

Association of CSF Glucocerebrosidase Activity With the Risk of Incident Dementia in Patients With Parkinson Disease

Linn Oftedal, PhD, Jodi Maple-Grødem, PhD, Ingvild Dalen, PhD, Ole-Bjørn Tysnes, PhD, MD, Kenn Freddy Pedersen, PhD, MD, Guido Alves, PhD, MD, and Johannes Lange, PhD

Neurology® 2023;100:e388-e395. doi:10.1212/WNL.000000000000201418

Correspondence

Dr. Lange
johannes.lange@sus.no

Abstract

Background and Objectives

Variations in the glucocerebrosidase gene (*GBA*) are common risk factors for Parkinson disease (PD) and dementia in PD (PDD) and cause a reduction in the activity of the lysosomal enzyme glucocerebrosidase (GCase). It is anticipated that GCase dysfunction might contribute to a more malignant disease course and predict cognitive impairment in PD, although evidence is lacking. We aimed to discover whether CSF GCase activity is altered in newly diagnosed patients with PD and associated with future development of dementia.

Methods

Patients with PD were participants of the ongoing population-based longitudinal ParkWest study in Southwestern Norway and were followed prospectively for up to 10 years. CSF was collected at diagnosis, and *GBA* carrier status was obtained. Control samples were from persons without neurodegenerative disorders. GCase activity was measured using a validated assay. PD dementia diagnosis was set according to the Movement Disorder Society criteria, and parametric accelerated failure time models were applied to analyze the association of GCase activity with dementia-free survival.

Results

This study enrolled 117 patients with PD (mean age 67.2 years, including 12 *GBA* non-synonymous variant carriers) and 50 control participants (mean age 64 years). At the time of diagnosis, GCase activity was reduced in patients with PD with (mean \pm SD, 0.92 ± 0.40 mU/mg, $n = 12$) or without *GBA* variations (1.00 ± 0.37 mU/mg, $n = 105$) compared with controls (1.20 ± 0.35 , $n = 50$). GCase activity at the time of diagnosis was lower in patients with PD who developed dementia within 10 years (0.85 ± 0.27 mU/mg, $n = 41$) than in those who did not (1.07 ± 0.40 mU/mg, $n = 76$, $p = 0.001$). A 0.1-unit reduction in baseline GCase activity was associated with a faster development of PDD (hazard ratio 1.15, 95% CI 1.03–1.28, $p = 0.014$).

Discussion

The association of early CSF GCase activity with long-term progression to PD dementia will have important implications for the design of clinical trials for GCase targeting therapies and patient management.

Classification of Evidence

This study provides Class III evidence that reduced CSF GCase activity at the time of PD diagnosis is associated with an increased risk for later development of PDD.

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From the The Norwegian Centre for Movement Disorders (L.O., J.M.-G., K.F.P., G.A., J.L.), Stavanger University Hospital, Norway; Department of Chemistry, Bioscience and Environmental Engineering (J.M.-G., G.A., J.L.), University of Stavanger, Norway; Department of Research (I.D.), Section of Biostatistics, Stavanger University Hospital, Norway; Department of Neurology (O.-B.T.), Haukeland University Hospital, Bergen; Department of Clinical Medicine (O.-B.T.), University of Bergen, Norway; and Department of Neurology (K.F.P., G.A.), Stavanger University Hospital.

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Glossary

CV% = coefficient of variation; GBA = glucocerebrosidase gene; GCase = glucocerebrosidase; HR = hazard ratio; IQR = interquartile range; LP = lumbar puncture; MMSE = Mini-Mental State Examination; PD = Parkinson disease; PDD = dementia in PD.

Mutations Variations in the glucocerebrosidase gene (*GBA*) are common genetic risk factors for Parkinson disease (PD).¹ *GBA* encodes the lysosomal enzyme glucocerebrosidase (GCase) that hydrolyzes the major glycolipid glucosylceramide into glucose and ceramide. Reduced GCase activity impairs the autophagy lysosomal pathway resulting in increased levels of α -synuclein, the main constituent of Lewy bodies found in the brain of patients with PD.^{2,3} Furthermore, substantial evidence suggests a bidirectional relationship between GCase dysfunction and the accumulation of α -synuclein aggregates.^{4,5}

Clinically, patients with PD carrying a *GBA* mutation (*GBA*-PD) present with an earlier age at onset of disease and have a higher risk of cognitive impairment and progression to dementia, compared with noncarriers. Variations in *GBA* can cause a reduction in GCase activity and protein levels,⁶ considered to underlie the more malignant disease course in *GBA*-PD. Notably, GCase is found to be decreased in the brain of both *GBA*-PD and noncarriers,⁷⁻¹¹ suggesting a role for GCase also in the pathogenesis of idiopathic PD. In this context, an important question is whether GCase dysfunction is associated with a more severe disease course in both *GBA*-PD and idiopathic PD.

In this study, we measured CSF GCase activity in patients with PD from the time of diagnosis and analyzed the association with the risk of PD. Furthermore, given the link between *GBA* carrier status and the development of dementia, we analyzed the possible association of GCase activity and the development of dementia in PD (PDD) within 10 years of prospective follow-up. The primary research questions are as follows: (1) Are GCase activity levels altered in patients with PD at the time of diagnosis and (2) Is GCase activity at the time of diagnosis associated with development of PDD?

Methods

Participants

This study enrolled patients with PD from the Norwegian ParkWest study, an ongoing, prospective, population-based, longitudinal cohort study of newly diagnosed patients with PD identified in Southwestern Norway from 2004 to 2006.¹² Only those with a confirmed clinical diagnosis of PD according to the UK brain bank criteria¹³ at their latest or final clinical visit or pathologic confirmation (if postmortem examination was performed) were included. Of 190 patients, CSF was available for 120 participants. The control group was a set of 51 subjects without any known brain disease who underwent elective neurologic examination or orthopedic surgery at Stavanger

University Hospital. Samples from 3 patients with PD and 1 control were excluded for technical reasons (see details below). Thus, 117 patients with PD and 50 controls were eligible for this study (eTable 1, links.lww.com/WNL/C427).

Clinical Assessments

General medical and neurologic examinations and semi-structured interviews were performed at the time of diagnosis to obtain medical, drug, and family history. Motor severity, global cognition, and disease stage were determined using the Unified Parkinson's Disease Rating Scale part III,¹⁴ Mini-Mental State Examination (MMSE),¹⁵ and Hoehn and Yahr scale,¹⁶ respectively. From the control group, demographic data and MMSE were obtained.

Patients with PD were followed prospectively over a period for up to 10 years with extensive clinical workup at baseline, after 1 year, and every other year thereafter and with basic clinical and neurologic assessments every 6 months. During this study, 44 participants were lost to follow-up: 40 died (median time to death 7.1 [interquartile range {IQR} 5.0] years), and 4 dropped out of the study (median follow-up time 7.5 [IQR 6.8] years). PDD diagnosis was set according to the Movement Disorder Society criteria¹⁷ by 2 experienced movement disorders and dementia specialists (G.A. and K.F.P.).¹⁸ A diagnosis of PDD was made when patients during follow-up (1) exhibited cognitive decline as judged by clinical interview, MMSE, and neuropsychological tests, (2) had deficits in 2 or more cognitive domains that interfered with daily living, and (3) showed functional impairment not attributable to motor, neuropsychiatric, or autonomic symptoms. None of the PDD diagnoses were attributed to comorbidities that could cause or contribute to mental impairment, such as acute confusion to systemic diseases or drug intoxication, major depression, or cerebrovascular disease. No patients met the diagnostic criteria for dementia with Lewy bodies, Alzheimer dementia, or other dementia syndromes.

Standard Protocol Approvals, Registrations, and Patient Consents

All participants provided informed written consent to lumbar puncture (LP) as a part of their diagnostic workup. All procedures and ethical guidelines were approved by the Regional Committee for Medical and Health Research Ethics of Western Norway (REC West, issued June 11, 2012).

CSF Samples

CSF samples were available from 120 participants who consented to LP at study entry (PD diagnosis). LP was performed after overnight fasting and within 24 hours of clinical examinations. Median delay between time of PD diagnosis and LP was 38 days.

LP and sample treatment were conducted according to standardized procedures.¹⁹ All CSF samples were immediately cooled on ice, followed by centrifugation at 2000×g for 10 minutes at 4°C. Thereafter, samples were frozen at –80°C in polypropylene tubes. Samples were subjected to an additional freeze-thaw cycle for aliquotation purposes.

CSF Measurements

GCase activity was analyzed in CSF using our previously validated GCase activity assay.²⁰ CSF samples (diluted 1:2 in assay buffer) were mixed with 4-methylumbelliferyl-β-D-glucopyranoside as substrate. After 3 hours of incubation at 37°C, the concentration of the fluorescent cleavage product, 4-methylumbelliferyl, was measured (excitation: 360 nm/emission: 446 nm). All samples were analyzed in triplicates. Single replicate values were excluded if they deviated more than two-fold from the mean of the other 2 replicates (this affected only 3 samples in total). The lower limit of quantification of the GCase activity assay was 0.074 mU/mL. Mean GCase activity in CSF samples was 0.9 mU/mL (range 0.1–1.8 mU/mL). Mean sample coefficient of variation [CV%] was 5.8 (range 0.2–38.6). Only 5 samples exceeded a CV of 20%. Intra-assay CV% was 7.9 (9 assay plates and 2 quality control samples on each plate). One sample failed the assay, and 1 outlier with a GCase activity (4.7 mU/mL) more than 5 SDs above the global mean was excluded from the study analysis.²¹ One unit of GCase activity was defined as amount of enzyme that hydrolyzes 1 nmol of substrate/min at 37°C. A detailed protocol was published alongside the assay validation.²⁰ Storage time of samples before analysis varied between 15.2 and 17.4 years. There was no correlation between GCase activity and storage time (Kendall tau b = 0.04, *p* = 0.522).

CSF total protein content was measured in duplicate with the Pierce bicinchoninic acid protein assay kit (#23227; Thermo Fisher Scientific, Waltham, MA) following the manufacturer's instructions and 1:2 sample dilution. The lower limit of quantification of the bicinchoninic acid assay at 1:2 sample dilution was 0.29 mg/mL. Mean CSF protein concentration was 0.84 mg/mL (range 0.37–1.60 mg/mL). Mean sample CV% was 4.5 (range 0.0–18.8), and the mean intra-assay CV% was 1.6 (6 plates and 2–4 quality control samples on each plate). Two outliers with a total protein concentration (3.28 and 10.67 mg/mL) more than 5 SDs above the global mean were excluded from the study analysis.²¹

GBA Carrier Analysis

The presence of *GBA* mutations in our PD population has been published earlier.²² All 117 eligible patients with PD were characterized by whole-exome sequencing, and 5 nonsynonymous variants were detected (N370S, T369M, E326K, V460L, and Y135C). The L444P genotype was determined using restriction fragment length polymorphism (PCR-RFLP) assays. All variations were confirmed by direct sequencing.

Statistical Analysis

Descriptive statistics for continuous variables are presented as mean with SDs. Categorical variables are presented with counts

and percentages. Univariate analysis of between-group differences was performed using independent *t* tests or χ^2 tests as appropriate. A one-way analysis of covariance F-test was used for analysis of between-group differences of GCase activity with adjustment for age and sex. Kendall tau was used to assess the correlation between GCase activity and total protein concentration.

Parametric accelerated failure time models were chosen to analyze the association of GCase activity with dementia-free survival because they allow for interval censoring (left, last clinical visit without PDD; right, date of PDD diagnosis or infinity for those who remained dementia-free). *t* = 0 was set at the time of PD diagnosis. The Weibull model was deemed optimal (over other parametric models) for time to PDD using both the Akaike and the Bayesian information criteria in models adjusted for age, sex, and years of education. Coefficients from the Weibull model were transformed into hazard ratios (HRs), which are presented with 95% CIs. Based on our a priori hypothesis that lower GCase activity is associated with increased risk of PDD, the scale for GCase activity was reversed to investigate the effects of a 0.1-unit reduction of enzyme activity. Previously published CSF amyloid β1–42 concentrations,¹⁹ measured by ELISA (Innotest β-amyloid[1–42], Fujirebio, Zwijnaarde, Belgium), were available for 104 (89%) patients and were used as an additional covariate in secondary analyses.

In secondary analysis, we ranked baseline GCase activity and divided patients into equally sized tertiles. The group with the highest GCase activity (high) was set as the reference group and compared with the medium and low GCase activity groups. Parametric accelerated failure time models were applied as described above, and the Weibull model was again deemed optimal in the adjusted models. Coefficients from the Weibull model were transformed into HR, which are presented with 95% CIs. The effect sizes were comparable after additional adjustment for baseline MMSE score (data not shown). Non-parametric maximum likelihood estimates of the survival distributions for onset of PDD were constructed for the 3 groups.

All analyses were performed using SPSS version 26 (IBM, Armonk) and R with package survival, functions survfit and survreg. The plots of survival curves were created with function ggsurvplot of package survminer. For our primary hypothesis, a 2-tailed *p* value <0.05 was considered statistically significant.

Data Availability

Anonymized data are available on request by qualified investigators for the purposes of replicating procedures and results.

Results

GCase Activity in Early Clinical Stages of PD

The study included 117 newly diagnosed patients with PD and 50 control participants. Demographic data and clinical information are listed in the Table. Groups were comparable for age and education, but there was a different distribution of sex and MMSE score between the groups.

The GCase activity per ml CSF increased with increasing total protein concentration (Kendall tau = 0.298; $n = 167$; $p < 0.001$), and for further analyses, GCase enzymatic activity was normalized to the CSF total protein content (specific activity)²³ and expressed as mU/mg. GCase activity was reduced in patients with PD compared with control subjects (−17.4%; $p = 0.030$; Table; all PD; Figure 1A). GCase activity remained significantly reduced in the PD group compared with controls when considering only the PD *GBA* carriers (−23.1%; $p = 0.047$; *GBA*-PD; Figure 1A) or only the noncarrier PD group (−16.7%; $p = 0.043$; idiopathic PD; Figure 1A). Within the PD group, *GBA* carriers had a lower level of GCase activity (−7.7%; mean \pm SD, 0.92 ± 0.40 mU/mg) compared with those without a *GBA* variation (1.00 ± 0.37 mU/mg); however, this difference was statistically not significant ($p = 0.369$).

GCase Activity and Long-term Risk of PD Dementia

During follow-up, 41 (35%) patients with PD were diagnosed with dementia. The median time to PDD diagnosis for these individuals was 5.1 years (IQR 4.8 years; min 1.9, max 10.2),

whereas the median follow-up time for those who remained dementia-free was 10.0 years (IQR 1.8 years; min 0.9, max 10.6). GCase activity at the time of PD diagnosis was lower in patients who developed PDD (−20.3%; mean \pm SD, 0.85 ± 0.27 mU/mg) compared with patients who remained dementia-free until the last clinical visit or death (1.07 ± 0.40 mU/mg; $p = 0.042$; Figure 1B). Furthermore, compared with the control group, the GCase activity was lower in patients who developed PDD (−29.1%, $p = 0.002$) but not in patients who remained dementia-free during follow-up (−11%, $p = 0.162$).

Survival analysis was applied to assess the effect of reduced baseline GCase activity on the time to develop dementia over the first 10 years of PD. A 0.1-unit reduction in GCase activity was associated with a 15% increased risk of developing dementia (HR 1.15; 95% CI 1.03–1.28; $p = 0.014$). Furthermore, the association between baseline GCase activity and the development of PDD remained nearly unchanged when also controlling for baseline CSF amyloid β_{1-42} level (HR 1.13; 95% CI 1.03–1.28; $p = 0.013$). In subgroup analysis, the prognostic performance of baseline CSF GCase activity was explored in the 105 patients with PD without *GBA* variations. Also in non-*GBA* carriers, a 0.1-unit reduction in GCase activity was associated with faster progression to dementia (HR 1.18; 95% CI 1.04–1.33; $p = 0.009$). Again, this association remained unchanged after additional adjustment for CSF amyloid β_{1-42} level (HR 1.17; 95% CI 1.04–1.31; $p = 0.010$).

To further explore the relationship between GCase activity and the risk of PDD, patients were stratified into tertiles based on the level of GCase activity. Among individuals with baseline GCase activity in the lowest tertile, 53.8% developed dementia by the 10-year time point, compared with only 17.9% of patients in the highest tertile (HR 3.10; 95% CI 0.72–4.68; $p = 0.014$; Figure 2). The group of patients in the lowest GCase activity group were also at higher risk of PDD compared with those in the high GCase activity group (HR 3.91; 95% CI 0.91–7.60; $p = 0.011$) when only the 105 patients with idiopathic PD were included in the analysis.

Classification of Evidence

This study provides Class III evidence that reduced CSF GCase activity at the time of PD diagnosis is associated with an increased risk for later development of PDD.

Discussion

This study shows that CSF GCase activity is reduced already in early clinical stages of idiopathic PD and that reduced GCase activity at the time of diagnosis is a risk factor for PDD. Our findings are based on population-based incident PD cases followed prospectively with a comprehensive clinical program for up to 10 years, ensuring high diagnostic accuracy and comprehensive evaluation of the development of dementia. Our study extends findings of previous studies showing reduced GCase activity in CSF from patients in more moderate

Table Baseline Characteristics and GCase Activity of the Cohort

	Controls	PD	<i>p</i> Value
N	50	117	
Age, y	64.0 \pm 12.0	67.2 \pm 9.5	0.096 ^a
Sex: male, n (%)	21 (42%)	76 (65%)	0.006 ^b
Education, y	11.0 \pm 3.4	11.2 \pm 3.1	0.735 ^a
MMSE, total score	28.8 \pm 1.0	27.7 \pm 2.4	<0.001 ^a
UPDRS III, total score	—	22.4 \pm 10.6	—
Hoehn and Yahr stage, \geq 3, n (%)	—	10 (8.5)	—
Stage 1, n (%)	—	21 (17.9)	—
Stage 1.5, n (%)	—	28 (23.9)	—
Stage 2, n (%)	—	39 (33.3)	—
Stage 2.5, n (%)	—	19 (16.2)	—
Stage 3, n (%)	—	9 (7.7)	—
Stage 4, n (%)	—	1 (0.9)	—
Stage 5, n (%)	—	0	—
CSF measures			
Total protein, mg/mL	0.81 \pm 0.22	0.85 \pm 0.20	0.195 ^a
GCase, mU/mg	1.20 \pm 0.35	0.99 \pm 0.37	0.030 ^c

Values are presented as mean \pm SD.

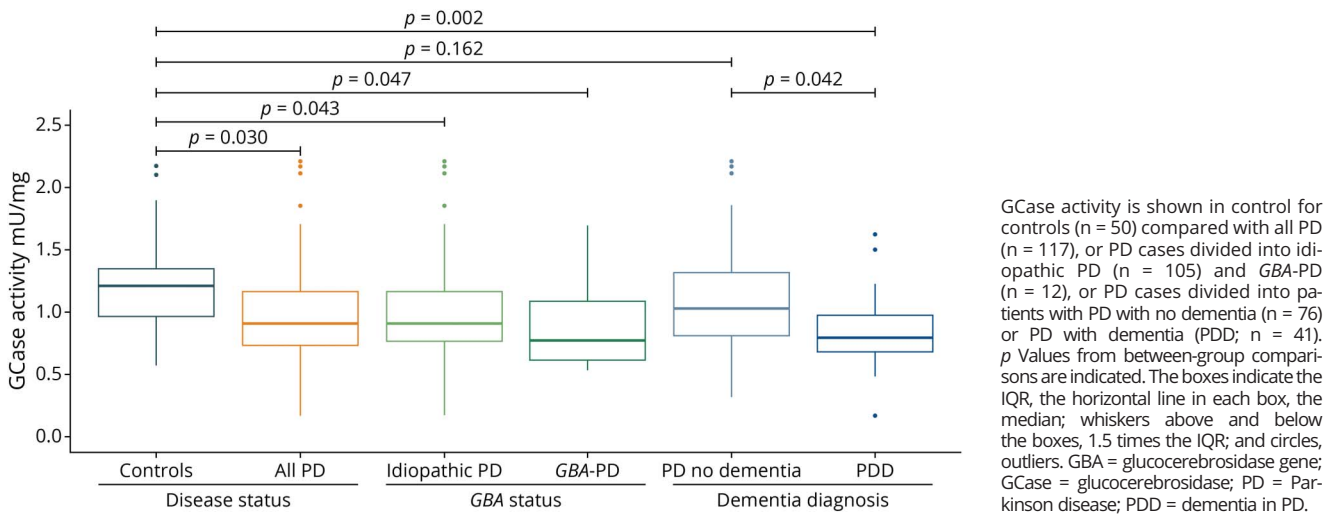
^a Independent samples *t* test.

^b χ^2 test.

^c One-way analysis of covariance F-test adjusted for age and sex.

Abbreviations: GCase = glucocerebrosidase; PD = Parkinson disease; UPDRS III: Unified Parkinson's Disease Rating Scale part III; MMSE = Minimal-Mental State Examination.

Figure 1 Distribution of CSF GCCase Activity Across the Different Groups

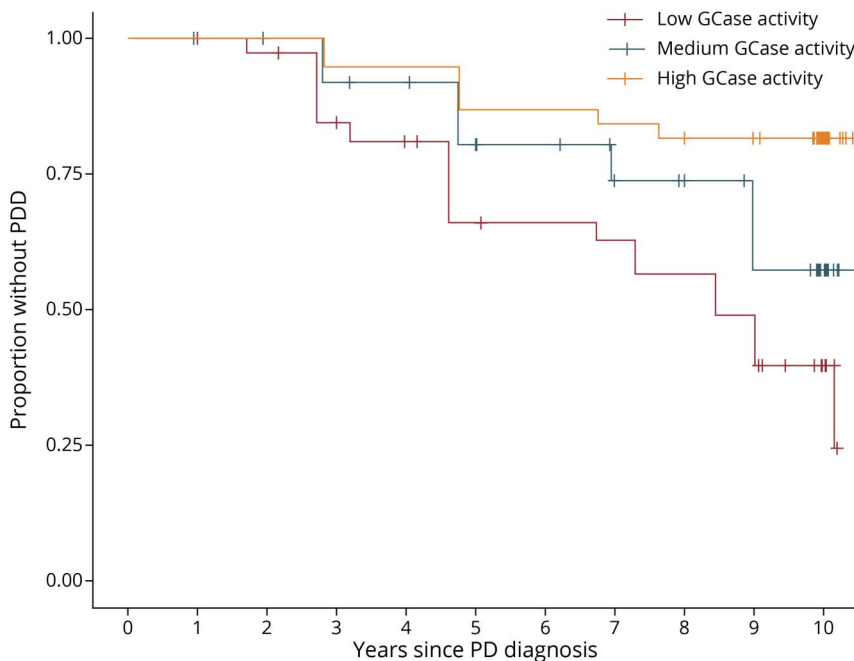


to advanced disease stages²³⁻²⁵ and in postmortem brains⁷⁻¹⁰ and identifies CSF GCCase activity as a promising early diagnostic marker of PD and prognostic marker of PDD.

We notably observed a reduction in CSF GCCase activity in patients independent of GBA carrier status mutations

compared with the controls. The relevance of GCCase dysfunction in idiopathic PD is reinforced by studies of both CSF from patients with a disease duration of 5–18 years²³ and postmortem brains,⁷⁻¹¹ that have similarly shown decreased GCCase activity in PD independent of GBA carrier status. In contrast, reduced GCCase activity in dried blood of patients

Figure 2 Survival Analysis for the Time to Develop Dementia for Patients With Low, Medium, or High Levels of GCCase Activity Defined by Tertiles



Number at risk:

+	39	39	38	36	36	33	33	32	31	29	13
+	39	38	37	34	33	28	26	22	20	14	10
+	39	39	37	31	28	22	21	20	18	16	5

GCCase = glucocerebrosidase.

with PD has repeatedly been found to be dependent of *GBA* carrier status.²⁶⁻²⁹ These discrepant findings raise an interesting question as to whether the GCase dysfunction observed in the blood of *GBA*-PD reflects only their genetic status rather than capturing the full extent of the disease pathology in the brain, where the feedback loop between GCase dysfunction and α -synuclein (and other disease mechanisms) could negatively affect GCase activity beyond that attributable to the *GBA* variation alone. Considering this, measurement of GCase activity in CSF might give a more precise snapshot of the extent of GCase dysfunction attributable to the patients' PD status. This has major consequences for the interpretation of studies of blood GCase activity and important implications for the choice of monitoring biofluids in clinical research and clinical trials in PD.

GBA carrier status is linked to an increased risk of developing dementia in PD,^{22,30-32} opening for the possibility that GCase dysfunction underlies the more severe disease course observed in some patients, although evidence is lacking. We found that patients with the lowest levels of GCase activity were more likely to develop PDD by 10 years than those in the high GCase activity group. This finding was also independent of *GBA* carrier status. One earlier study investigated the link between GCase activity in dried blood and the future development of mild cognitive impairment or dementia, but found no association between GCase and cognitive status and surprisingly that higher GCase activity over time was associated with poorer performance in cognitive tests.²⁹ Although these findings are seemingly at odds with our study, notably the participants were only followed for 3 years in the early stages of PD, and a longer period is likely required to detect differences in cognitive phenotype. Indeed, in the same population, *GBA* variant status was similarly not associated with cognitive status after 3 years²⁹ Furthermore, a study of dried blood GCase activity failed to show any link between GCase activity and clinical phenotype,³³ whereas a small CSF study has shown that a reduction in GCase activity was associated with worse cognitive performance assessed by MoCA score in patients with a disease duration of 5–18 years²³ In light of these methodological differences, our study provides important information on the prognostic value of GCase activity in CSF from the time of PD diagnosis.

Increasing brain GCase activity is a promising therapeutic strategy to reduce α -synuclein levels and addresses the underlying pathophysiology of PD. Our data show that timely intervention could be vital with GCase activity being reduced already at early stages of the disease. To date, several clinical trials of GCase-targeting compounds have implemented a precision medicine approach for patients with genetic forms of PD under the assumption that patients with *GBA*-PD are most likely to benefit from the interventions.^{34,35} The findings from our study suggest that

selecting trial candidates in the lowest tertile of CSF GCase activity could provide a powerful tool to identify an idiopathic PD group who will also benefit from GCase targeting therapies. Furthermore, the link between GCase activity and the development of PDD indicates that cognitive outcomes should be pursued in future trials and that GCase activity status (high vs low) could increase power for clinical trials by including only those with a high risk of future cognitive progression.

Limitations of this study include the sample size, especially of the *GBA*-PD group, and the lack of information on *GBA* status and cognitive decline for the controls. Furthermore, we were not able to assess all potential biological mechanisms that may contribute to cognitive decline, although in consideration of the 2 most common forms of dementia, we accounted for CSF β -amyloid 42 (a biomarker of Alzheimer dementia) in our analysis, and no patients met the criteria for vascular dementia. Not all participants consented to donate CSF; however, the clinical and demographic characteristics of these individuals did not differ from the makeup of the whole cohort. Finally, all the participants were of Norwegian ethnicity and had confirmed diagnosis of PD at their final clinical visit or autopsy, and future work should assess the generalizability for these results in other populations, including early-stage patients with suspected PD. Samples had been stored frozen more than 15 years before analysis; however, we observed no correlation between storage time and GCase activity, indicating a relative stability over time.

CSF GCase dysfunction is evident at the earliest clinical stages of PD and is linked to the future development of dementia in both the *GBA*-PD and idiopathic PD populations. This is in contrast to GCase activity measured in dried blood, which appears to be only an endophenotype of *GBA* carrier status, and highlights the promise of CSF GCase activity as early diagnostic and prognostic biomarker for both idiopathic PD and *GBA*-PD and the importance of biofluid selection in research and clinical trial settings.

Acknowledgment

The authors thank the participants of the ParkWest study and CSF donors for their contributions and all the members of the Norwegian ParkWest study group and other personnel involved in the study. The authors further thank the Norwegian Research Council (grants 287842 and 177966), the Norwegian Parkinson's Research Foundation, the Norwegian Health Association (grant 16152), the Western Norway Regional Health Authority (911218), and Reberg's Legacy for financial support.

Study Funding

This work was funded by the Research Council of Norway (Project Number 287842), the Norwegian Parkinson's Research Foundation, and the Norwegian Health Association (16152). The Norwegian ParkWest study has received funding from the Research Council of Norway (177966), The

Western Norway Regional Health Authority (911218), the Norwegian Parkinson's Research Foundation, and Reberg's Legacy. The funding organizations had no role in design and conduct of the study; collection, management, analysis, and interpretation of data; in the writing, preparation, reviewing, or approval of the manuscript; and in the decision to submit the manuscript for publication.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* February 1, 2022. Accepted in final form August 31, 2022. Submitted and externally peer reviewed. The handling editor was Peter Hedera, MD, PhD.

Appendix Authors

Name	Location	Contribution
Linn Oftedal, PhD	The Norwegian Centre for Movement Disorders, Stavanger University Hospital, Stavanger, Norway	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Jodi Maple-Grødem, PhD	The Norwegian Centre for Movement Disorders, Stavanger University Hospital, Stavanger, Norway; Department of Chemistry, Bioscience and Environmental Engineering, University of Stavanger, Stavanger, Norway	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Ingviold Dalen, PhD	Department of Research, Section of Biostatistics, Stavanger University Hospital, Stavanger, Norway	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Ole-Bjørn Tysnes, PhD, MD	Department of Neurology, Haukeland University Hospital, Bergen; Department of Clinical Medicine, University of Bergen, Norway	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Kenn Freddy Pedersen, PhD, MD	The Norwegian Centre for Movement Disorders, Stavanger University Hospital, Stavanger, Norway; Department of Neurology, Stavanger University Hospital, Stavanger	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Guido Alves, PhD, MD	The Norwegian Centre for Movement Disorders, Stavanger University Hospital, Stavanger, Norway; Department of Chemistry, Bioscience and Environmental Engineering, University of Stavanger, Stavanger, Norway; Department of Neurology, Stavanger University Hospital, Stavanger	Additional contributions: obtained funding; drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data

Appendix (continued)

Name	Location	Contribution
Johannes Lange, PhD	The Norwegian Centre for Movement Disorders, Stavanger University Hospital, Stavanger, Norway; Department of Chemistry, Bioscience and Environmental Engineering, University of Stavanger, Stavanger, Norway	Additional contributions: obtained funding; drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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Neurology 2023;100:e388-e395 Published Online before print October 17, 2022

DOI 10.1212/WNL.0000000000201418

This information is current as of October 17, 2022

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