GBA1 mutation carriers with Parkinson's disease, H&Y = Hoehn and Yahr, IPD = idiopathic Parkinson's disease participants without GBA1 mutations, Non-PD carriers: GBA1 mutation carriers without Parkinson's disease, *vs.* = *versus*.

[a] nmol/mg protein/hour.