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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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-

TABLE 1. Demographics and biochemical data of the study cohort

	HC n = 40	GBA-PD n = 29	NM-PD n = 37	P (between)		
				p1	p2	p3
Male, n (%)	15 (38)	20 (69)	25 (68)	0.25	0.07	1.0
Age (y)	60.6 ± 7.1	58.7 ± 9.4	61.2 ± 6.7	0.18	1.0	0.14
Age at onset (y)		51.1 ± 10.3	57.2 ± 9.2	—	—	0.01[a]
Disease duration (y)		6.6 ± 4.8	7.7 ± 4.7	—	—	0.36
Plasma total α-synuclein (ng/mL)	14.7 ± 3.1	15.8 ± 3.4	14.1 ± 4.5	0.30	0.61	0.07
Exosomal α-synuclein (pg/mL)	14.2 ± 10.9	22.0 ± 16.1	22.9 ± 10.2	< 0.001[a]	< 0.001[a]	0.41
PBMCs — α-synuclein (% HC)	100.5 ± 19.9	145.3 ± 42.9	103.8 ± 26.7	< 0.001[a]	0.84	< 0.001[a]
PBMCs — GCase activity (nmol/mg protein/h)	10.0 ± 2.9	5.5 ± 1.1	9.3 ± 2.9	< 0.001[a]	0.51	< 0.001[a]
PBMCs — LIMP-2 protein (% HC)	103.3 ± 33.2	107.1 ± 30.5	92.8 ± 25.3	0.44	0.14	0.01[a]
PBMCs — saposin C protein (% HC)	100.7 ± 14.6	92.0 ± 17.1	106.8 ± 19.2	0.06	0.30	0.002[a]
PBMCs — LAMP-1 protein (% HC)	100.9 ± 16.0	99.4 ± 33.5	96.0 ± 22.9	0.50	0.12	0.79
PBMCs — GCase protein (% HC)	101.5 ± 28.9	109.9 ± 67.7	120.4 ± 58.2	1.0	0.33	0.32
PBMCs — cathepsin D protein (% HC)	100.3 ± 25.1	99.9 ± 34.7	97.3 ± 23.2	0.83	0.70	1.0

Data are reported as mean ± standard deviation. Group comparisons were performed with the Kruskal–Wallis test followed by post hoc analysis with the Dunn's pairwise comparison test (Bonferroni correction).
[a]Significant difference.
p1, HC vs GBA-PD; p2, HC vs NM-PD; p3, GBA-PD vs NM-PD.

linked immunosorbent assay.[11] 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.[13,14] Along with a better understanding of the molecular mechanisms predisposing to PD, clinical-
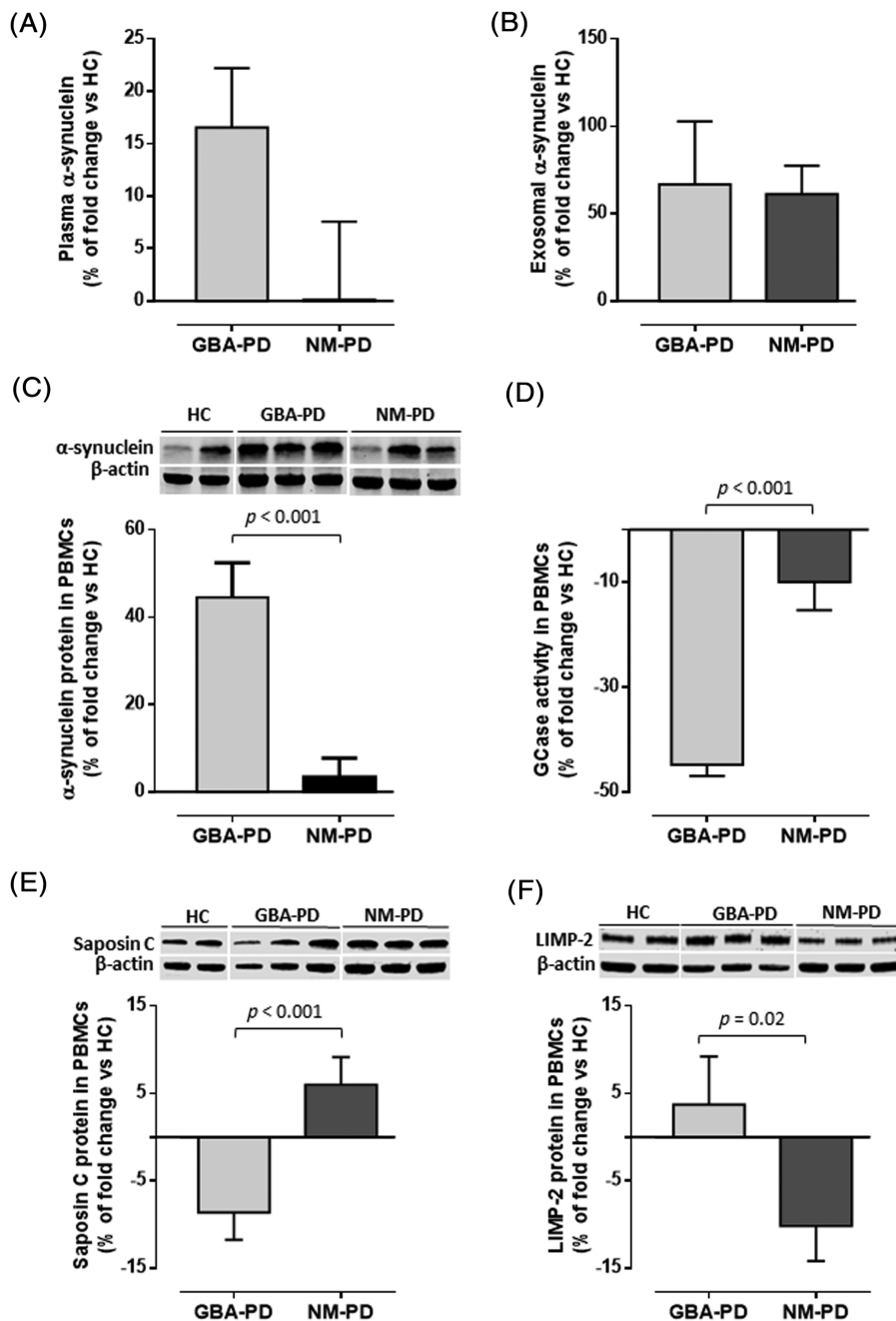
FIG. 1. Bar graph of the percentage fold changes of (**A**) plasma α-synuclein, (**B**) exosomal α-synuclein, (**C**) α-synuclein in PBMCs, (**D**) GCase activity in PBMCs, (**E**) PBMC levels of saposin C, and (**F**) LIMP-2 in GBA-PD and NM-PD relative to controls.

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

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.[19,20] 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.[12,21,22] It was previously shown that pharmacological modulation of GCase activity in vivo was able to increase exosome-associated α-synuclein levels.[10] 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[23] and other PD-associated lysosomal dysfunctions.[9]

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.[24,25] This difference could result from the synergistic effect of impaired GCase activity and dysregulation of chaperone-mediated autophagy observed in PBMCs of GBA-PD,[26,27] 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 biomarkers. Moreover, we observed a negative correlation between PBMC α-synuclein levels and MoCA scores in GBA-PD, suggesting that increased α-synuclein could mirror more rapid progression of the disease, particularly on the cognitive side.

We did not observe any difference in GCase activity levels between NM-PD and HC. Despite some studies having reported a reduction in GCase activity in the brains of NM-PD patients,[28,29] data concerning this activity in peripheral blood are still conflicting, showing small or negligible variations compared with HC.[16,30,31]

In addition to GCase and α-synuclein, PBMCs from GBA-PD patients also showed distinctive alterations in saposin C and LIMP-2 levels compared with NM-PD patients. Saposin C facilitates GCase activity and protects the enzyme from intracellular proteolysis and α-synuclein-mediated inhibition.[32] The observed reduction of saposin C in GBA-PD is a potential consequence of a negative feedback loop from increased α-synuclein or GCase unavailability within lysosomes[33,34] and might further affect GCase function, increasing cell

susceptibility to α-synuclein accumulation. Conversely, the increased levels of GCase transporter LIMP-2 could represent a compensatory mechanism to sustain GCase trafficking toward the lysosomes and, consequently, functionality. Accordingly, increased expression of LIMP-2 was observed in induced Pluripotent Stem Cells (iPSCs) derived from PD patients carrying the heterozygous GBA N370S mutation, compared with HC.[35] In our study, the lack of significant differences in LIMP-2 levels between GBA-PD and HC could possibly relate to the limited sample size in both groups and the presence of distinct mutations that can affect GCase function differently, as demonstrated by stratified analysis.

Overall, our findings highlight the key role of PBMCs as potential sources of biomarkers for PD[36,37] and suggest for the first time that lysosomal alterations in these cells may be considered valuable parameters to identify a biochemical profile distinctive of GBA-PD. Importantly, PBMCs can be collected easily and repeatedly throughout minimally invasive procedures in comparison with CSF or skin biopsy, supporting their usefulness also in clinical trials.

We acknowledge that a limitation of our study relates to the small sample sizes of the 3 groups 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.[8,38,39] 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. ■

Data Availability Statement

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

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Supporting Data

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