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

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ABSTRACT

**Background and Objectives:** Mutations in the glucocerebrosidase gene (*GBA*) are common risk factors for Parkinson’s 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 if CSF GCase activity is altered in newly diagnosed PD patients and associated with future development of dementia.

**Methods:** PD patients 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* mutation 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 MDS 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 PD patients (mean age 67.2 years, including 12 GBA mutation carriers) and 50 control subjects (mean age 64 years). At the time of diagnosis GCase activity was reduced in PD patients with (mean ± SD, 0.92 ± 0.40 mU/mg, n=12) or without *GBA* mutations (1.00 ± 0.37 mU/mg, n=105) compared to controls (1.20 ± 0.35, n=50). GCase activity at time of diagnosis was lower in PD patients 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 (HR 1.15, 95% CI 1.03 to 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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INTRODUCTION

Mutations in the glucocerebrosidase gene (GBA) are common genetic risk factors for PD.\(^1\) GBA encodes the lysosomal enzyme Glucocerebrosidase (GCase) that hydrolyses the major glycolipid glucosylceramide into glucose and ceramide. Reduced GCase activity impairs the autophagy lysosomal pathway resulting in increased levels of \(\alpha\)-synuclein, the main constituent of Lewy bodies found in the brain of PD patients.\(^2,3\) Further, substantial evidence suggests a bi-directional relationship between GCase dysfunction and the accumulation of \(\alpha\)-synuclein aggregates.\(^4,5\)

Clinically, PD patients 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 to non-carriers. Mutations in GBA 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 non-carriers,\(^7-11\) 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 PD patients from time of diagnosis and analyzed the association with the risk of PD. Further, given the link between GBA mutation status and the development of dementia, we analyzed the possible association of GCase activity and the development of PDD within 10 years of prospective follow-up.

The primary research questions are: Are GCase activity levels altered in PD patients at time of diagnosis and is GCase activity at time of diagnosis associated with development of PDD?
MATERIALS AND METHODS

Participants

This study enrolled PD patients from the Norwegian ParkWest study, an ongoing, prospective, population based, longitudinal cohort study of newly diagnosed PD patients identified in Southwestern Norway from 2004 to 2006. Only those with a confirmed clinical diagnosis of PD according to the UK brain bank criteria at their latest or final clinical visit or pathological confirmation (if postmortem examination was performed) were included. Of 190 patients, cerebrospinal fluid was available for 120 participants. The control group was a set of 51 subjects without any known brain disease who underwent elective neurological examination or orthopedic surgery at Stavanger University Hospital. Samples from three PD patients and one control were excluded for technical reasons (see details below). Thus, 117 PD patients and 50 controls were eligible for this study (eTable 1).

Clinical assessments

General medical and neurological examinations and semi-structured interviews were performed at 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 (UPDRS) part III, Mini-Mental State Examination (MMSE), and Hoehn and Yahr scale, respectively. From the control group, demographic data and MMSE were obtained.

PD patients were followed prospectively over a period for up to 10 years with extensive clinical workup at baseline, after one year and every other year thereafter, and with basic clinical and neurological assessments every six months. During this study, 44 participants were lost to follow up: 40 died (median time to death 7.1 (IQR 5.0) years and four dropped out of the study (median follow up time 7.5 (IQR 6.8) years. PDD diagnosis was set according
to MDS criteria\(^{17}\) by two 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 two 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 diagnostic criteria for dementia with Lewy bodies, Alzheimer dementia, or other dementia syndromes.

**Standard Protocol Approval, Registrations, and Patient Consents**

All participants provided informed written consent to lumbar puncture 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).

**Cerebrospinal fluid samples**

CSF samples were available from 120 participants who consented to lumbar puncture (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 was conducted according to standardized procedures.\(^{19}\) All CSF samples were immediately cooled on ice, followed by centrifugation at 2000 x g for 10 min 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. CSF samples (diluted 1:2 in assay buffer) were added 4-methylumbelliferyl-β-D-glucopyranoside as substrate. After three hours 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 two replicates (this affected only three samples in total). The LLOQ 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). Mean sample CV% was 5.8 (Range 0.2-38.6). Only five samples exceeded a CV of 20%. Intra-assay CV% was 7.9 (Nine assay plates, two quality control samples on each plate). One sample failed the assay and one outlier with a GCase activity (4.7 mU/ml) more than five standard deviations above the global mean was excluded from the study analysis. One unit of GCase activity was defined as amount of enzyme that hydrolyses 1 nmol of substrate/min at 37°C. A detailed protocol can be found in the supplementary material of Oftedal et al. Storage time of samples prior to analysis varied between 15.2 and 17.4 years. There were no correlation between GCase activity and storage time (Kendall’s tau b = 0.04, p = 0.522).

CSF total protein content was measured in duplicate with the Pierce BCA protein assay kit (#23227, ThermoFisher Scientific, USA) following the manufacturer’s instructions and 1:2 sample dilution. The LLOQ of the BCA 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). Mean sample CV% was 4.5 (Range 0.0 -18.8) and the mean intra-assay CV% was 1.6 (Six plates, two to four quality control samples on each plate. Two outliers with a total protein concentration (3.28 and 10.67 mg/ml) more than five standard deviations above the global mean were excluded from the study analysis.
GBA carrier analysis

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

Statistical analysis

Descriptive statistics for continuous variables are presented as means with standard deviations. Categorical variables are presented with counts and percentages. Univariate analysis of between group differences were performed using independent t-tests, or Chi-square tests, as appropriate. One-way ANCOVA F-test was used for analysis of between group differences of GCase activity with adjustment for age and sex. Kendall’s tau was used to assess 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 that remained dementia free). \( t=0 \) was set at 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 (HR), which are presented with 95% confidence intervals (CI). 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 \( \beta_{1-42} \) concentrations, measured by ELISA (Innotest \( \beta \)-amyloid(1-42), Fujirebio,
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 to 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% confidence intervals CI. The effect sizes were comparable after additional adjustment for baseline MMSE score (data not shown). Nonparametric maximum likelihood estimates of the survival distributions for onset of PDD were constructed for the three groups.

All analysis were performed using SPSS version 26 (IBM, Armonk, USA) 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 two-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 Parkinson’s disease

The study included 117 newly diagnosed patients with PD and 50 control participants.

Demographic data and clinical information are listed in Table 1. 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’s 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 PD patients compared to control subjects (-17.4%; $p = 0.030$; Table 1; all PD; Figure 1A). GCase activity remained significantly reduced in the PD group compared to controls when considering only the PD GBA carriers (-23.1%; $p = 0.047$; GBA-PD; Figure 1A) or only the non-carrier 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 ± SD, 0.92 ± 0.40 mU/mg) compared to those without a GBA mutation (1.00 ± 0.37 mU/mg), however this difference was statistically not significant ($p = 0.369$).

**GCase activity and long-term risk of Parkinson’s disease 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; min 1.9, max 10.2), while the median follow up time for those that remained dementia free was 10.0 years (IQR 1.8; min 0.9, max 10.6). GCase activity at the time of PD diagnosis was lower in patients who developed PDD (-20.3%; mean ± SD, 0.85 ± 0.27 mU/mg) compared to patients that remained dementia free until the last clinical visit or death (1.07 ± 0.40 mU/mg; $p = 0.042$; Figure 1B). Further, compared to the control group, the GCase activity was lower in patients who developed PDD (-29.1%, $p = 0.002$) but not in patients that remained dementia free during follow-up (-11%, $p = 0.162$).

Survival analysis was applied to assess the impact of reduced baseline GCase activity on the time to develop dementia over the first ten 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 to 1.28; \( p = 0.014 \)). Further, the association between baseline GCase activity and the development of PDD remained nearly unchanged when also controlling for baseline CSF amyloid \( \beta_{1-42} \) level (HR 1.13; 95% CI 1.03 to 1.28; \( p = 0.013 \)). In subgroup analysis, the prognostic performance of baseline CSF GCase activity was explored in the 105 PD patients without \( GBA \) mutations. 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 to 1.33; \( p = 0.009 \)). Again, this association remained unchanged after additional adjustment for CSF amyloid \( \beta_{1-42} \) level (HR 1.17; 95% CI 1.04 to 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 to only 17.9% of patients in the highest tertile (HR 3.10; 95% CI 0.72 to 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 to those in the high GCase activity group (HR 3.91; 95% CI 0.91 to 7.60; \( p = 0.011 \)) when only the 105 idiopathic PD patients 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 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 ten 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 to advanced disease stages\(^{23-25}\) and in post mortem brains,\(^{7-10}\) and identifies CSF GCase activity as a promising early diagnostic marker of PD and prognostic marker of PDD.

We notably observed a reduction in CSF GCase activity in patients independent of \(GBA\) mutations compared to the controls. The relevance of GCase dysfunction in idiopathic PD is reinforced by studies of both CSF from patients with a disease duration of 5 to 18 years\(^{23}\) and post mortem brains,\(^{7-11}\) that have similarly shown decreased GCase activity in PD independent of \(GBA\) mutation status. In contrast, reduced GCase activity in dried blood of PD patients 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 \(\alpha\)-synuclein (and other disease mechanisms) could negatively affect GCase activity beyond that attributable to the \(GBA\) mutation 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 mutation status is linked to an increased risk of developing dementia in PD,\textsuperscript{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.\textsuperscript{29} Whilst 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 years.\textsuperscript{29} Furthermore, a study of dried blood GCase activity failed to show any link between GCase activity and clinical phenotype,\textsuperscript{33} whilst 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 to 18 years.\textsuperscript{23} 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 shows 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 GBA-PD patients are most likely to benefit from the interventions.\textsuperscript{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. Further, the link between GCase activity and the development of PDD indicates 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 GBA-PD group, and the lack of information on GBA status and cognitive decline for the controls. Further, we were not able to assess all potential biological mechanisms that may contribute to cognitive decline, although in consideration of the two most common forms of dementia, we accounted for CSF amyloid beta 42 (a biomarker of AD) in our analysis and no patients met the criteria for vascular dementia. Not all participants consented to donate CSF, however the clinical and demographic of these individuals did not differ from the makeup of the whole cohort. Finally, all of 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 prior to analysis, however, we observed no correlation between storage time and GCase activity, indicating a relative stability over time.

CONCLUSION

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 mutation 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.
REFERENCES


Table 1 – Baseline characteristics and GCase activity of the cohort

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<th></th>
<th>Controls</th>
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<td>N</td>
<td>50</td>
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<td></td>
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<tr>
<td>Age, years</td>
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<td>67.2 ± 9.5</td>
<td>0.096 $^a$</td>
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<td>Sex Male, n (%)</td>
<td>21 (42%)</td>
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<td>0.006 $^b$</td>
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<td>Education, years</td>
<td>11.0 ± 3.4</td>
<td>11.2 ± 3.1</td>
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<td>MMSE, total score</td>
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<td>27.7 ± 2.4</td>
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<td>-</td>
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<td>19 (16.2)</td>
<td>-</td>
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<td>Stage 3, n (%)</td>
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<td>Total protein, mg/ml</td>
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<td>0.85 ± 0.20</td>
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<td>0.99 ± 0.37</td>
<td>0.030 $^c$</td>
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</table>

Values are presented as mean ± SD. $^a$: Independent samples t-test; $^b$: Chi-square test; $^c$: One-way ANCOVA F-test adjusted for age and sex.

Abbreviations: UPDRS III: Unified Parkinson’s Disease Rating Scale part III; MMSE: Minimal-Mental State Examinations.
Figure legends

**Figure 1. Distribution of cerebrospinal fluid GCase activity across the different groups.**

GCase activity is shown in control subjects (n = 50) compared to all PD (n = 117), or PD cases divided into idiopathic PD (n = 105) and GBA-PD (n = 12), or PD cases divided into PD patients with no dementia (n = 76) or PD with dementia (PDD; n = 41). P values from between group comparisons are indicated. The boxes indicate the IQR, the horizontal line in each box, the median; whiskers above and below the boxes, 1.5 times the IQR; and circles, outliers.
Figure 2. Survival analysis for the time to develop dementia for patients with low, medium or high levels of GCase activity defined by tertiles.
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