For patients with EA4, gabapentin enables an uneventful shopping experience down the grocery aisles, depending less on the shopping cart as a gait-assisting device.

Although we feel these observations may provide insight into the neuropathology of this rare disease, we do not propose that they can be generalized. We do not recommend the use of gabapentin to treat vertigo of any other etiology at this time. More investigation is needed.

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References

1. Bird TD. Hereditary ataxia overview. In: Adam MP, Arndiger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle, WA: University of Washington; 1993-2018. 1998 Oct 28 [Updated 2019 Jul 25]. https://www.ncbi.nlm.nih.gov/books/NBK1138/. Accessed September 26, 2020.

2. Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD. MIM Number: 606552: June 11, 2019: World Wide Web. https://omim.org/entry/606552. Accessed September 26, 2020.

3. Farmer TW, Mustian VM. Vestibulocerebellar ataxia. A newly defined hereditary syndrome with periodic manifestations. Arch Neurol 1963;8:471–480.

4. Vance JM, Pericak-Vance MA, Payne CS, Coin JT, Olanow CW. Linkage and genetic analysis in adult onset periodic vestibulocerebellar ataxia: report of a new family. Am J Hum Genet 1994;56(suppl):788.

5. Farris BK, Smith JL, Ayyar DR. Neuro-otrophalmologic findings in Vestibulocerebellar Ataxia. Arch Neurol 1986;43:1050–1053.

6. Small KW, Pollock SC, Vance JM, Stajich JM, Pericak-Vance M. Ocular motility in North Carolina autosomal dominant ataxia. J Neuroophthalmol 1996;16:91–95.

7. Damji KF, Allingham RR, Pollock SC, et al. Periodic vestibulocerebellar ataxia, an autosomal dominant ataxia with defective smooth pursuit, is genetically distinct from other autosomal dominant ataxias. Arch Neurol 1996;53:338–344.

8. Merrill MJ, Nai D, Ghosh P, Edwards NA, Hallett M. Ray-Chaudhury A. Neuropathology in a case of episodic ataxia type 4. Neuropathol Appl Neurobiol 2000;26:231–239.

9. Kheradmand A, Zee DS, Cerebellum and ocular motor control. Frontiers Neurol 2011; 2(Article 53): 1–15. https://www.frontiersin.org/article/10.3389/fneur.2011.00053. Accessed September 26, 2020.

10. Andrews CO, Fischer JH. Gabapentin. A new agent for the management of epilepsy. Ann Pharmacother 1994;28:1188–1196.

11. Tjandrawinata RA, Setiawati E, RSI P, et al. Single dose pharmacokinetic equivalence study of two gabapentin preparations in healthy subjects. Drug Des Devel Ther 2014;8:1249–1255.

12. Gee NS, Brown JP, Dissanayake VUK, Offord J, Thurlow R, Woodruff GN. The novel anticonvulsant drug, gabapentin (neurontin),binds to the α2β subunit of a calcium channel. J Biol Chem 1996;271:5768–5776.

13. Brown JP, Gee NS. Cloning and deletion mutagenesis of the α2β Calcium Channel subunit from porcine cerebral cortex: expression of a soluble form of the protein that retains [3H] gabapentin binding activity. J Biol Chem 1998;273:25458–25465.

14. Wang M, Offord J, Oxender DL, Tri-Zhi S. Structural requirement of the calcium-channel subunit α2β for gabapentin binding. Biochem J 1999;342:313–320.

15. Marais E, Klughauer N, Hofmann F. Calcium channel α2β subunits - structure and gabapentin binding. Mol Pharmacol 2001;59: 1243–1248.

16. Dolphin A. Calcium channel auxiliary α2β and β subunits: trafficking and one step beyond. Nat Rev Neurosci 2012;13:542–555.

17. Davies A, Douglas I, Hendrich J, et al. The calcium channel α2β-2 subunit partitions with CaV2.1 into lipid rafts in cerebellum: implications for localization and function. J Neurosci 2006;26:8748–8757.

18. Gazzola J, Tintoré M. The P/Q-type voltage-dependent calcium channel as pharmacological target in spinocerebellar ataxia type 6: gabapentin and pregabalin may be of therapeutic benefit. Med Hypotheses 2007;68:131–136.

19. Nakamura K, Yoshioka K, Miyazaki D, Morita H, Ikeda S. Spinocerebellar ataxia type 6 (SCA6): clinical pilot trial with gabapentin. J Neurol Sci 2009;278:107–111.

20. Averbuch-Heller L, Tusa RJ, Fuhrly L, et al. A double-blind controlled study of gabapentin and baclofen as treatment for acquired nystagmus. Ann Neurol 1997;41:818–825.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.

Profiling the Biochemical Signature of GBA-Related Parkinson’s Disease in Peripheral Blood Mononuclear Cells

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ABSTRACT: Background: GBA mutations are the commonest genetic risk factor for Parkinson’s disease (PD) and also impact disease progression. 

Objective: The objective of this study was to define a biochemical profile that could distinguish GBA-PD from non-mutated PD.

Methods: 29 GBA-PD, 37 non-mutated PD, and 40 controls were recruited; α-synuclein levels in plasma, exosomes, and peripheral blood mononuclear cells were analyzed, GCase and main GCase-related lysosomal proteins in peripheral blood mononuclear cells were measured.

Results: Assessment of plasma and exosomal α-synuclein levels did not allow differentiation between GBA-PD and non-mutated PD; conversely, measurements in peripheral blood mononuclear cells clearly distinguished GBA-PD from non-mutated PD, with the former group showing significantly higher α-synuclein levels, lower GCase activity, higher LIMP-2, and lower Saposin C levels.

Conclusion: We propose peripheral blood mononuclear cells as an easily accessible and manageable model to provide a distinctive biochemical profile of GBA-PD, potentially useful for patient stratification or selection in clinical trials. © 2021 The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: α-synuclein; glucocerebrosidase; Parkinson’s disease; exosomes; phenotyping

Parkinson’s disease (PD) is a common neurodegenerative disorder mainly characterized by dopaminergic neuronal loss in the substantia nigra and α-synuclein protein aggregation.

Genetic factors are well known to contribute to PD susceptibility. In particular, heterozygous mutations in the GBA gene, encoding lysosomal enzyme glucocerebrosidase (GCase), represent the commonest genetic risk factor for PD, occurring in 7%–15% of PD patients and conferring a 5%–25% increased risk of developing the disease.1–3 Given the relevance and frequency of GBA-related PD (GBA-PD) and the intensive research efforts toward the development of targeted therapeutic strategies, the identification of reliable biomarkers for this genetic PD subtype represents a still unmet need.

Although the mechanisms linking GBA mutations to PD still remain unclear, a vicious circle between GCase and α-synuclein has been elucidated, with GCase reduction leading to α-synuclein accumulation and, in turn, increased α-synuclein inhibiting residual GCase function.4,5 Because lysosomes are known to play a major role in α-synuclein degradation,6 the levels of GCase and other lysosomal enzymes have been measured in cerebrospinal fluid (CSF) of patients in combination with pathological α-synuclein, suggesting these values could provide a biochemical fingerprint of PD.7,8 CSF collection, however, requires a relatively invasive procedure, not suitable for mass screenings.

Pathological α-synuclein, as well as other misfolded proteins, can spread from cell to cell through exosomes. These are extracellular vesicles that can be easily isolated from peripheral blood and whose content may reflect disease-specific changes. In the presence of dysfunctional lysosomal activity, the accumulation of cytosolic α-synuclein may result in its increased release through exosomes,9,10 making them a promising biomarker for PD.11,12

Here we attempted to define a biochemical profile of GBA-PD by comparing α-synuclein levels in plasma, exosomes, and peripheral blood mononuclear cells (PBMCs), as well as GCase-related lysosomal proteins (GCase, lysosomal integral membrane protein-2 [LIMP-2], saposin C, cathepsin D, and lysosome-associated membrane glycoprotein 1 [LAMP-1]) in PBMCs obtained from PD patients with and without GBA mutations.

Methods

The details are in the Supplementary File.

Subjects

We recruited 66 PD (29 GBA-PD and 37 non-mutated [NM-PD]) and 40 healthy individuals (HC) as a control group. The study was approved by the local ethics committee. PD patients underwent a complete neurological assessment to detect and quantify motor and nonmotor signs.

Biochemical Assessment

A 35-mL blood sample was obtained for isolation of whole plasma, exosomes, and PBMCs. The α-synuclein levels in plasma and exosomes were tested by enzyme-
linked immunoassay. In PBMCs, expression of α-synuclein, GCase, LIMP-2, Saposin C, cathepsin D, and LAMP-1 was assessed by Western blotting, whereas GCase activity was measured fluorometrically.

**Statistics**

Statistical analysis was performed using Stata 13.0 (StataCorp, College Station, TX). Biochemical data comparison among the 3 groups was performed by the Kruskal–Wallis test followed by Dunn’s pairwise test (Bonferroni adjustment). GBA-PD patients were further divided into subgroups according to mutation severity; group comparison was performed using the analysis described above. The percentage of fold changes (relative to controls) for each biochemical parameter was next calculated in GBA-PD and NM-PD groups; differences were analyzed using Student’s t test. Correlations between biochemical and clinical parameters were assessed by the Spearman test.

**Results**

Groups were comparable for age, although GBA-PD subjects had an earlier disease onset but similar disease duration (Table 1), and showed worse scores on the Montreal Cognitive Assessment (MoCA), REM behavior Disorder Questionnaire (RBDsq), Parkinson’s Disease Sleep Scale (PDSS), Movement Disorder Society - Unified Parkinson’s Disease Rating Scale - motor subscale (MDS-UPDRS part III), Beck’s Depression Inventory (BDI), University of Pennsylvania Smell Identification Test (UPSIT) and Scale for Outcomes in Parkinson Disease – Autonomic (SCOPA-AUT) scales (Table S1).

On the biochemical side, both the GBA-PD and NM-PD groups showed significantly higher levels of exosomes, but not plasma or α-synuclein, compared with controls. When assessing PBMCs, GBA-PD significantly differed from other groups for higher α-synuclein and lower GCase activity, whereas the NM-PD group behaved similarly to controls (Table 1).

When comparing relative changes, we did not observe significant differences between GBA-PD and NM-PD groups in both plasma and exosomal α-synuclein levels, the latter being similarly elevated in both groups (Fig. 1A,B). Conversely, biochemical analysis of PBMCs disclosed a GBA-PD-specific profile, characterized by significantly higher α-synuclein and significantly lower GCase activity compared with NM-PD (Fig. 1C,D). Moreover, measurement of GCase-related lysosomal proteins showed lower saposin C and higher LIMP-2 in GBA-PD compared with NM-PD (Fig. 1E,F). No significant differences between groups were found for the other GCase-related lysosomal proteins (Fig. S1).

When GBA-PD participants were stratified by mutation type, carriers of severe variants showed higher PBMC α-synuclein compared with other categories, whereas GCase activity was significantly higher in carriers of risk variants than in the other subgroups (Table S3).

Investigation of clinical-biochemical links in the GBA-PD group showed a negative correlation between PBMC α-synuclein and MoCA scores ($r = -0.44$, $P = 0.01$; Table S4).

**Discussion**

Given the high frequency of GBA mutations among PD patients, a deep phenotypic and biochemical characterization of this genetic subgroup is now becoming mandatory. Along with a better understanding of the molecular mechanisms predisposing to PD, clinical-
biochemical profiles could be crucial to predicting PD development in GBA carriers, also paving the way to personalized treatment strategies.

As α-synuclein is the best-known player in PD pathogenesis and progression, most biomarker studies have focused on the relationship between defective GCase activity and α-synuclein levels in biological fluids. Indeed, lower GCase activity and reduced α-synuclein levels have been reported in the cerebrospinal fluid (CSF) of GBA-PD patients compared with NM-PD, with differences related to the severity of the mutation.7,8,15 Yet, only a few studies have explored this relationship in easily accessible body tissues such as the blood of GBA mutation carriers, showing good correlation between GCase activity reduction and increased oligomeric α-synuclein in plasma and dimeric α-synuclein in erythrocytes.16,17

To our knowledge, this is the first study reporting a thorough biochemical profiling of GBA-PD in blood, compared with both NM-PD patients and HC. First, we assessed α-synuclein levels not only in total plasma but also in plasma exosomes, because of their ability to reflect brain-related pathological changes.12,18 Then we

FIG. 1. Bar graph of the percentage fold changes of (A) plasma α-synuclein, (B) exosomal α-synuclein, (C) α-synuclein in PBMCs, (D) GCase activity in PBMCs, (E) PBMC levels of saposin C, and (F) LIMP-2 in GBA-PD and NM-PD relative to controls.
performed a complete characterization of PBMCs by measuring α-synuclein levels, GCase activity, and the expression of several GCase-related lysosomal proteins.

Although small variations in plasma α-synuclein levels were observed in GBA-PD and NM-PD compared with HC, no statistical differences emerged among groups, showing that this parameter is not distinctive for the GBA-PD condition and confirming its unreliability as a surrogate marker of synucleinopathy. Conversely, we found significantly higher exosome-associated α-synuclein in both PD groups compared with HC, in line with previous studies that specifically associated increased exosomal α-synuclein with PD. It was previously shown that pharmacological modulation of GCase activity in vivo was able to increase exosome-associated α-synuclein levels. However, the similar increase of exosomal α-synuclein in both PD groups suggests that this parameter is likely unrelated to GCase deficiency; but rather might rather reflect the overall neurodegenerative process and other PD-associated lysosomal dysfunctions.

Interestingly, PBMCs showed a unique biochemical profile that clearly distinguished GBA-PD from NM-PD. In fact, in addition to the clear reduction in GCase activity, we reported for the first time a significant increase in α-synuclein in PBMCs of GBA-PD compared with HC and NM-PD, whereas the 2 latter groups showed comparable levels, in line with previous data. This difference could result from the synergistic effect of impaired GCase activity and dysregulation of chaperone-mediated autophagy observed in PBMCs of GBA-PD, representing a potentially relevant biomarker of GBA-related disease. Of note, these parameters not only were able to differentiate GBA-PD from NM-PD and HC, but they also varied according to mutation severity, suggesting potential utility as stratification or selection in clinical trials and, within GBA-PD, to the limited number of subjects carrying mutations of different severity, which could mask additional significant differences. Thus, our data warrant replication in larger cohorts, especially to strengthen the outcome of stratification analysis by mutation type. Indeed, it is now clearly emerging that GBA mutation severity may influence PD characteristics and disease progression, and this could also potentially impact the biochemical profile.

A second limitation may reside in the semiquantitative nature of Western blot analysis, albeit this technique is routinely employed for biomarker discovery.

In conclusion, we propose PBMCs as a widely accessible and manageable model providing a distinctive biochemical profile of GBA-PD. If replicated in larger independent cohorts, this signature may serve as classifier for patient stratification or selection in clinical trials and would also deserve exploitation in prospective longitudinal studies to assess its value in monitoring disease progression and response to treatment or in detecting GBA carriers at higher risk of PD conversion, who would benefit from early start of neuroprotective strategies.

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Data Availability Statement

The data sets generated during the current study are available in the ZENODO repository (10.5281/zenodo.4300469).
References

1. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson’s disease. N Engl J Med 2009;361(17):1651–1661.

2. Goker-Alpan O, Lopez G, Vithayathil J, Davis J, Hallett M, Sidransky E. The spectrum of Parkinsonian manifestations associated with glucocerebrosidase mutations. Arch Neurol 2008;65(10):1333–1337.

3. Blandini F, Cilia R, Cerri S, et al. Glucocerebrosidase mutations and synucleinopathies: toward a model of precision medicine. Mov Disord 2019;34(1):9–21.

4. Schapira AHV, Chiasserini D, Becatti T, Parnetti L. Glucocerebrosidase in Parkinson’s disease: insights into pathogenesis and prospects for treatment. Mov Disord 2016;31(6):830–835.

5. Mazzulli JR, Xu YH, Sun Y, et al. Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell 2011;146(1):37–52.

6. Wong YC, Krainc D. Lysosomal trafficking defects link Parkinson’s disease with Gaucher disease. Mov Disord 2016;31(11):1610–1618.

7. Parnetti L, Chiasserini D, Persichetti E, et al. Cerebrospinal fluid α-synuclein and glucocerebrosidase increases exosome-mediated α-synuclein release and transmis-

8. Lerche S, Wurster I, Roeben B, et al. Parkinson’s disease: glucocerebrosidase 1 mutation severity is associated with CSF alpha-synuclein. Mov Disord 2014;29(8):1019–1027.

9. Alvarez-Erritx S, Seow Y, Schapira AH, et al. Lysosomal dysfunction increases exosome-mediated alpha-synuclein release and transmission. Neurobiol Dis 2011;42(3):360–367.

10. Papadopoulos VE, Nikolopoulos G, Antoniadou I, et al. Modulation of β-glucocerebrosidase increases α-synuclein secretion and exosome release in mouse models of Parkinson’s disease. Hum Mol Genet 2018;27(10):1696–1710.

11. Cerri S, Ghezzi C, Sampieri M, et al. The exosomal/total α-Synuclein ratio in plasma is associated with glucocerebrosidase activity and correlates with measures of disease severity in PD patients. Front Cell Neurosci 2018;12(May):125.

12. Shi M, Sheng L, Stewart T, Zabetian CP, Zhang J. New windows into the brain: central nervous system-derived extracellular vesicles in blood. Prog Neurobiol 2019;175:96–106.

13. Avenali M, Toffoli M, Mullin S, et al. Evolution of prodromal parkinsonian features in a cohort of GBA mutation-positive individuals: a 6-year longitudinal study. J Neurol Neurosurg Psychiatry 2019;90(10):1091–1097.

14. Mullin S, Beavan M, Bestwick J, et al. Evolution and clustering of prodromal parkinsonian features in GBA1 carriers. Mov Disord 2019;34(9):1365–1373.

15. Lerche S, Machtzan G, Wurster I, et al. Dementia with lewy bodies: GBA1 mutations are associated with cerebrospinal fluid alpha-synuclein profile. Mov Disord 2019;34(7):1069–1073.

16. Pchelina S, Emeljanov A, Baydakova G, et al. Oligomeric α-synuclein and glucocerebrosidase activity levels in GBA-associated Parkinson’s disease. Neurosci Lett 2017;636:70–76.

17. Papagianakis N, Korkos C, Stamelou M, et al. Alpha-synuclein dimerization in erythrocytes of patients with genetic and non-genetic forms of Parkinson’s disease. Neurosci Lett 2018;672:143–149.

18. Liu W, Bai X, Zhang A, Huang J, Xu S, Zhang J. Role of exosomes in central nervous system diseases. Front Mol Neurosci 2019;12(240):1–13.

19. Malek N, Swallow D, Grosse KA, Anichtchik O, Spillantini M, Grosset DG. Alpha-synuclein in peripheral tissues and body fluids as a biomarker for Parkinson’s disease - a systematic review. Acta Neurol Scand 2014;130(2):59–72.

20. Emmanouilidou E, Papagianakis N, Kouloula S, et al. Peripheral alpha-synuclein levels in patients with genetic and non-genetic forms of Parkinson’s disease. Parkinsonism Relat Disord 2020;73:33–40.

21. Zhao Z-H, Chen Z-T, Zhou R-L, Zhang X, Ye Q-Y, Wang Y-Z. Increased DJ-1 and α-synuclein in plasma neural-derived exosomes as potential markers for Parkinson’s disease. Front Aging Neurosci 2018;10:438.

22. Jiang C, Hopfner F, Katsikoudi A, et al. Serum neuronal exosomes predict and differentiate Parkinson’s disease from atypical parkinsonism. J Neurol Neurosurg Psychiatry 2020;91(7):720–729.

23. Ghidoni R, Benussi L, Bini G. Exosomes: the Trojan horses of neurodegeneration. Med Hypotheses 2008;70(6):1226–1227.

24. Prigione A, Piazza F, Brighina L, et al. Alpha-synuclein nitration and autophagy response are induced in peripheral blood cells from patients with Parkinson disease. Neurosci Lett 2010;477(1):6–10. https://doi.org/10.1016/j.neulet.2010.04.022.

25. Miki Y, Shimoyma S, Kon T, et al. Alteration of autophagy-related proteins in peripheral blood mononuclear cells of patients with Parkinson’s disease. Neurobiol Aging 2018;63:33–43.

26. Papagianakis N, Xilouri M, Korkos C, et al. Lysosomal alterations in peripheral blood mononuclear cells of Parkinson’s disease patients. Mov Disord 2015;30(13):1830–1834.

27. Ichinose Y, Ishiura H, Tanaka M, et al. Neuromaging, genetic, and enzymatic study in a Japanese family with a GBA gross deletion. Parkinsonism Relat Disord 2019;61:57–63.

28. Rocha EM, Smith GA, Park E, et al. Progressive decline of glucocerebrosidase in aging and Parkinson’s disease. Ann Clin Transl Neurol 2015;2(4):433–438.

29. Gegg ME, Burke D, Heales SJR, et al. Glucocerebrosidase deficiency in substantia nigra of parkinson disease brains. Ann Neurol 2012;72(3):453–463.

30. Alcalay RN, Levy OA, Waters CC, et al. Glucocerebrosidase activity in Parkinson’s disease with and without GBA mutations. Brain 2015;138(9):2648–2658.

31. Atashrazm F, Hammond D, Perera G, et al. Reduced glucocerebrosidase activity in monocytes from patients with Parkinson’s disease. Sci Rep 2018;8(1):15446.

32. Yap TL, Gruschus JM, Velayati A, Sidransky E, Lee JC. Saposin C protects glucocerebrosidase against α-synuclein inhibition. Biochemistry 2013;52(41):7161–7163.

33. Ron L, Horowitz M. ER retention and degradation as the molecular basis underlying Gaucher disease heterogeneity. Hum Mol Genet 2005;14(16):2387–2398.

34. Garcia-Sanz P, Orgaz L, Bueno-Gil G, et al. N370S-GBA1 mutation causes lysosomal cholesterol accumulation in Parkinson’s disease. Mov Disord 2017;32(10):1429–1432.

35. Fernandez HJR, Hartfield EM, Christian HC, et al. ER stress and autophagic perturbations lead to elevated extracellular α-synuclein in GBA-N370S Parkinson’s iPSC-derived dopamine neurons. Stem Cell Reports 2016;6(3):342–356.

36. Petrillo S, Schirripa T, Di Lazzaro G, et al. Systemic activation of Nrf2 pathway in Parkinson’s disease. Mov Disord 2020;35(1):180–184.

37. Blandini F, Sinforiani E, Pacchetti C, et al. Peripheral proteasome and caspase activity in Parkinson disease and Alzheimer disease. Neurology 2006;66(4):529–534.

38. Cila R, Tunesi S, Marotta G, et al. Survival and dementia in GBA-associated Parkinson’s disease: the mutation matters. Ann Neurol 2016;80(5):662–673.

39. Jesús S, Huertas I, Bernal-Bernal J, et al. GBA variants influence motor and non-motor features of Parkinson’s disease. PLoS One 2016;11(12):e0167749.