Cognitive-Driven Activities of Daily Living Impairment as a Predictor for Dementia in Parkinson Disease: A Longitudinal Cohort Study

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ABSTRACT

Objectives

One-third of Parkinson’s disease (PD) patients with mild cognitive impairment (PD-MCI) convert to dementia within a few years. Markers with a high prognostic value for dementia conversion are needed. Loss of everyday function primarily caused by cognitive dysfunction is the core criterion for the diagnosis of PD dementia, with an onset of more complex instrumental activities of daily living (IADL) dysfunction in the prodromal stage. This study evaluated the phenotype associated with cognitive IADL impairment and its predictive value for defining a high-risk group for PD dementia.

Methods

An observational longitudinal study using cognitive and clinical scores in addition to genetic and CSF biomarkers was conducted. The Functional Activities Questionnaire (FAQ) quotient (cut-off ≥ 1), indicating more cognitive than motor-driven IADL impairment, defined cognitive IADL impairment status at baseline. Hazard ratios (HR) were used to compare the impact of baseline classifications on dementia conversion.

Results

Of 268 patients with PD assessed at baseline, 108 (40.3%) had PD-MCI. After a period of 3.78±0.84 years, 164 (61.2%) patients were re-assessed. At follow-up, 93 (56.7%) patients had no cognitive impairment, 54 (32.9%) fulfilled PD-MCI criteria, and 17 (10.4%) had developed dementia. The HR of baseline cognitive IADL impairment (n=37) for dementia conversion was descriptively higher than for PD-MCI, but highest in patients with both markers (HR=12.01, 95%-CI 4.47-32.22, p<0.001). In the follow-up sample, nearly half of patients (n=10, 47.6%) with baseline classification of cognitive IADL impairment and PD-MCI converted to dementia. Baseline status of cognitive IADL impairment was associated with higher non-motor burden, worse cognitive performance, and more severe IADL progression over the study period.

Conclusion

The importance of differentiating between cognitive and motor aspects on ADL function in PD and monitoring cognitive ADL impairment in the prodromal stage of dementia is paramount. Patients with PD-MCI and cognitive IADL impairment may be a valuable target group for clinical trials aiming to slow down development of dementia.

Trial Registration Information

ClinicalTrials.gov NCT03687203.

Classification of Evidence
This study provides Class II evidence that impairment of cognitive activities of daily living is associated with progression from mild cognitive impairment to dementia among patients with Parkinson's disease.

INTRODUCTION

Patients with Parkinson's disease (PD) have an almost 6-fold increased risk of developing cognitive impairment and dementia (PDD) compared to age-matched controls.\(^1\) Identification of a high-risk group for those converting to PDD (i.e., those who are in the prodromal dementia phase) is essential to develop and implement early and effective treatments for preventing or delaying dementia. Mild cognitive impairment (PD-MCI) is one of the greatest risk factors for future PDD.\(^2\) A recent meta-analysis found that, on average, 31% of patients with PD-MCI converted to PDD within seven years; however, 24% of patients with PD-MCI reverted back to normal cognitive function.\(^3\) Consequently, the false positive rate for predicting PDD among patients with PD-MCI is high, and better predictive markers to define patients at high risk for PDD development are urgently needed.

The fundamental feature differentiating PDD from PD-MCI is the loss of the ability to perform activities of daily living (ADL),\(^4\) which can be divided into basic ADL (e.g., dressing or bathing) and instrumental ADL (IADL, e.g., shopping or managing medication).\(^5\) While basic ADL skills are generally preserved longer during the disease course, the more complex IADL skills can be impaired even in early stages of cognitive decline.\(^6\) IADL impairment assessed by various measures (e.g., questionnaires, objective tests) can be observed in about 30%-50% of patients with PD-MCI,\(^7,8\) suggesting that cognition affects IADL even in the prodromal stage of PDD. To date, studies suggest progression of IADL is associated with worsening of some cognitive measures and future cognitive test performance, but with inconclusive results for predicting cognitive diagnosis due to a scarcity of longitudinal studies.\(^6,9\)

On a cross-sectional level, not all studies confirm a direct link between cognition and function in PD,\(^10,11\) implying that not all instruments are suitable for detecting cognitive-driven IADL and might be confounded by other non-cognitive effects. Importantly, the impairments in daily function necessary to define PDD must be primarily caused by cognitive deficits, mainly reflecting deficits in IADL.\(^1,12\) However, motor impairments can also affect IADL ratings,\(^13,14\) highlighting the challenge of identifying impairments indicative of dementia in patients with PD. To overcome this obstacle, research has focused on creating new comprehensive instruments, such as the Penn Parkinson Daily Activities Questionnaire.\(^15\)
A recent study developed novel subscores using the Functional Activities Questionnaire (FAQ) to differentiate cognitive and motor contributions to IADL impairment in patients with PD without dementia by examining associations between each FAQ item and a measure of global cognition (to create the cognition subscore) as well as a measure of motor severity (to create the motor subscore). A quotient (FAQ\textsubscript{Q}) was calculated by dividing the cognitive by the motor subscore, to define a subgroup of patients with more cognitive compared to motor-driven IADL impairment. Further analyses revealed this group scored lower on attention and language tests, suggesting more advanced cognitive deterioration in patients with cognitive IADL dysfunction.

Based on these previous results, the main goal of this study was to examine cognition and IADL function in a longitudinal PD cohort. The primary research aim (1) was to evaluate whether patients with cognitive IADL impairment, defined according to the FAQ\textsubscript{Q} (cut-off >1), are at higher risk for the development of PDD, and to determine whether the combination of PD-MCI and cognitive IADL impairment better predicts conversion to PDD than either marker alone. We hypothesized that patients with both PD-MCI and cognitive IADL impairment are at a higher risk for conversion to PDD than patients with motor IADL impairment. The following secondary research aims were addressed: (2) to define the baseline phenotype associated with cognitive IADL impairment, expecting a profile of lowered cognitive performance and higher rate of genetic risk variants and cerebrospinal fluid (CSF) biomarkers related to impaired cognition; (3) to investigate progression in function over time reflected by change in the FAQ subscores hypothesizing that patients with either a baseline classification of PD-MCI or cognitive IADL impairment would have higher values in the FAQ subscores at follow-up.

**METHODS**

**Design and Recruitment**

Baseline visit was conducted between March 2014 and December 2017 within the frame of the single-site “Amyloid-Beta in cerebrospinal spinal fluid as a risk factor for cognitive dysfunction in Parkinson’s Disease” (ABC-PD) study. Patients with PD were recruited from a movement disorders population through the Neurology Department of the University Hospital in Tübingen and regional neurologists and assessed in-house. Patients were included if they were fluent German speakers, were aged 50-85 years, were able to give informed consent, had a diagnosis of PD according to the UK Brain Bank criteria, had no concomitant neurological...
diseases affecting cognition (stroke, traumatic brain injury, encephalitis) or diagnosis of PDD, had no Deep Brain Stimulation, and agreed to a lumbar puncture.\textsuperscript{16}

Follow-up visit was conducted via the “Cognitive-driven ADL impairment as a predictor for Parkinson’s disease dementia” study. Between July 2018 and September 2020, all patients of the ABC-PD study were contacted for re-examination. Inclusion criteria for follow-up participation were age between 50-90 years and ability to communicate with the investigator and understand the purpose of the study. Patients with concomitant diseases affecting cognition or who had received a neurological diagnosis other than PD between visits were excluded. Medical history was obtained through detailed anamnesis at both visits as well as a thorough review of hospital medical records to identify concomitant diseases or other neurological diagnoses. As long-term effects of Deep Brain Stimulation on ADL are unclear, these patients were excluded from analyses. Assessments took place either in-house or at patients’ homes. Minimal assessments, where relevant medical records and ADL questionnaires were obtained from patients or caregivers, were conducted if patients were too impaired for neuropsychological testing. Figure 1 shows a detailed recruitment flowchart.

\textbf{Standard Protocol Approvals, Registrations, and Patient Consents}

Both studies were approved by the Ethics Committee of the Medical Faculty of the University of Tübingen (Baseline 686/2013BO1; Follow-up 284/2018BO1). The follow-up study was registered at ClinicalTrials.gov, Identifier: NCT03687203. Written informed consent was obtained from patients or a proxy (if necessary) for both studies, and additionally from informants for the follow-up study.

\textbf{Assessments and outcomes}

Demographics (age, sex, formal education, and age at disease onset) were collected at baseline; all clinical variables were assessed at both visits. The motor part of the Movement Disorder Society (MDS) Unified Parkinson’s Disease Rating Scale (MDS-UPDRS-III) and Hoehn & Yahr scale assessed severity of motor symptoms.\textsuperscript{17} Anti-parkinsonian medication intake was expressed using the levodopa equivalent daily dose. German versions of the Non-Motor Symptoms Questionnaire (NMSQ)\textsuperscript{18} and the Beck Depression Inventory-II (BDI-II)\textsuperscript{19} measured non-motor symptom burden. These baseline variables were considered as potential between-group covariates.
IADL: The 10-item FAQ assessed IADL (see eTable 1 for item descriptions and scoring). The FAQ total score (0-30 points) was calculated, and the following novel subscores were defined: FAQ cognition score – primarily associated with cognitive aspects (items 1,2,7,8,9), FAQ motor score – primarily associated with motor aspects (items 3,4,5,6,7,8,10), and the FAQ quotient \( \text{FAQ}_Q = (\text{FAQ cognition score} + 1)/(\text{FAQ motor score} + 1) \). A cut-off score > 1 on the FAQ\(_Q\), indicating more cognitive- compared to motor-driven IADL impairment, was used to differentiate patients with more cognitive (FAQ\(_Q > 1\)) from more motor (FAQ\(_Q \leq 1\)) IADL impairment. Progression in function over time was reported for the FAQ total, FAQ cognition, FAQ motor, and FAQ\(_Q\) scores. At baseline, the FAQ was completed by either an informant or the patient themselves if no informant was available; follow-up FAQ data was obtained from the same source as the baseline data.

Cognition: Patients underwent comprehensive neuropsychological testing at both visits that has been described in detail elsewhere. In short, the Consortium to Establish a Registry for Alzheimer’s Disease–Plus Battery (CERAD-PLUS), three subtests from the Wechsler Intelligenztest für Erwachsene (WIE; German version of the Wechsler intelligence test for adults), and one subtest from the “Leistungsprüfsystem 50+” (LPS50+; cognitive test battery for adults aged 50 and above) were used. The Montreal Cognitive Assessment (MoCA) measured global cognitive functioning. Raw scores were converted to age- or age- and education-corrected \( z \)-scores, and composite domain scores (attention, executive functions, memory, visuospatial abilities, and language) were calculated from respective \( z \)-scores (see Table 1). Patients were classified as PD-MCI according to Level-II MDS recommendations if cognitive impairment (performance on at least two tests below 1.5 standard deviations of the population mean reported in the test manuals) was present but did not significantly interfere with everyday function. PDD was defined according to MDS Task Force criteria if cognitive impairment was present and severe enough to impair ADL function unrelated to motor or autonomic symptoms, and at least one behavioral symptom was present to support diagnosis. Cognitive impairment was defined according to Level-I (impairment of global cognition) for patients with minimal assessments, or Level-II (performance on at least two tests below 1.5 standard deviation of the population mean reported in the test manuals) for patients assessed using a full cognitive battery. Patients not meeting either of the diagnostic criteria were classified as cognitively normal (PD-CN). Cognitive status at follow-up was defined as the primary study outcome.
Genetics and biomarkers: Genetic variants and CSF biomarkers were derived from baseline samples. Due to confounding factors, CSF values were indeterminable for one patient. CSF $A\beta_{1-42}$, total tau and phosphorylated tau levels were determined using commercially available ELISA kits (Fujirebio Europe, Gent, Belgium). Genotyping with the NeuroChip was conducted. Based on a literature review of cognitive worsening in PD and/or neurodegeneration, ten candidate genetic variants in the genes $APOE$, $MAPT$, $SNCA$, $TREM2$, $BDNF$, $DYRK1A$ and $COMT$, as well as carrier status of rare $GBA$ mutations, were selected for analysis in a hypothesis-driven approach. GBA mutations (c.115+1G>A, R78C(R39C), T336S(T297S), E365K(E326K), R398*(R359X), T408M(T369M), N409S(N370S), and L483P(L444P) were determined by Sanger sequencing.

Statistical Analyses

All data were collected and managed using REDCap electronic data capture tools hosted at the Hertie Institute for Clinical Brain Research. Analyses were run using R (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/) and IBM SPSS Statistics for Windows version 27 (IBM Corp., Armonk, N.Y., USA). Alpha was set to 0.05; the Shapiro-Wilk test was applied to test for normal distribution. Continuous predictors were standardized in linear models. No corrections for multiple testing were applied for the characterization of study groups to be able to identify covariates for the outcome analyses.

Between-group comparisons at both visits were conducted using Mann-Whitney-$U$ or Welch tests (two groups) or Jonckheere-Terpstra tests (>2 groups, R-package “clinfun”, version 1.0.15, 1000 permutations) for numerical variables and Chi²-tests or Exact Fisher Test for categorical variables. Comparisons of patient and informant ratings of the FAQ (items, total score, and subscores) were conducted using Exact Fisher and Mann-Whitney-$U$ tests (eTables 1 and 2). Effect sizes were calculated as appropriate [Mann-Whitney-$U$ test: $r = \frac{Z}{\sqrt{N}}$, Confidence Intervals (CI) were bootstrapped with 1000 samples; Chi-Square-test and Exact Fisher Test: Cramer’s $V$].

All following hypotheses were tested a priori; no post-hoc corrections of $p$-values were conducted. The predictive values (aim 1) of baseline IADL stratification ($FAQ_{Q\leq1}$ vs. $FAQ_{Q>1}$), cognitive status (PD-CN vs. PD-MCI), and both markers combined (PD-MCI+$FAQ_{Q>1}$ vs. other categories) were calculated using multivariate Cox proportional hazard models (R package “survival”, version 3.2-11), correcting for covariates (characteristic variables significantly different between each cohort at baseline, see also Table 1 and eTable 3). To correct for selection bias, models were run using an uncensored cohort (including only
patients with follow-up data) and using a right-censored cohort (including dropouts assuming an outcome of PD-CN at time of drop-out). Akaike’s information criterion (AIC) and concordance index (C-index)\(^26\) were used as model fit indices. Survival curves were adjusted by conditionally balancing the sample across baseline covariates (R package “survminer”, version 0.4.9). In the total baseline sample, available clinical, genetic, and CSF data were compared between patients with cognitive (FAQ\(_{Q>1}\)) and motor IADL (FAQ\(_{Q≤1}\)) impairment using logistic regression analyses and linear regression models (Wald statistics), correcting for BDI-II and NMSQ score (aim 2).

Generalized linear mixed effects models (GLMMs) evaluated performance on the FAQ over time (aim 3). Three binomial models were calculated including either FAQ total, cognition, or motor score as dependent variables modelled as proportions using La Place approximation and Wald parameter estimates (R package “lme4”, version 1.1-27). Main effects of time of visit (baseline vs. follow-up), baseline cognitive (PD-CN vs. PD-MCI) and baseline status of cognitive IADL impairment (FAQ\(_{Q≤1}\) vs. FAQ\(_{Q>1}\)), as well as three lower order interactions (visit*cognitive status, visit*cognitive IADL status, cognitive IADL status*cognitive status) were examined. To determine whether baseline FAQ\(_{Q>1}\) and PD-MCI statuses were associated with worse follow-up FAQ outcomes, a three-way interaction (visit*cognitive IADL status*cognitive status) was included into the model. Baseline covariates (see eTable 3 for details), were added as main effects, and participants were included as random intercepts. Theoretical marginal R\(^2\)_M and conditional R\(^2\)_C values were calculated (R package “MuMIn”, version 1.43.17). Bobyqa optimizer was used and the FAQ total and motor score models were corrected for overdispersion.

As a post-hoc exploratory analysis to identify which subscore best predicted PDD conversion, Receiver Operating Characteristic (ROC) curves were calculated for all FAQ scores. The optimal score/cut-off was chosen according to the highest Youden Index.

Data availability

The corresponding author will consider any requests for access to the data reported in this manuscript (including de-identified participant data and the corresponding data dictionary). Due to restrictions imposed by the Ethics Committee of the Medical Faculty of the University of Tübingen, data access must be in accordance with the approved patient consent procedure to protect patient privacy.

RESULTS
Baseline characteristics and cognitive IADL phenotyping

Two-hundred sixty-eight patients were enrolled at baseline; 160 (60.7%) were classified as PD-CN and 108 (40.3%) as PD-MCI. Patients were predominantly male ($n=168, 62.7\%$) and in mild to moderate disease stages according to Hoehn & Yahr score (see Table 1 for cohort characteristics).

According to the a priori defined FAQ cut-off, 64 (23.9\%) patients had cognitive IADL impairment ($\text{FAQ}_{>1}$) and 204 (76.1\%) scored below this cut-off ($\text{FAQ}_{\leq 1}$). Patients with $\text{FAQ}_{>1}$ reported more non-motor symptoms and depression compared to patients in the $\text{FAQ}_{\leq 1}$ group (Table 1). Patients in the $\text{FAQ}_{>1}$ group also had more impairments in most neuropsychological subtests and cognitive domains, except for performance on visuospatial and executive function domain scores. $\text{FAQ}_{>1}$ status was associated with a lower probability of carrying MAPT H1/H1 variant (Odds ratio, OR=0.42, $p=0.009, 95\%\text{-CI 0.22-0.80}$, Nagelkerkes $R^2=0.11$; Table 2). The A-Allele of $\text{DYRK1A}\ rs9974126$ was descriptively less associated with the baseline status of $\text{FAQ}_{>1}$ (OR=0.76, $p=0.08, 95\%\text{-CI 0.54-1.04}$, Nagelkerkes $R^2=0.08$). Further logistic regression analyses revealed that no CSF marker differed between patients FAQ groups.

Follow-up characteristics

Of the baseline cohort, 164 patients (61.2\%) were re-analyzed with a mean follow-up interval of 3.78±0.84 years ($\text{range 1.67-5.79 years}$). Most patients lost to follow-up were either not interested in re-examination or deceased (Figure 1). Patients lost to follow up or excluded for analyses were older and had more depression, motor severity, cognitive impairment, and functional impairment at baseline (eTable 4). The number of patients with baseline status of cognitive IADL impairment was not significantly different between patients who dropped out compared to those who were included.

Regarding the primary outcome, 17 (10.4\%) patients converted to PDD, with 12 (70.6\%) fulfilling Level-II diagnostic criteria for PDD – two of them between study visits without Level-II confirmation at follow-up (minimal assessments). Four (23.5\%) patients were diagnosed by a neurologist (Level-I), and one (5.9\%) patient was diagnosed by a general physician. Fifty-four (32.9\%) patients were classified as PD-MCI at follow-up, with diagnosis in 31 (18.9\%) patients stable across both visits, and 93 (56.7\%) patients were classified as PD-CN, with 79 (48.2\%) patients cognitively normal at both visits. Significant differences were found between all cognitive groups for age, education, motor severity, non-motor
symptoms, depression severity, FAQ subscores, and neuropsychological test scores (eTable 5).

For patients completing both visits, 90 (54.9%) FAQ scores were rated by an informant while 74 (45.1%) patients filled out the FAQ themselves. There were no significant differences on FAQ items, total, and subscore values between patient and informant ratings (eTables 1 and 2). At follow-up, 37 (21.3%) patients had a baseline status of cognitive IADL impairment (FAQ_Q>1) and 127 (78.7%) patients had a baseline FAQ_Q≤1. There was no significant difference between cognitive IADL groups regarding follow-up interval [Welch-Test: t(60.65)=-1.67, p=0.10; FAQ_Q>1 mean 3.68±0.85 years, FAQ_Q≤1 mean 3.94±0.81 years].

**Prediction of PDD conversion according to baseline cognitive IADL impairment**

In the follow-up (uncensored) cohort, 11 (29.7%) patients with baseline status of cognitive IADL impairment (FAQ_Q>1) converted to PDD during the study period compared to only six (4.7%) in the FAQ_Q≤1 group (Figure 2). Additionally, 13 (22.4%) patients who had a baseline diagnosis of PD-MCI were diagnosed as PDD at follow-up. Out of 21 with baseline PD-MCI and cognitive IADL impairment (FAQ_Q>1), 10 (47.6%) progressed to PDD during the study period. In contrast, only three patients (8.1%) classified as PD-MCI with motor IADL impairment (FAQ_Q≤1) developed PDD within the study period (Figure 2).

Results of the Cox proportional hazard models for both the censored and uncensored cohort (excluding dropouts), correct for covariates, are reported in eTable 6. In the censored cohort (including dropouts), hazard ratios (HR; corrected for between-group covariates) for predicting conversion to PDD was descriptively higher for patients with baseline cognitive IADL impairment (HR=6.57, 95%-CI 2.38-18.17, AIC=152.00, C-Index=0.82) than for diagnosis of PD-MCI (HR=5.34, 95%-CI 1.70-16.73, AIC=161.70, C-Index=0.80), but highest in patients with both PD-MCI and FAQ_Q>1 (HR=12.01, 95%-CI 4.47-32.23, AIC=142.98, C-Index=0.89, Figure 3).

**Change in FAQ scores over time**

In all three GLMMs calculated for the (uncensored) FAQ total, motor, and cognition scores, the three-way interaction of time of visit (baseline vs. follow-up), baseline cognitive status of PD-CN or PD-MCI, and baseline cognitive IADL status of FAQ_Q≤1 vs. FAQ_Q>1 was significant (p≤0.05). This indicates that only patients with both PD-MCI and FAQ_Q>1 showed increase in these FAQ scores between visits (see Figure 4 and eTable 7). Lower education status (p=0.048) was associated with higher scores in the FAQ cognition score at both
baseline and follow-up visit. Higher scores in FAQ motor score were related to more severe motor and non-motor impairment at baseline (MDS-UPDRS-III: \( p = 0.009 \); NMSQ: \( p = 0.041 \))

**Post-hoc ROC analysis**

To verify whether the a priori defined FAQ best defined PDD at follow up, a ROC curve analysis evaluating predictive ability of all FAQ subscores were performed. According to the highest Youden Index (\( J = 0.48 \); sensitivity=64.7%; specificity=83.7%), a baseline FAQ cut-off value of 1.008 (area under the curve, AUC=0.72, 95%-CI 0.64-0.78, \( p = 0.0016 \)) was identified to best predict onset of PDD among all scores. The identified cut-off was, therefore, slightly higher than the a priori defined FAQ cut-off >1 used to define cognitive IADL impairment in our sample. Only two patients with baseline status of FAQQ, in our sample scored below the newly identified FAQ cut-off of 1.008 resulting in a total of 35 (21.3%) patients with values above this defined cut-off. For the FAQ cognition score (AUC=0.70, 95%-CI 0.62-0.77, \( p = 0.001 \)) and FAQ total score (AUC=0.67, 95%-CI 0.60-0.75, \( p = 0.005 \)), Youden indices of 0.44 and 0.36, respectively, were identified. The FAQ motor score (AUC=0.60, 95%-CI 0.52-0.67, \( p = 0.13 \)) was not associated with PDD conversion.

**Classification of Evidence**

This study provides Class II evidence that impairment of cognitive IADL is associated with progression from PD-MCI to PDD.

**DISCUSSION**

The current prospective longitudinal cohort study demonstrates that the presence of cognitive IADL impairment, defined using the FAQ cut-off>1, predicts PDD conversion within a short time period. The prognostic ability of this defined IADL marker was found to substantially add to the prognostic value of PD-MCI diagnosis, where the combination of cognitive and IADL status best predicted future development of PDD.

In PD, cognition, in addition to other non-motor aspects, has been confirmed to predict functional decline, but knowledge about the predictive ability of cognitive IADL impairment is sparse. Estimated conversion rates from PD-MCI to PDD vary between 20% and 31%, with higher conversion rates with longer follow-up interval. In this study, nearly 50% of patients with PD-MCI and cognitive IADL impairment at baseline converted to PDD, compared to only 8.1% of patients with PD-MCI motor IADL impairment. As PD-MCI is frequent in PD, the rate of non-PDD converters out of this group is substantial, which
negatively affects calculation of risk ratios to define the predictive value. Our data suggests that the combination of PD-MCI and cognitive IADL status can aid in narrowing down patients at high risk for PDD. In addition, only patients with this risk marker profile showed increased progression of IADL function (on all FAQ scores) in our uncensored sample between visits, further strengthening the assumption that IADL function declines in both PDD and its prodromal stage. This high-risk group might be a valuable target group for clinical trials evaluating the effect of intervention strategies to prevent or delay PDD.

Older age, male sex, and more severe and progressive motor dysfunction has been associated with IADL impairment. In our, sample depressive symptomatology and higher PD-related non-motor symptoms, but no other demographic or clinical variables, were associated with cognitive IADL impairment. Higher non-motor burden has previously been reported to be correlated to more severe progression in motor and non-motor associated function in PD. Furthermore, patients with cognitive IADL impairment showed poorer cognitive function in attention, memory, and language domains, reaffirming previously reported results of this baseline cohort and supporting our hypothesis. Previous literature associates worsening of complex performance based functional impairment with decline in the attention, executive function, memory, and visuospatial abilities domains. In particular, attentional performance is one of the strongest predictors of everyday function in PDD.

While we also expected a differing profile of CSF biomarkers between patients with cognitive or motor IADL impairment, our current results were not able to show any significant differences in amyloid-beta or tau biomarkers, which needs further evaluation in larger PD cohorts. The predictive value of amyloid-beta burden on cognitive worsening and PDD has been verified in previous studies, however, the neurobiology underlying IADL function in PD is still unclear. Amyloid-beta burden has been shown to be related to IADL impairment in older age persons with mild cognitive impairment, but to date, studies relating amyloid-beta values to IADL function in PD are lacking. Regarding the genetic risk variants, we did find some differences between patients with cognitive and motor IADL impairment. The role of the \textit{MAPT} gene, which encodes tau, as a risk factor of dementia in PD has been controversially discussed. As the frequency of the \textit{MAPT} risk H1/H1 genotype was lower in patients with cognitive IADL impairment, who generally showed worse cognitive performance, than patients with motor IADL impairment, our data are in accordance with studies not confirming a link between cognitive function and PD. Additionally, we identified a trend for the A-Allele of rs9974126 (which is in high linkage disequilibrium
(r²=0.93) with rs2248244, a risk factor for PD\textsuperscript{36} in the gene \textit{DYRK1A}, encoding a protein that phosphorylates alpha-synuclein, amyloid-beta precursor protein (APP), and tau.\textsuperscript{37}

In PD, differentiation between cognition- and motor-driven IADL impairment is difficult, as PD-related motor deficits, along with cognitive dysfunction, contribute to IADL impairment.\textsuperscript{14,16,40} With sensitive measures, impairments in daily function primarily related to cognitive dysfunction can be identified in patients with PD without dementia, even in early disease stages.\textsuperscript{11,15,40} To date, few measurements have been specifically designed to assess IADL function in PD whilst being independent of motor impairments.\textsuperscript{15,16} In our post-hoc ROC analysis we revealed that FAQ\textsubscript{Q} score best predicted development of PDD among FAQ subscores, whereas motor-related IADL had no impact on the prediction of PDD conversion. The optimal cut-off identified was slightly higher than the a priori defined FAQ\textsubscript{Q} cut-off published previously.\textsuperscript{16} Future studies are needed to validate the predictive value of this novel cut-off.

Some limitations of this study need to be mentioned. Although IADL is commonly assessed by an informant who can reliably give information regarding patients’ level of functioning, FAQ data was collected from both patients and informants in our study. While discrepancies between self- and informant ratings are greatest in PDD patients,\textsuperscript{41} between-group comparisons on item, total, and subscore levels did not show differences between raters. However, it is known that self-reports on the impact of cognitive changes on IADL function are more sensitive in early stages of cognitive decline.\textsuperscript{42} Future studies are needed to evaluate the predictive values of patient versus caregiver ratings in relation to cognitive worsening and dementia. A further limitation is subject attrition, a potential problem for longitudinal studies, and especially so for older PD patients who are at greater risk of developing other health conditions, institutionalization, and death.\textsuperscript{43,44} Approximately 40% of participants did not participate in follow-up examination, which may have resulted in the loss of valuable information regarding development of PDD. However, other longitudinal studies examining cognitive decline have reported similar attrition rates: 50% after 5 years,\textsuperscript{45} and 46% after 4 years.\textsuperscript{46} Patients in our sample lost to follow-up were older and had more severe motor and cognitive impairments, similar to previous reports.\textsuperscript{46} The number of patients with cognitive IADL impairment was not different between patients who dropped out compared to those who were included, suggesting presence of cognitive IADL impairment did not impact attrition. There was also a variable length in time to follow-up; however, as the FAQ\textsubscript{Q} groups had similar mean intervals, we infer that time to follow-up did not have a significant effect on our results. Future studies examining predictive value of cognitive IADL impairment should
aim for shorter follow-up intervals to minimize attrition and evaluate function at more time points. To minimize selection and non-participation bias, we included dropouts in the hazards model classified as PD-CN, the most conservative approach which argues against our hypothesis that baseline IADL status increases the likelihood of PDD. However, we cannot be sure that we identified every patient in the sample who may have developed dementia, or that the clinical profile of patients lost to follow-up might have biased our results. Not all patients with PDD were diagnosed according to Level-II criteria; however, as cognitive testing is not always possible in patients with dementia, detailed medical records were also used for diagnoses. Finally, we cannot rule out that other underlying factors (e.g., vascular burden or cortical atrophy) may have contributed to faster progression to PDD. There is little research examining how neurobiology or structural brain changes affect IADL function over time. Our data therefore need confirmation in future multi-centered studies with a more comprehensive examination including brain imaging to control for underlying neuropathological effects.

In conclusion, patients with both PD-MCI and cognitive IADL impairment could be a valuable target group for clinical trials evaluating the effect of pharmacological and non-pharmacological intervention strategies to prevent or delay PDD. Our data argue for the importance of standardized IADL assessment in the prodromal stage of PDD, which is discussed controversially.47 Especially in early stages of cognitive impairment, systematic assessment of everyday function might be neglected by physicians in the clinical daily routine. We propose a two-step screening approach: first, the application of a standardized IADL scale to screen for patients with cognitive IADL impairment, and second, the evaluation of the impact of these problems in a patient-centered interview for diagnostic purposes.


REFERENCES


doi:10.1136/jnnp-2013-306381
Figure Legends

Figure 1 Flow-chart of patient recruitment including cognitive diagnosis at follow-up
Legend: CSF=Cerebrospinal fluid; FU=follow-up; PD=Parkinson’s Disease; PD-CN=Parkinson’s Disease Cognitively Normal; PD-MCI=Parkinson’s disease with Mild Cognitive Impairment; PDD=Parkinson’s Disease Dementia.
Figure 2 Alluvial plots detailing progression of cognitive impairment over time in uncensored data

Legend: a) Patients with motor IADL impairment (FAQ\textsubscript{Q≤1}). b) Patients with cognitive IADL impairment (FAQ\textsubscript{Q>1}). IADL=instrumental activities of daily living; PD-CN= Parkinson’s Disease Cognitively Normal; PDD=Parkinson’s Disease Dementia; PD-MCI=Parkinson’s disease with Mild Cognitive Impairment.

Figure 3 Survival curves in censored data showing predictive values for PDD using different baseline stratifications

Legend: Survival curves were adjusted for covariates and based on multivariate Cox regression models of censored data. a) Predictive values for PDD in patients stratified by baseline IADL status. b) Predictive values for PDD in patients stratified by baseline cognitive status. c) Predictive values for PDD in patients with a combination of cognitive IADL impairment and PD-MCI vs. patients with all other statuses. FAQ\textsubscript{Q>1}= cognitive IADL impairment; FAQ\textsubscript{Q≤1}=motor IADL impairment; HR= hazard ratio; IADL=instrumental activities of daily living; PDD=Parkinson’s Disease Dementia; PD-MCI=Parkinson’s disease with Mild Cognitive Impairment.
Figure 4 Change in the Functional Activities Questionnaire total score between uncensored baseline and follow-up data

Legend: a) PD-CN patients split according to baseline IADL status. b) PD-MCI patients split according to baseline IADL status. Black lines: FAQ_1 = cognitive IADL impairment, Grey lines FAQ_1 = motor IADL impairment. *Patients classified as both PD-MCI and FAQ_1 at baseline showed a significant increase between baseline and follow-up visit in the FAQ total scores than patients with baseline status of either PD-CN, FAQ_1, or both (three-way interaction, visit*cognitive IADL status*cognitive status, p=0.001). IADL=instrumental activities of daily living; PD-CN=Parkinson’s Disease Cognitively Normal; PD-MCI=Parkinson’s disease with Mild Cognitive Impairment.
Table 1. Baseline characterization of patients with cognitive (FAQ<sub>Q>1</sub>) and motor (FAQ<sub>Q≤1</sub>) IADL impairment

<table>
<thead>
<tr>
<th>N/</th>
<th>Total Cohort</th>
<th>FAQ&lt;sub&gt;Q≤1&lt;/sub&gt;</th>
<th>FAQ&lt;sub&gt;Q&gt;1&lt;/sub&gt;</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>268/100</td>
<td>204/76.1</td>
<td>64/23.9</td>
<td></td>
</tr>
</tbody>
</table>

**Demographics**

| | Male sex, n/| 168/62.7 | 126/61.8 | 42/65.6 | 0.68 |
| | Age yr.      | 66.2/13.4 | 66.3/14.1 | 65.9/11.1 | 0.90 |
| | Education yr.| 13/4      | 13/4      | 12/4     | 0.07 |
| | Age at Onset yr.| 60.9/14.9 | 61.1/14.2 | 60.7/12.1 | 0.90 |
| | Disease duration yr.| 4.1/5.7 | 4.0/5.2 | 4.4/6.7 | 0.59 |
| | Levodopa equivalent daily dose | 511/515 | 508/517 | 555/446 | 0.44 |

**Motor and Non-motor scales**

| | MDS-UPDRS-III | 25/16 | 25/15 | 26/16 | 0.89 |
| | Hoehn & Yahr, n/| 0.81 |
| | 1 | 35/13.1 | 26/12.8 | 9/14.1 |
| | 2 | 152/56.7 | 118/57.8 | 34/53.1 |
| | 3 | 78/29.1 | 58/28.4 | 20/31.3 |
| | 4 | 3/1.1 | 2/0.9 | 1/1.6 |
| | Beck Depression Inventory-II | 7/8 | 6/7 | 9/10 | 0.002 |
| | Non-Motor Symptoms Questionnaire | 7/6 | 7/6 | 10/8 | <0.001 |

**IADL**

| | FAQ total score | 1/3 | 0/2 | 3/4 | 0.002 |
| | FAQ cognition score | 0/0.07 | 0/0 | 0.13/0.13 | <0.001 |
| | FAQ motor score | 0/0.10 | 0/0.10 | 0.05/0.11 | 0.68# |

**Cognition**

| | Montreal Cognitive Assessment [11] | 26/5 | 26/4 | 25/4 | 0.01 |
| | Attention [3] | -0.10/1.00 | -0.10/0.8 | -0.60/0.93 | <0.001 |
| | -Digit-Symbol Test (WIE) [2] | -0.20/0.60 | -0.20/0.9 | -0.60/0.8 | 0.015# |
| | -Letter-Number-Sequencing (WIE) [1] | 0/1.40 | 0/1.4 | -0.60/1.6 | <0.001# |
| | Executive Functions [5] | -0.23/1.75 | -0.20/1.8 | -0.43/1.65 | 0.17# |
| | -Semantic Fluency (CERAD-PLUS) | -0.50/1.30 | -0.40/1.35 | -0.55/1.16 | 0.26# |
| | -Phonemic Fluency (CERAD-PLUS) [1] | 0.10/1.20 | 0/1.20 | -0.10/1.10 | 0.62# |
| | -Trail Making Test Part B (CERAD-PLUS) [4] | -0.30/1.90 | -0.20/1.60 | -0.70/1.95 | 0.048 |
| | Memory [1] | -0.30/1.28 | -0.10/1.13 | -0.58/1.41 | 0.005 |
| | -Word List Learning (CERAD-PLUS) | -0.20/1.90 | 0/1.85 | -0.70/1.78 | 0.032 |
| | -Word List Recall (CERAD-PLUS) | -0.20/1.40 | -0.10/1.30 | -0.55/1.73 | 0.11# |
| | -Constructional Praxis Recall (CERAD-PLUS) [1] | -0.50/1.75 | -0.40/1.80 | -0.80/1.65 | 0.024# |
| | Visuospatial Abilities | -0.50/1.35 | -0.35/1.35 | -0.78/1.16 | 0.11# |
| | -Constructional Praxis (CERAD-PLUS) | -0.70/2.03 | -0.70/2.10 | -0.70/1.95 | 0.50# |
| | -Fragmented Words (LPS 50+) | -0.40/1.50 | -0.30/1.50 | -0.80/1.60 | <0.001 |
| | Language [1] | 0.10/1.00 | 0.15/1.00 | -0.23/1.30 | <0.001# |
| | -Boston Naming Test (CERAD-PLUS) | 0.40/1.50 | 0.50/1.50 | -0.25/1.93 | 0.008# |
| | -Similarities (WIE) [1] | -0.20/1.00 | 0/1.40 | -0.60/1.00 | 0.001# |

Unless otherwise indicated, values are reported as median/interquartile range (IQR=Q3-Q1). Boldface denotes statistically significant values. Missing values are reported in brackets []. #Non-Motor Symptoms Questionnaire was a significant covariate (p<0.05). CERAD-PLUS=Consortium to Establish a Registry for Alzheimer’s Disease, FAQ=Functional Activities Questionnaire, FAQ<sub>Q</sub>=Functional Activities Questionnaire quotient; FAQ<sub>Q>1</sub>=cognitive instrumental activities of daily living impairment, FAQ<sub>Q≤1</sub>=motor instrumental activities of daily living impairment, IADL=instrumental Activities of daily living, LPS 50+=Leistungsprüfsystem 50+, PD-CN=Parkinson’s Disease Cognitively Normal, PDD=Parkinson’s Disease Dementia, PD-MCI=Parkinson’s Disease with Mild Cognitive Impairment, MDS-UPDRS-III=Movement Disorder Society Unified Parkinson’s Disease Rating Scale part III, WIE= Wechsler Intelligenztest für Erwachsene, yr.=years.
Table 2. Results of binary logistic regression analyses comparing baseline genetic variants and CSF biomarkers between patients with cognitive (FAQ\(\geq 1\)) and motor IADL impairment (FAQ\(\leq 1\)).

<table>
<thead>
<tr>
<th>Genetic variants</th>
<th>FAQ(\leq 1)</th>
<th>FAQ(\geq 1)</th>
<th>(p)-value†</th>
<th>Model Fit indices</th>
<th>(\beta) coefficient (95%-CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/%</td>
<td>203/75.7</td>
<td>64/23.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Genetic variants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>APOE</em> ε4 allele carrier</td>
<td>48/23.6</td>
<td>10/15.6</td>
<td>0.24</td>
<td>0.08</td>
<td>-0.46 (-1.23, 0.31)</td>
</tr>
<tr>
<td><em>MAPT</em> H1/H1 carrier</td>
<td>139/68.5</td>
<td>33/51.6</td>
<td><strong>0.009</strong></td>
<td>0.11</td>
<td>-0.86 (-1.50, -0.22)</td>
</tr>
<tr>
<td><em>SNCA</em> rs356220 [24]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.62 (0.07)</td>
</tr>
<tr>
<td>C/C</td>
<td>48/23.6</td>
<td>18/28.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/T</td>
<td>101/49.8</td>
<td>25/39.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>37/18.2</td>
<td>14/21.9</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><em>SNCA</em> rs7681440 [25]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.51 (0.07)</td>
</tr>
<tr>
<td>G/G</td>
<td>47/23.2</td>
<td>14/21.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/G</td>
<td>97/47.8</td>
<td>28/43.8</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C/C</td>
<td>41/20.2</td>
<td>15/23.4</td>
<td></td>
<td></td>
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<tr>
<td><em>TREM2</em> R62H carrier</td>
<td>6/3.0</td>
<td>2/3.1</td>
<td>0.69</td>
<td>0.07</td>
<td>0.35 (-1.32, 2.01)</td>
</tr>
<tr>
<td><em>BDNFV66M</em> carrier</td>
<td>70/34.5</td>
<td>22/34.4</td>
<td>0.85</td>
<td>0.07</td>
<td>-0.06 (-0.69, 0.57)</td>
</tr>
<tr>
<td><em>DYRK1A</em> ts2835713 [24]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.28 (0.08)</td>
</tr>
<tr>
<td>A/A</td>
<td>126/62.1</td>
<td>44/68.8</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>A/G</td>
<td>54/26.6</td>
<td>11/17.2</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>G/G</td>
<td>6/3.0</td>
<td>2/3.1</td>
<td></td>
<td></td>
<td>-0.28 (-0.61, 0.04)</td>
</tr>
<tr>
<td><em>DYRK1A</em> rs9974126 [24]</td>
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<td></td>
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<tr>
<td>G/G</td>
<td>84/41.4</td>
<td>32/50.0</td>
<td></td>
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<tr>
<td>A/G</td>
<td>83/40.9</td>
<td>23/34.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/A</td>
<td>19/9.4</td>
<td>3/4.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>COMT</em> V158M carrier</td>
<td>56/27.6</td>
<td>18/28.1</td>
<td>0.95</td>
<td>0.07</td>
<td>0.02 (-0.64, 0.68)</td>
</tr>
<tr>
<td><em>COMT</em> L136L [24]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.47 (0.07)</td>
</tr>
<tr>
<td>C/C</td>
<td>66/32.5</td>
<td>23/35.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/G</td>
<td>87/42.9</td>
<td>27/42.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>33/16.3</td>
<td>7/10.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>GBA</em> mutation carrier*</td>
<td>22/10.8</td>
<td>8/12.5</td>
<td>0.77#</td>
<td>0.08</td>
<td>0.14 (-0.75, 1.02)</td>
</tr>
<tr>
<td><strong>Cerebrospinal fluid markers</strong></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>A(\beta) [1]</td>
<td>-0.04/0.99</td>
<td>0.13/1.02</td>
<td>0.39#</td>
<td>0.09</td>
<td>0.13 (-0.16, 0.41)</td>
</tr>
<tr>
<td>phosphorylated tau</td>
<td>0.03/1.08</td>
<td>-0.08/0.68</td>
<td>0.09#</td>
<td>0.10</td>
<td>-0.29 (-0.63, 0.05)</td>
</tr>
<tr>
<td>total Tau</td>
<td>0.05/1.08</td>
<td>-0.14/0.68</td>
<td>0.24#</td>
<td>0.09</td>
<td>-0.20 (-0.53, 0.13)</td>
</tr>
</tbody>
</table>

Results are expressed as n/% for Genetic Variants and median/interquartile range (IQR=Q3-Q1) for CSF markers. Nagelkerke \(R^2\) was used as model fit index. Missing values are reported in brackets [ ]. †\(p\)-values were corrected for Beck Depression Inventory-III, and Non-Motor Symptoms Questionnaire. *Mutations in the *GBA* gene include c.115+1G>A, R78C(R39C), T336S(T297S), E365K(E326K), R398*(R359X), T408M(T369M), N409S(N370S) and L483P(L444P). #Non-Motor Symptoms Questionnaire was a significant covariate (\(p<0.05\)). *\(APOE=\)Apolipoprotein E, *\(BDNF=\)Brain derived neurotrophic factor, CI=confidence interval, *\(COMT=\)catechol-O-methyltransferase, *\(DYRK1A=\)Dual specificity tyrosine phosphorylation regulated kinase 1, *\(GBA=\)Glucosylceramidase beta, *\(MAPT=\)Microtubule associated protein tau, *\(SNCA=\)alpha-synuclein, *\(TREM2=\)Triggering receptor expressed on myeloid cells 2.
Cognitive-Driven Activities of Daily Living Impairment as a Predictor for Dementia in Parkinson Disease: A Longitudinal Cohort Study
Sara Becker, Merle Bode, Kathrin Brockmann, et al.
Neurology published online September 2, 2022
DOI 10.1212/WNL.0000000000201201

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