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Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study

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Summary

Background—Parkinson's disease is associated with an increased incidence of cognitive impairment and dementia. Predicting who is at risk of cognitive decline early in the disease course has implications for clinical prognosis and for stratification of participants in clinical trials. We assessed the use of clinical information and biomarkers as predictive factors for cognitive decline in patients with newly diagnosed Parkinson's disease.

Methods—The Parkinson's Progression Markers Initiative (PPMI) study is a cohort study in patients with newly diagnosed Parkinson's disease. We evaluated cognitive performance (Montreal Cognitive Assessment [MoCA] scores), demographic and clinical data, *APOE* status, and biomarkers (CSF and dopamine transporter [DAT] imaging results). Using change in MoCA scores over 2 years, MoCA scores at 2 years' follow-up, and a diagnosis of cognitive impairment (combined mild cognitive impairment or dementia) at 2 years as outcome measures, we assessed the predictive values of baseline clinical variables and separate or combined additions of *APOE* status, DAT imaging, and CSF biomarkers. We did univariate and multivariate linear analyses with MoCA change scores between baseline and 2 years, and with MoCA scores at 2 years as dependent variables, using backwards linear regression analysis. Additionally, we constructed a prediction model for diagnosis of cognitive impairment using logistic regression analysis.

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Contributors

AS designed the analysis and wrote the first draft of the paper. AS, UFS, and ZA did the analyses. DW and JMS contributed to the interpretation of the data and writing of the manuscript.

Declaration of interests

AS reports grants from Economic and Social Research Council, GE Healthcare, Parkinson's UK, EU FP7, and the Movement Disorders Society; and personal fees from Medtronic and AstraZeneca. JMS reports personal fees from Roche and Eli Lilly, grants and non-financial support from AVID Radiopharmaceuticals, and serves on a data safety management board for Axon Neuroscience. UFS, ZA, and DW declare no competing interests.

Findings—390 patients with Parkinson's disease recruited between July 1, 2010, and May 31, 2013, and for whom data on MoCA scores at baseline and 2 years were available. In multivariate analyses, baseline age, University of Pennsylvania Smell Inventory Test (UPSIT) scores, CSF amyloid β ($A\beta_{42}$) to t-tau ratio, and *APOE* status were associated with change in MoCA scores over time. Baseline age, MoCA and UPSIT scores, and CSF $A\beta_{42}$ to t-tau ratio were associated with MoCA score at 2 years (using a backwards p-removal threshold of 0.1). Accuracy of prediction of cognitive impairment using age alone (area under the curve 0.68, 95% CI 0.60–0.76) significantly improved by addition of clinical scores (UPSIT, Rapid Eye Movement Sleep Behaviour Disorder Screening Questionnaire [RBDSQ], Geriatric Depression Scale, and Movement Disorder Society Unified Parkinson's Disease Rating Scale motor scores; 0.76, 0.68–0.83), CSF variables (0.74, 0.68–0.81), or DAT imaging results (0.76, 0.68–0.83). In combination, the five variables showing the most significant associations with cognitive impairment (age, UPSIT, RBDSQ, CSF $A\beta_{42}$, and caudate uptake on DAT imaging) allowed prediction of cognitive impairment at 2 years (0.80, 0.74–0.87; $p=0.0003$ compared to age alone).

Interpretation—In newly diagnosed Parkinson's disease, the occurrence of cognitive impairment at 2 year follow-up can be predicted with good accuracy using a model combining information on age, non-motor assessments, DAT imaging, and CSF biomarkers.

Introduction

Dementia occurs in at least 75% of patients who have had Parkinson's disease for more than 10 years, and deterioration in cognition is a substantial contributor to the disability associated with Parkinson's disease.^{1,2} Mild cognitive impairment is a term used to denote cognitive impairment that does not fulfil criteria for dementia in Parkinson's disease.³ Evidence suggests that almost all patients with Parkinson's disease who have mild cognitive impairment will eventually fulfil criteria for dementia.^{3,4} Early identification of individuals at risk of developing cognitive impairment could help stratify the early Parkinson's disease population for clinical trials and prognostic information, and improve understanding of the pathophysiology of cognitive decline in these patients.

There are several possible mechanisms by which cognitive impairment develops in Parkinson's disease. Findings from pathological studies show that Alzheimer's disease (amyloid β [$A\beta$] plaques and tau neurofibrillary tangles) and Parkinson's disease pathology (cortical Lewy bodies) commonly coexist.⁵ Dopaminergic deficits are suggested as a pathophysiological mechanism underlying cognitive impairment by the improvement of cognitive symptoms, especially in functions of attentional control, early in the disease course through the administration of levodopa.⁶ Besides, neuroimaging studies have shown associations between caudate and putamen dopamine transporter density with cognitive dysfunction in patients with Parkinson's disease.⁷

Research in context

Evidence before this study

Previous evidence supports the association of several clinical, genetic, CSF, and imaging markers with development of cognitive impairment in Parkinson's disease. In

Alzheimer's disease research, several risk models are available to aid the prediction of dementia using clinical features and biomarker measures, but only a few studies have combined clinical features and biomarkers as predictors of cognitive decline in Parkinson's disease. We searched PubMed for reports published up to Nov 14, 2015, with the search terms "Parkinson's disease" AND "predictors" AND "dementia" as well as "Parkinson's disease" AND "predictors" AND "cognitive impairment". There were no language restrictions. We included studies in which participants underwent longitudinal assessments that enabled assessment of predictive value of baseline markers. We found no previous studies that reported on the combination of clinical, CSF, and dopamine transporter (DAT) imaging markers, or studies that calculated the predictive value of these variables for development of cognitive impairment in Parkinson's disease.

Added value of this study

This study reports on the predictive value of clinical, genetic, CSF, and DAT imaging markers, separately and in combination, for the development of cognitive impairment in a longitudinal sample of patients with Parkinson's disease. Additionally, a risk calculation for cognitive impairment associated with each of these markers is provided. According to the results of our cohort study, the occurrence of cognitive impairment 2 years after diagnosis of Parkinson's disease can be predicted with good accuracy using a combination of age, non-motor assessments, DAT imaging, and CSF examination. To our knowledge, this the first study to report the predictive value of these combined clinical markers, imaging markers, and biomarkers for the development of cognitive impairment in Parkinson's disease.

Implications of all the available evidence

The findings of our study about the risk of cognitive impairment can support prognostic and management decisions in clinical practice, aid understanding of pathophysiological processes, and allow for planning of future trials to delay cognitive impairment in Parkinson's disease.

Older age, sex, lower education, cognitive score, higher severity of motor symptoms, hyposmia, and rapid eye movement (REM) sleep behaviour disorder (RBD) have all been suggested as predictors of cognitive decline in patients with Parkinson's disease.^{8,9} Results from biomarker studies have shown that dopamine deficit on dopamine transporter (DAT)-imaging is associated with subsequent cognitive decline in patients with Parkinson's disease. Various studies have also examined the association of cognitive impairment with CSF levels of α -synuclein, A β ₄₂, total tau (t-tau), phosphorylated tau 181p (p-tau), and ratio of A β ₄₂ to t-tau; and with apolipoprotein (APO)E ϵ 4 status.^{10,11} However, the results are conflicting regarding the contribution of CSF biomarkers in the prediction of cognitive impairment in Parkinson's disease^{12–16} and, to our knowledge, no study has previously combined clinical, CSF, and DAT imaging parameters, or calculated the predictive value of these variables for development of cognitive impairment in Parkinson's disease. In this study, we investigated the extent to which the various clinical, imaging, biomarker, and genetic measures, both individually and in combination, can be used to predict the development of cognitive impairment. Specifically, we hypothesised that the addition of CSF and DAT imaging results

to clinical assessments would contribute substantially to prediction of cognitive deterioration at 2 years of follow-up.

Methods

Study design and participants

In this cohort study, we investigated the clinical and biomarker predictors of cognitive decline in the early stage of Parkinson's disease using data from the Parkinson's Progression Marker Initiative (PPMI). PPMI started in 2010 and is an ongoing multicentre, observational clinical and biomarker study of patients with Parkinson's disease and healthy controls in 33 sites in the USA, Europe, Israel, and Australia that aims to identify biomarkers of Parkinson's disease progression and thus inform the design of clinical trials of disease-modifying therapies.¹⁷ The participants in our study were enrolled between July 1, 2010, and May 31, 2013. For this study, assessments comprise clinical evaluation of motor and non-motor features, CSF examination, and iodine-123-labelled ioflupane DAT single photon emission CT (SPECT; DATSCAN) imaging at baseline visit. The de-identified data were made available to investigators.

Only data from patients with Parkinson's disease with 2 year follow-up were included in this analysis. We downloaded data from the PPMI database on April 1, 2015. At baseline, participants were required to be over 30 years old; have an asymmetric resting tremor or asymmetric bradykinesia, or two of the three signs of bradykinesia, resting tremor, and rigidity; have a recent Parkinson's disease diagnosis; be in Hoehn and Yahr stage 1 or 2; be not treated with medications for Parkinson's disease within 60 days of the baseline visit; not be expected to require Parkinson's disease medication within at least 6 months from baseline; have a DAT deficit on imaging; not be treated with medication that might interfere with DAT imaging or CSF collection; and not have used investigational drugs or devices within 60 days of the baseline visit. For comparison, we also analysed results in the PPMI healthy control group who were recruited from the same sites, were over 30 years old, had no first-degree relative with Parkinson's disease, were matched for age and sex, and had the same assessments as the patients (see protocol for more details). Exclusion criteria were clinically significant neurological disorders, a first degree relative with Parkinson's disease, Montreal Cognitive Assessment (MoCA) score of 26 or lower, medication intake that might interfere with DAT imaging or preclude CSF collection, and use of investigational drugs or devices within 60 days of the baseline visit. The PPMI study was approved by the institutional review board at each site, and participants provided written informed consent to participate.¹⁸

Outcomes

We evaluated cognitive decline using change in MoCA, a scale for global cognitive abilities validated for use in Parkinson's disease, from baseline to 2 year follow-up; MoCA score at the 2 year assessment; and categorisation as cognitively impaired at 2 years of follow-up. Cognitive tests to classify cognitive function were the Hopkins Verbal Learning Test-Revised (HVLT-R) for memory; the Benton Judgment of Line Orientation 15-item (split-half) version for visuospatial function; the Symbol-Digit Modalities Test for processing

speed-attention; the Letter-Number Sequencing for executive function and working memory; and semantic (animal) fluency test. Individuals were categorised as having normal cognition, mild cognitive impairment, or dementia, according to the PPMI protocol. Mild cognitive impairment was defined as scores on two or more of the HVLT total recall, HVLT recognition discrimination, Benton Judgment of Line Orientation, Letter-Number Sequencing, semantic (animal) fluency test, or Symbol-Digit Modalities Test of more than 1.5 standard deviations below normal, and no functional impairment due to cognition impairment. A diagnosis of dementia also required evidence of functional impairment attributable to cognitive impairment sufficient to interfere with activities of daily life.

Clinical variables included in our study, which have previously been reported to be associated with cognitive decline in Parkinson's disease, were age, sex, years of education, disease duration, sense of smell assessed using the University of Pennsylvania Smell Identification Test (UPSIT),¹⁹ RBD measured using the RBD Screening Questionnaire (RBDSQ),²⁰ depression measured using the 15-item Geriatric Depression Scale (GDS),²¹ Parkinson's disease severity measured using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor score, tremor-dominant subtype, postural instability and gait difficulty subtype, and indeterminate motor subtype.²² For biomarker studies, we included DAT imaging data for mean caudate and putaminal uptake relative to uptake in the occipital area, and asymmetry of caudate and putaminal uptake (side with highest divided by side with lowest uptake; see research documents and standard operating procedures for more details); and *APOE* ϵ 4 status (ϵ 4 homozygous, heterozygous, or negative). We assessed CSF for α -synuclein (repeated for those with CSF haemoglobin <200 ng/mL, because the high α -synuclein content in blood can lead to high α -synuclein levels in traumatic taps), $A\beta_{42}$, total tau (t-tau) calculated ratio of $A\beta_{42}$ to t-tau, phosphorylated tau₁₈₁ (p-tau), and total protein as described previously.¹¹

Statistical analysis

We analysed data collected at baseline or screening (MoCA and DAT imaging) and at 2 year follow-up. The MoCA change score was calculated as the difference in MoCA baseline and 2 year scores. We analysed variables for missing data. We compared groups using χ^2 tests, *t* tests for normally distributed variables, and Mann-Whitney tests for non-parametric data. We examined the residuals to ensure they fulfilled all linear regression assumptions. The residuals were not negatively skewed when tested in the final model, and when checked both graphically and using normality tests, and homoscedasticity and independence also applied. We did univariate and multivariate linear analyses with MoCA change scores between baseline and 2 year assessment and with MoCA score at 2 years as dependent variables using backwards linear regression analysis. All variables with $p < 0.2$ in the univariate models were included in a backward elimination procedure with p -removal=0.1.²³ If variables were highly correlated, the variable with the lower *p* value was entered as the independent variable. We did not include MoCA scores at baseline in multivariate linear regression analyses to predict the change of MoCA score from baseline to 2 years to avoid including them on both sides of the regression equation,²⁴ but they were included in the analysis with MoCA scores at 2 years. Univariate logistic regression analysis was used to identify possible risk factors for cognitive impairment (defined as either mild cognitive impairment or

dementia) at 2 years. We used the Benjamini-Hochberg procedure controlling for a false discovery rate of 0.05, which resulted in a significance level of $p < 0.0167$ for this univariate comparison.

Several multivariate logistic regression models were then developed with cognitive impairment at 2 year follow-up as dependent variable: using age only; then age with clinical variables; age with DAT imaging results; age with CSF biomarkers; and age with clinical, DAT imaging, and CSF biomarkers. For these logistic regression models, we included independent variables if they were not highly correlated ($r > 0.5$) and were significantly different between those with and those without cognitive impairment ($p < 0.05$). For the model with combined clinical and biomarker variables, only independent variables with $p < 0.005$ were included to restrict the number of predictors for ease of use in clinical practice and to avoid overfitting of the model.²⁵ We applied a bootstrap resampling procedure with 1000 repetitions to the final risk model. To confirm the accuracy of prediction for internal validation, we used ten-fold cross-validation and cohort splitting. Bootstrapping replicates the process of sample generation from an underlying population by drawing samples with replacement from the original data set, which is of the same size as the original data set, whereas in ten-fold cross-validation the data set is divided into k subsets, and the holdout method is repeated k times. Each time, one of the k subsets is used as the test set and the other $k-1$ subsets are put together to form a training set. Moreover, we separated the original dataset in development and validation samples, comprising 70% and 30% of the original data set, respectively (cohort splitting). Discrimination of the models was quantified by use of an area under a receiver operating characteristic curve (AUC); the predictive ability was determined with Nagelkerke's R^2 index, and we tested calibration with the Hosmer-Lemeshow test for goodness of fit. The logistic regression models were repeated and presented with imputation of missing data in the independent variables using variable means. Statistical analysis was carried out with STATA (version 13.0).

To predict risk of individual patients, we constructed a risk model to calculate predicted risk in the following way:

$$\frac{\text{patient's risk of cognitive impairment at 2 years} = \exp(\text{patient's risk score})}{(1 + \exp[\text{patient's risk score}])}$$

where

$$\begin{aligned} \text{patient's risk score} = & \text{intercept} + (\text{b variable 1} \times \\ & \text{variable 1}) + (\text{b variable 2} \times \text{variable 2}) + (\text{b variable 3} \times \\ & \text{variable 3}) + (\text{b variable 4} \times \text{variable 4}) + (\text{b variable 5} \times \\ & \text{variable 5}) \end{aligned}$$

and b variable 1, b variable 2, b variable 3, b variable 4, and b variable 5 are the regression coefficients that describe how a patient's values of the predictor variables affect risk.

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

393 individuals with newly diagnosed Parkinson's disease, who were enrolled into the PPMI study between July 1, 2010, and May 31, 2013, had 2 year follow-up assessments. Three individuals did not have baseline MoCA data and were excluded. Baseline characteristics of the healthy controls and the patients with Parkinson's disease who were included in the study are shown in table 1. 318 (82%) of 390 patients had 2 year MoCA results available at the time of data download from the PPMI study database, 314 (81%) of whom had been assessed for cognitive impairment at follow-up. No significant difference was noted in the tested variables between individuals with and without 2 year cognitive follow-up data, except mean caudate asymmetry, which was greater in those without cognitive assessment at 2 years (data not shown; $p=0.02$).

No data were missing for age, sex, years in education, disease duration, baseline MoCA score, UPSIT scores, MDS-UPDRS motor scores, and motor subtype. Data were missing for two patients for the GDS and for 34 patients for the RBDSQ. *APOE* status data were missing in 37 patients. No DAT imaging data were missing. Baseline CSF data were missing for A β_{42} and α -synuclein in ten patients, for p-tau in 12 patients, for t-tau in 14 patients, and for total protein in 31 patients. We repeated analyses by imputing missing predictor variable data with means. These missing data did not alter the overall results of any analysis (data not shown).

In multivariate analyses of the predictors of change in cognitive function, change in MoCA scores from baseline to 2 year follow-up was associated with age, UPSIT score, *APOE* status, and CSF A β_{42} to t-tau ratio (table 2). In healthy controls ($n=178$), change in MoCA score from baseline to 2 year follow-up was associated with age, sex, and CSF A β_{42} (appendix p 6).

In multivariate analyses of the predictors of cognitive function at 2 years, MoCA score of patients with Parkinson's disease at 2 year follow-up was associated with age, baseline MoCA and UPSIT scores, and CSF A β_{42} to t-tau ratio (table 2). In healthy controls, MoCA score at 2 years was associated with age, sex, baseline MoCA score, and CSF A β_{42} (appendix p 6).

49 (16%) of 314 participants with Parkinson's disease were classified as having mild cognitive impairment at 2 year follow-up, three (1%) participants were classified as having dementia (overall 52 [17%] participants were classified as having cognitive impairment), and 262 (83%) were classified as being cognitively healthy. Only two (1%) of 178 healthy controls were classified as having mild cognitive impairment and none had dementia at 2 years; the two healthy controls who had mild cognitive impairment were not analysed further. At 2 years' follow-up, 233 (89%) of 262 participants without cognitive impairment

and 48 (92%) of 52 individuals with cognitive impairment had been treated with antiparkinsonian medication ($p=0.47$). Four (8%) of 52 patients in the group with cognitive impairment had been given medication for cognitive impairment. At baseline, 52 participants with Parkinson's disease later classified as cognitively impaired (mild cognitive impairment or dementia) were older, had higher RBDSQ scores at baseline, lower UPSIT scores, lower CSF $A\beta_{42}$ and $A\beta_{42}$ to t-tau ratios, and lower mean caudate uptake and caudate and putaminal asymmetry than those without cognitive impairment at 2 year follow-up (table 3).

In a logistic regression analysis with cognitive impairment as dependent variable, using as independent variables age and the clinical variables that showed univariate association ($p<0.05$) with cognitive impairment at 2 years (MDS-UPDRS motor score, GDS, UPSIT, and RBDSQ scores), prediction accuracy for cognitive impairment was higher than for age alone (AUC 0.76 [95% CI 0.68–0.83] for age and clinical variables vs 0.68 [0.60–0.76] for age alone, $p=0.025$; figure A). DAT imaging parameters with univariate association with cognitive impairment (mean caudate uptake and caudate and putaminal asymmetries) also increased the AUC compared with age alone (0.76 [0.68–0.83] for age and DAT imaging parameters vs 0.68 [0.60–0.76] for age alone, $p=0.018$; figure B), as did CSF $A\beta_{42}$ (0.74 [0.68–0.81] for age and CSF $A\beta_{42}$ vs 0.68 [0.60–0.76], $p=0.0195$; figure C). Combining the five variables most strongly associated with cognitive impairment in univariate analysis (age, UPSIT score, RBDSQ score, CSF $A\beta_{42}$, and mean caudate uptake) gave an AUC of 0.80 (95% CI 0.74–0.87, $p=0.0003$ compared with age alone; figure D). All risk models produced good discrimination and calibration, with the final risk model giving an AUC of 0.80, Nagelkerke's R^2 of 0.20, and acceptable goodness of fit (Hosmer-Lemeshow χ^2 6.27, 8 degrees of freedom; $p=0.62$) in the final risk model. Although each model was significantly better at predicting cognitive impairment at 2 years than age alone, no significant differences in AUC were observed between the models with clinical variables, CSF, and DAT imaging parameters combined with age when compared in pairs (appendix pp 1–3). However, AUCs of the models using age and clinical variables and using age and CSF parameters alone were significantly different from the final model ($p=0.03$ for clinical parameters and $p=0.02$ for CSF parameters; appendix pp 1–3). The AUC for the model with DAT imaging parameters was not significantly different from the final model ($p=0.13$; appendix p 3).

Results of the bootstrapped logistic regression analysis of the final model are given in table 4, which includes the variables age, RBDSQ score, UPSIT score, CSF $A\beta_{42}$, and mean caudate uptake. The association of mean caudate uptake with cognitive impairment was not significant in this model ($p=0.09$), but removal of mean caudate uptake from the analysis did not change the scores derived for the other factors.

The results of the ten-fold cross-validation confirmed the final model, showing no significant difference in the performance of the final model between ten different samples ($p=0.88$; appendix p 4). When the original dataset was separated in a development and a validation sampled, we did not find any significant difference in the AUCs (appendix p 5).

Using an example for the final model, a 70-year-old patient with newly diagnosed Parkinson's disease who has an UPSIT score of 22 and an RBDSQ score of 5, with a CSF

A β_{42} of 399 pg/mL, and a mean caudate uptake of 1.99 striatal binding ratio has a predicted risk of cognitive impairment at 2 years of 13% (95% CI 7–18). If the patient were 50 years old, the predicted risk with these results would be 5% (1–9). If the 70-year-old patient had a CSF A β_{42} of 310 pg/mL, an UPSIT score of 17, an RBDSQ score of 7, and a mean caudate uptake of 1.79 striatal binding ratio, the predicted risk would be 34% (25–43).

Discussion

In this study, we have identified clinical and biomarker predictors of cognitive impairment in the first 2 years after a diagnosis of Parkinson's disease. Early cognitive decline, a strong predictor of development of dementia in Parkinson's disease, was associated with a number of clinical variables, irrespective of whether the outcome at 2 years was change in MoCA scores, absolute MoCA scores, or classification of cognitive impairment (mild cognitive impairment or dementia), based on investigator assessment and detailed cognitive testing. Apart from older age, the strongest clinical predictors were reduced sense of smell, the presence of RBD and, to a lesser extent, depression and motor scores. There was evidence for a relation between *APOE* genotype and change in MoCA score, similar to findings reported previously in the general population and in patients with Parkinson's disease.²⁶ A significant association was also seen between change in MoCA scores and low CSF A β_{42} to t-tau ratio. DAT imaging results (ie, reduced mean caudate uptake and asymmetry and, to a lesser extent, lower putaminal asymmetry) were also predictive of cognitive impairment after 2 years of follow-up.

The prevalence of cognitive impairment in both the general population and in patients with Parkinson's disease is known to increase with age,^{27,28} and age was the strongest clinical predictor of cognitive impairment in this analysis in both patients and healthy controls. Although fewer years in formal education has previously been reported to be a risk factor for cognitive deterioration in the general population and in patients with Parkinson's disease,²⁸ the association was not significant in the multivariate analyses for cognitive impairment after 2 years in this study. Male sex did not contribute to prediction of cognitive impairment in participants with Parkinson's disease, although this previously identified risk factor for cognitive decline⁸ was identified in our healthy control population (appendix p 6).

Patients with more severe motor symptoms (as assessed on the MDS-UPDRS) and those with higher depression scores (as assessed on the GDS) were more likely to be classified as cognitively impaired than those with less severe motor symptoms and depression scores, in line with previous reports of motor severity and depression being predictors of cognitive deterioration in Parkinson's disease.²⁷ The previously postulated association of the postural instability and gait difficulty subtype with worse cognition^{27,29} was not seen in this early phase study.

Some of the strongest associations with cognitive decline were seen with baseline UPSIT and RBDSQ scores. Hyposmia has been reported as a risk marker for both Parkinson's disease and Alzheimer's disease and has previously been associated with cognitive decline in Parkinson's disease.⁸ Deterioration in sense of smell has been postulated to reflect extrastriatal neurodegeneration in both Alzheimer's disease and Parkinson's disease, and

although the exact pathological basis is unclear, this deterioration in sense of smell might suggest early involvement of the olfactory bulb in both disorders.³⁰ Similarly, RBD, even when assessed using a questionnaire (RBDSQ) rather than a formal sleep study, was a useful predictor of cognitive impairment in this early disease sample. Reduced and asymmetric DAT-tracer uptake particularly in the caudate was associated with cognitive deterioration in line with previous studies that have implicated the caudate and, to a lesser extent, the putamen in cognitive function in both healthy individuals³¹ and patients with Parkinson's disease.³²

CSF A β ₄₂ results at baseline also contributed to the prediction of cognitive deterioration. CSF A β ₄₂ concentration is a marker of A β pathology, which inversely correlates with A β plaque load in the brain. Reduced CSF A β ₄₂ is a core feature of Alzheimer's disease, but is also seen in other neuro-degenerative diseases and notably in dementia with Lewy bodies and Parkinson's disease dementia, which is probably due to comorbid Parkinson's and Alzheimer's disease pathology in the brain.³³ This study is not able to establish the extent of Alzheimer's or Lewy body pathology contributing to cognitive decline, but suggests that amyloid deposition might be an important contributor to the development of cognitive impairment in early Parkinson's disease. Notably, CSF t-tau was also associated with MoCA score at 2 years, potentially reflecting the contribution of neuronal loss in this neurodegenerative process. At least in Alzheimer's disease studies, concentrations of CSF tau correlate more with measures of neurodegeneration (eg, atrophy) and cognitive decline than does CSF A β ₄₂.³⁴ Previous studies examining the value of CSF markers as predictors of cognitive decline in Parkinson's disease have produced inconsistent results. In some studies, reduced concentrations of CSF A β ₄₂ without contribution of p-tau or t-tau were reported,^{12,14,35,36} whereas high concentrations of CSF p-tau, but not low levels of A β ₄₂, were associated with cognitive decline in early Parkinson's disease in the DATATOP study.¹⁵ Some studies also reported that high concentrations of CSF α -synuclein predicted cognitive decline,^{14,36} but results from the DATATOP study suggested that this association is only seen in early disease,¹³ whereas in the same study high p-tau and p-tau to A β ₄₂ ratio were associated with cognitive decline in patients with advanced disease, suggesting that different mechanisms are involved at different disease stages.¹⁵ In this study, CSF α -synuclein and p-tau concentrations, which have previously been reported to be significantly lower in this Parkinson's disease population than in controls,¹¹ were not helpful in predicting early cognitive deterioration. These differences between findings might reflect differences in sample sizes,^{12,14} disease stages,^{12,14} variability in measurements of the CSF proteins, or in assessment methods between these studies, and highlight the need for careful standardisation of CSF protein measurements.

The main purpose of our analysis was to establish the value of clinical markers and various widely available biomarkers at the time of diagnosis of Parkinson's disease in predicting the development of cognitive impairment over 2 years. Clinical markers, particularly age, UPSIT, and RBDSQ, provided useful discriminative value over and above age alone. Similarly, addition of CSF A β ₄₂, or caudate uptake and caudate and putaminal asymmetry on DAT imaging markers increased the discriminative value of age for prediction of cognitive impairment, with similar predictive values in all three models. Compared with age alone, a model taking into account both clinical variables and biomarkers increased the

predictive value of the model with the greatest predictive accuracy. Combining these clinical and biomarker variables could be helpful in clinical practice, but most importantly, in clinical trials aiming to identify people at risk of cognitive decline; in this context, being able to estimate a 5% risk, compared with a 13% or a 34% risk, is likely to be clinically useful.

Our study has some limitations. In the absence of pathological confirmation, the current data cannot establish the pathological mechanism of early cognitive decline in Parkinson's disease, which is likely to be multifactorial. Furthermore, the nigrostriatal dopaminergic deficit showed on DAT imaging does not necessarily reflect dopaminergic deficits in other brain areas. However, this analysis suggests that the nigrostriatal deficit, which underlies the motor symptoms of Parkinson's disease, is not the sole driver of cognitive changes seen at this early stage after diagnosis.

This study only included a follow-up of the first 2 years after diagnosis, with median duration since diagnosis of 4 months at baseline. Therefore, few patients developed Parkinson's disease dementia by clinical cognitive assessment. Although mild cognitive impairment is considered a pre-dementia phase, not all patients will develop dementia; however, previous studies have reported a very high conversion rate of mild cognitive impairment to dementia in patients with Parkinson's disease with new diagnosis of mild cognitive impairment.⁴ Our results should therefore be considered in the context of predicting cognitive impairment rather than dementia. Additionally, classification of cognitive impairment according to predefined criteria was not usually done at the start of the study. However, even if mild cognitive impairment had been noted at inclusion, this finding might suggest that cognitive decline had already developed in the long pre-diagnostic phase of Parkinson's disease, as time of diagnosis depends on many variables, including health-seeking behaviour and access to a movement disorders specialist. The changes in the main outcomes examined in this early disease population are too small to distinguish patients with slower or faster progression to clinical dementia, for which prolonged follow-up will be required. Finally, the prediction model presented here should be further validated in other cohorts and interpreted in the appropriate clinical context.

Strategies to identify individuals with Parkinson's disease at risk of developing cognitive impairment might be useful, for example, for the stratification of patients in clinical trials to prevent or slow the onset of cognitive decline. For instance, assessment of whether acetylcholinesterase inhibitors, which have proven benefits in Parkinson's disease dementia, are beneficial at early stages of Parkinson's disease would be useful. Although these results need confirmation in further studies, they show that a simple algorithm combining age, presence of hyposmia and RBD, as well as CSF and DAT imaging parameters can predict cognitive decline and, in the appropriate clinical context, clinicians and researchers can use the proposed method to calculate risk of cognitive decline over 2 years for individuals with early Parkinson's disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure. Receiver operating characteristic curves for prediction of cognitive impairment at 2 year follow-up in patients newly diagnosed with Parkinson's disease

Predictive value of (A) age only and age with clinical variables (MDS-UPDRS motor, GDS, UPSIT, and RBDSQ scores), (B) age with DAT imaging (mean caudate uptake, and caudate and putaminal asymmetry), (C) age with CSF $A\beta_{42}$, and (D) age with clinical variables, DAT imaging results and CSF $A\beta_{42}$ combined. DAT=dopamine transporter. GDS=Geriatric Depression Scale. MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale. RBDSQ=Rapid Eye Movement Sleep Behaviour Disorder Screening Questionnaire. UPSIT=University of Pennsylvania Smell Inventory Test.

Table 1

Baseline characteristics

	Patients (n=390)	Controls (n=178)
Demographic and clinical characteristics		
Age, years	61.2 (9.8)	60.7 (11.0)
Men	254 (65%)	112 (63%)
Education, years	15.6 (2.9)	16.1 (2.9)
Disease duration, months	4 (2–8)	NA
MoCA score	27.2 (2.3)	28.3 (1.1)
GDS score	2 (1–3)	1 (0–2)
MDS-UPDRS motor score	20 (14–26)	0 (0–2)
UPSIT score	22.1 (8.2)	34.1 (4.5)
RBDSQ score	5.5 (3.1)	2.9 (2.4)
Motor subtype		
Tremor-dominant	329 (84%)	NA
Postural instability and gait difficulty	32 (8%)	NA
Indeterminate	29 (7%)	NA
APOE, CSF, and DAT imaging markers		
<i>APOE</i> ε4 status		
Heterozygous	82 (23%)	38 (24%)
Homozygous	8 (2%)	4 (2%)
DAT imaging (striatal binding ratio)		
Mean putaminal uptake	0.8 (0.3)	2.1 (0.6)
Mean caudate uptake	2.0 (0.6)	3.0 (0.6)
Putaminal asymmetry	1.5 (0.4)	1.1 (0.1)
Caudate asymmetry	1.2 (0.2)	1.1 (0.6)
CSF markers, pg/mL		
Aβ ₄₂	373.0 (100.3)	378.1 (115.8)
α-synuclein	1861.0 (783.8)	2230.9 (1109.9)
Total tau	44.8 (17.9)	53.3 (27.7)
Phosphorylated tau	15.8 (10.1)	18.5 (12.0)
Aβ ₄₂ :tau ratio	9.2 (3.1)	8.4 (3.3)
Total protein	44.1 (21.1)	40.8 (15.8)

Data are mean (SD), median (IQR), or n (%). MoCA=Montreal Cognitive Assessment. GDS=Geriatric Depression Scale. MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale. UPSIT=University of Pennsylvania Smell Inventory Test. RBDSQ=Rapid Eye Movement Sleep Behaviour Disorder Screening Questionnaire. NA=not applicable. DAT=dopamine transporter.

Analyses of the association between baseline clinical features and biomarkers with change of MoCA scores over 2 years and with MoCA score at 2 years in patients with newly diagnosed Parkinson's disease

Table 2

	Change in MoCA score				MoCA follow-up score at 2 year follow-up			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Coefficient	p value	Coefficient	p value	Coefficient	p value	Coefficient	p value
Demographic and clinical characteristics								
Age	0.061	0.0001*	0.045	0.01	-0.106	<0.0001*	-0.049	0.003*
Sex								
Women	Ref				Ref			
Men	0.167	0.61	..	..	-0.764	0.03*	..	..
Education	-0.059	0.28	..	..	0.064	0.30	..	..
Disease duration	-0.034	0.13	..	..	-0.001	0.96	..	..
Motor subtype								
Tremor-dominant	Ref		Ref		Ref		Ref	
Postural instability and gait difficulty	0.268	0.57	..	..	-0.047	0.96	..	..
Indeterminate	0.585		..		0.172		..	
MoCA baseline score					0.667	<0.0001*	0.572	<0.0001*
GDS score	0.070	0.25	..	..	-0.063	0.35	..	..
MDS-UPDRS motor score	0.038	0.03*	..	..	-0.068	0.0004*	..	..
UPSIT score	-0.064	0.001*	-0.035	0.08	0.089	<0.0001*	0.045	0.01
RBDSQ score	0.075	0.15*	..	..	-0.078	0.18*	..	..
APOE, CSF, and DAT imaging markers								
APOE ε4 status								
No APOE ε4 allele	Ref		Ref		Ref			
Heterozygous	0.740	0.03*	0.658	0.01	-0.532	0.33	..	..
Homozygous	2.240		3.701		-1.047		..	..
DAT imaging (striatal binding ratio)								

	Change in MoCA score				MoCA follow-up score at 2 year follow-up			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Coefficient	p value	Coefficient	p value	Coefficient	p value	Coefficient	p value
Mean putaminal uptake	-0.798	0.14 *	..	..	1.122	0.06 *	..	..
Mean caudate uptake	-0.641	0.02 *	..	..	0.574	0.06 *	..	..
Putaminal asymmetry	-0.470	0.21	..	..	0.900	0.03 *	..	..
Caudate asymmetry	0.804	0.39	..	..	0.414	0.69	..	..
CSF markers, pg/mL								
A β ₄₂	-0.006	0.0002 *	..	..	0.004	0.02 *	..	..
α -synuclein	-0.0003	0.21	..	..	0.0001	0.57	..	..
α -synuclein (participants with haemoglobin <200 ng/mL) [†]	-0.0003	0.23	..	..	0.0001	0.68	..	..
Total tau	0.019	0.03 *	..	..	-0.035	0.0004 *	..	..
Phosphorylated tau	-0.003	0.83	..	..	-0.010	0.56	..	..
A β :tau ratio	-0.197	0.0002 *	-0.125	0.03	0.271	<0.0001 *	0.162	0.002
Total protein	0.015	0.07 *	..	..	-0.018	0.05 *	..	..

Ref=reference. MoCA=Montreal Cognitive Assessment. GDS=Geriatric Depression Scale, MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale. UPSIT=University of Pennsylvania Smell Inventory Test. RBDSQ=Revised Behavioural Sleep Questionnaire. DAT=dopamine transporter.

* Included in multivariate linear regression analysis (p<0.2).

[†] n=302.

Table 3

Characteristics of the patients with Parkinson's disease with or without cognitive impairment at 2 year follow-up

	Patients without cognitive impairment at 2 years (n=262)	Patients with cognitive impairment at 2 years (n=52)	p value *
Demographic and clinical characteristics			
Age, years	60.2 (9.9)	66.1 (7.8)	<0.0001
Men	170 (65%)	38 (73%)	0.25 [‡]
Education, years	15.7 (2.6)	14.6 (3.8)	0.06
Disease duration, months	4 (2–8)	4 (2.5–9)	0.84 [‡]
MoCA score	27.3 (2.3)	26.9 (2.4)	0.38
GDS score [‡]	2 (1–3)	2 (1–3)	0.03
MDS-UPDRS motor score	20.4 (8.4)	23.2 (10.4)	0.04
UPSIT score	22.9 (8.0)	17.5 (8.4)	<0.0001
RBDSQ score	5.2 (2.8)	7.0 (3.5)	0.0003
Motor subtype			
Tremor-dominant	227 (87%)	39 (75%)	
Postural instability and gait difficulty	18 (7%)	8 (15%)	
Indeterminate	17 (7%)	5 (10%)	0.11 [‡]
APOE, CSF, and DAT imaging markers			
APOE e4 status			0.93 [‡]
Heterozygous	53 (22%)	11 (25%)	
Homozygous	5 (2%)	1 (2%)	
DAT imaging (striatal binding ratio)			
Mean putaminal uptake	0.8 (0.3)	0.8 (0.4)	0.07
Mean caudate uptake	2.1 (0.5)	1.8 (0.6)	0.0003
Putaminal asymmetry	1.5 (0.4)	1.4 (0.4)	0.03
Caudate asymmetry	1.2 (0.2)	1.15 (0.1)	0.009
CSF markers, pg/mL [§]			
Aβ ₄₂	381.6 (97.9)	310.5 (80.9)	<0.0001
α-synuclein	1864.0 (799.2)	1753.1 (688.5)	0.36
α-synuclein (participants with haemoglobin <200 ng/mL) [¶]	1819.9 (737.1)	1849.5 (677.5)	0.22
Total tau	44.5 (16.8)	46.0 (21.1)	0.57
Phosphorylated tau	12 (7.4)	11.6 (10.2)	0.49
Aβ ₄₂ :tau ratio	9.4 (3.0)	7.8 (3.1)	0.0006
Total protein	42.9 (18.9)	48.9 (23.7)	0.06

Data are mean (SD), median (IQR), or n (%). MoCA=Montreal Cognitive Assessment. GDS=Geriatric Depression Scale. MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale. UPSIT=University of Pennsylvania Smell Inventory Test. RBDSQ=Rapid Eye Movement Sleep Behaviour Disorder Screening Questionnaire. DAT=dopamine transporter.

* Wilcoxon test.

[†] χ^2 test.

[‡] Non-parametric statistics (median, IQR, Mann-Whitney test).

[§] Patients without cognitive impairment at 2 years (n=255); patients with cognitive impairment at 2 years (n=50).

[¶] n=302.

Table 4

Model for prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease

	Regression coefficient	Odds ratio (95% CI)	p value
RBDSQ	0.123	1.131 (1.001–1.277)	0.048
CSF A β ₄₂	−0.006	0.994 (0.990–0.997)	0.001
UPSIT	−0.061	0.941 (0.896–0.988)	0.015
Mean caudate uptake	−0.578	0.561 (0.283–1.113)	0.090
Age	0.051	1.053 (1.005–1.103)	0.029
Intercept	−1.051	0.350	0.605

Bootstrapped results of multivariate logistic regression with all statistically significant ($p < 0.0005$) clinical and biomarker variables (including imputed missing values). RBDSQ=Rapid Eye Movement Sleep Behaviour Disorder Screening Questionnaire. UPSIT=University of Pennsylvania Smell Inventory Test.