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Cerebrospinal Fluid Levels of Kininogen-1 Indicate Early Cognitive Impairment in Parkinson's Disease

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ABSTRACT: Background: Cognitive impairment is common in patients with PD. Core markers of Alzheimer's dementia have been related also to PD dementia, but no disease-specific signature to predict PD dementia exists to date.
Objectives: The aim of this study was to investigate CSF markers associated with cognition in early PD.
Methods: A high-throughput suspension bead array examined 216 proteins in CSF of 74 PD patients in the AETIONOMY project. Cognitive function was assessed with Repeatable Battery for the Assessment of the Neuropsychological Status, Montreal Cognitive Assessment, and Mini-Mental State Examination.
Results: Of 69 patients with complete data, 34 had high (≥90) and 35 had low Repeatable Battery for the Assessment of the Neuropsychological Status total score (<90). Of 14 proteins in CSF that differed in levels between groups, increased kininogen-1, validated with several antibodies, was independently associated with lower Repeatable Battery for the Assessment of the Neuropsychological Status and Montreal Cognitive Assessment scores after adjustment for confounders.
Conclusions: Kininogen-1 levels in CSF may serve as a marker of cognitive impairment in PD. © 2020 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: cognition; kininogen-1; neurodegeneration; Parkinson's disease

Cognitive impairment is a common feature in Parkinson's disease (PD), associated with increased morbidity and mortality.[1] Two distinct subtypes of cognitive dysfunction have been suggested in PD, including frontal executive dysfunction associated with dopaminergic loss, and the posterior/temporal subtype that affects visuospatial and semantic fluency function and correlates with cholinergic loss.[2,3] Reduced cerebrospinal fluid (CSF) levels of alpha synuclein,[4] and increased plasma levels of soluble tumor necrosis factor receptor[5] and higher frequency of the apolipoprotein E e4 allele carriership[6] have been associated with executive dysfunction in PD. Visuospatial and semantic fluency deficit is associated with tau pathology and has a predictable progress that eventually leads to PD dementia.[3] In a meta-analysis, markers of Alzheimer's

pathology, including increased CSF tau and decreased beta-amyloid$_{1-42}$, were associated with PD dementia.[7] Current treatment of PD dementia comprises pharmacological, symptomatic therapy with cholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist, memantine, with only marginal, short-lasting effects.[8]

The aim of this multicenter study was to investigate potential alterations of CSF protein levels associated with overall and domain-specific cognitive performance in early PD patients.

Participants and Methods

Patients

In total, 405 persons were recruited in the PD cohort of the AETIONOMY project in six university hospitals in France, Germany, and Sweden, between September 2015 and December 2017, including 251 patients with idiopathic PD, 25 with familial PD, 39 persons at risk for PD, and 90 healthy controls.[9] The study protocol was reviewed and approved by the ethical review boards of the three participating countries. All study subjects received oral and written information for the project and provided written informed consent before any study-specific activity was performed. Idiopathic PD patients with available CSF (n = 74) were included in the analyses.

Clinical Assessment

Clinical evaluation of study subjects was performed as previously described.[9] Cognitive function was assessed with the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Repeatable Battery for the Assessment of the Neuropsychological Status (RBANS). CSF was collected by lumbar puncture, and samples were centrifuged at 4°C (within 1 hour) for 10 minutes at 2,000g. Aliquots were immediately stored at –80°C. Samples were collected, processed, and stored locally at each site following the established standard operating procedures (SOPs). Samples were then distributed at the collaborating centers for specific analyses; proteomic studies were undertaken at SciLifeLab in Stockholm, Sweden.

Proteomic Assay

A suspension bead array procedure was performed, as described previously,[10] utilizing polyclonal rabbit antibodies generated within the Human Protein Atlas project (www.proteinatlas.org) targeting 216 proteins. Proteins were selected either based on potential association to PD according to literature or by our previous neuroproteomic efforts. As a validation procedure, levels of kininogen in CSF were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (ab108876; Abcam, Cambridge, UK). Dilution ratio was 1:100. Absorbance was measured by a Tecan Spark 10-M plate reader (Tecan Group Ltd., Männedorf, Switzerland).

Statistical Analysis

RBANS total index score was dichotomized at the level of 90, the threshold for average performance (score < 90 comprises subjects classified as "low average" [80–89], "borderline" [70–79], and "extremely low" [<69] that represent 25% of the normal population). Comparisons between study groups were evaluated with Wilcoxon's rank-sum test. Proteins that were significantly associated with the RBANS group ($P \leq 0.01$) were further investigated to examine whether age, sex, disease duration, and lifestyle and clinical parameters differentially distributed ($P < 0.1$) between groups confounded the observed associations. Multivariate linear regression models were fit, and confounding was considered present if the adjusted coefficient differed from the crude coefficient by >10%.

Logistic regression analysis was applied to investigate the strength of association of selected proteins as predictors of cognitive status (high vs. low RBANS), in separate multivariate models including also sex, disease duration, Hospital Anxiety and Depression Scale anxiety score (HADS-A), University of Pennsylvania Smell Identification Test (UPSIT) score, and International Parkinson and Movement Disorder Society/UPDRS part 4 score (n = 68/69 because of one missing UPSIT score). Receiver operating characteristic (ROC) curves were used to visualize the models' separation potential between high and low RBANS score. Multivariate linear regression analysis was also applied to investigate all three cognitive scales (ie, RBANS, MoCA, and MMSE total scores) as dependent, continuous variables with the same independent variables as in the logistic regression model. Results were further validated by randomly splitting the patient sample in two equally sized sample sets, and investigating the model with linear regression analysis, where RBANS total score was the dependent variable. Requiring findings to be significant in both subsamples offers protection against type 1 errors.

Spearman's correlation was used to investigate the strength of association between selected pairs of proteins. Stata software (version 12.0; StataCorp LP, College Station, TX) and the open source software, R,[11] were used for data analyses and graphs.

Results

Patient Demographic and Clinical Characteristics

RBANS score was available in 69 of 74 patients in this cohort, of whom 34 (49%) had high (≥90) and 35 (51%) had low RBANS total score (<90). Age at PD diagnosis, disease duration, and sex distribution were similar in the two groups. There were few differences between groups in lifestyle habits, somatometric measurements, comorbidities, and clinical scales of motor and nonmotor symptom severity (Supporting Information Table S1).
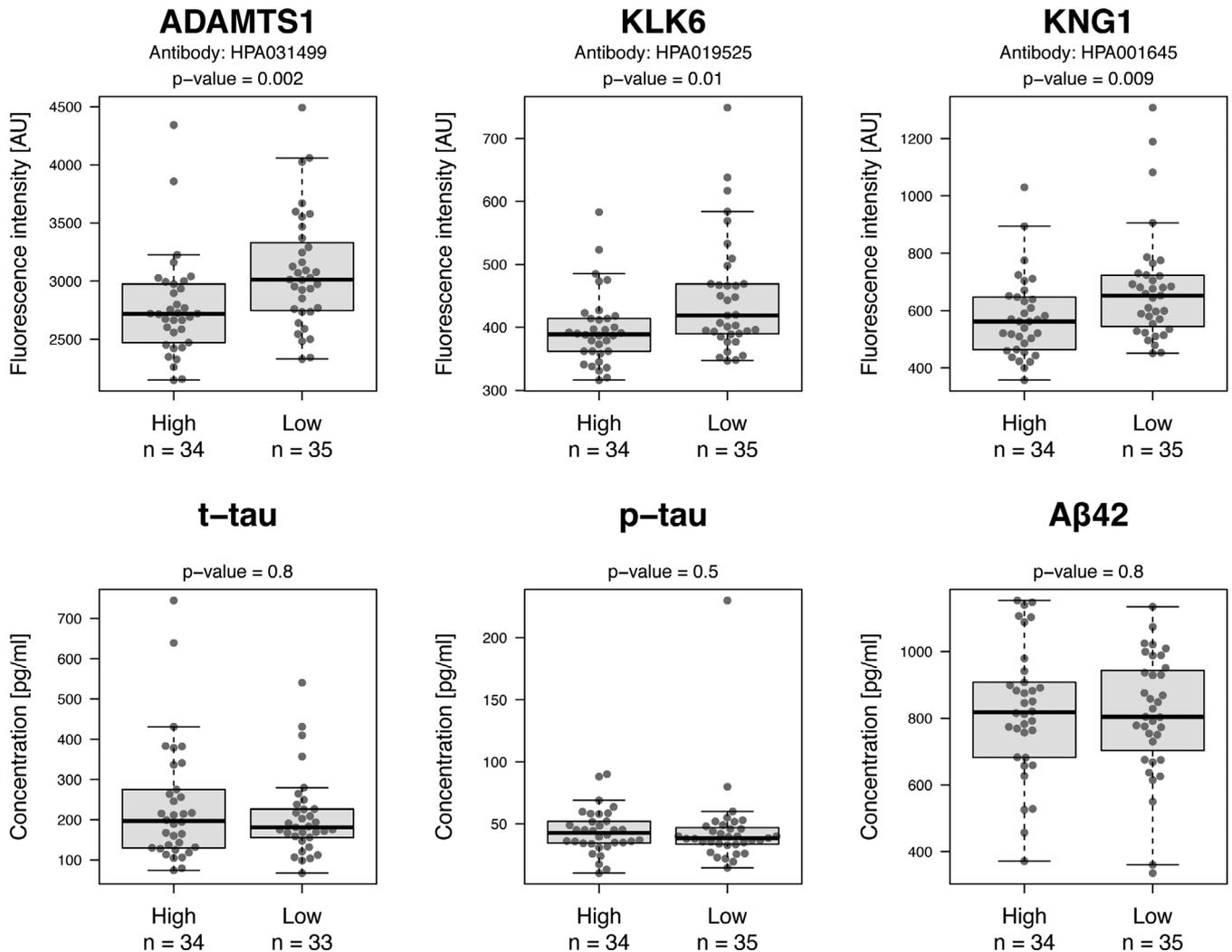
FIG. 1. Boxplots of the three proteins with altered CSF levels in PD patients with high and low RBANS total score and CSF total tau, phospho-tau, and beta-amyloid$_{1-42}$ (Aβ42) levels in high versus low RBANS total score. AU, arbitrary units.

Protein Analysis

In the first step, protein profiling in patients with PD was performed, and 14 proteins were found at altered levels in patients with high versus low RBANS score (Supporting Information Table S2). Supporting Information Fig. S1A shows the correlation matrix of these proteins, and the string plot of protein-protein interactions is presented in Supporting Information Fig. S1B. Subsequently, in multivariate, linear regression analyses adjusting for potential confounders, a disintegrin and metalloproteinase with thrombospondin motifs 1 (ADAMTS1; antibody HPA031499), kallikrein-6 (KLK6; antibody HPA019525), and kininogen-1 (KNG1; antibody HPA001645) remained significant in all fitted models and were higher in patients with low versus high RBANS score (Fig. 1).

Logistic regression analysis was then applied to investigate the strength of association of each of these proteins (ie, KNG1, KLK6, and ADAMTS) as predictors of high/low RBANS. Significant predictors of outcome in the first model were KNG1 (odds ratio [OR]: 1.005; 95% confidence interval [CI]: 1.001–1.010; $P = 0.03$) and HADS-A score (OR, 1.2; 95% CI: 1.01–1.40; $P = 0.03$). ADAMTS1 (OR, 1.001; 95% CI: 0.990–1.003; $P = 0.06$) and KLK6 (OR, 1.009; 95% CI: 1.00–1.02; $P = 0.05$) were not statistically significant in the multivariate model. ROC analyses were used to visualize the model's potential to separate between low and high RBANS. The area under the ROC was determined to be 0.80 (95% CI: 0.70–0.91; Fig. 2).

Multivariate linear regression analysis showed that KNG1 was significantly associated with RBANS total score (B, –0.034; 95% CI: –0.054, –0.014; $P = 0.001$) in the whole sample set, as well as in the training (n = 33; B, –0.0393; 95% CI: –0.062, –0.017; $P = 0.001$) and the validation set (n = 35; B, –0.0388; 95% CI: –0.078, 0.0002; $P = 0.05$).

Model with KNG1
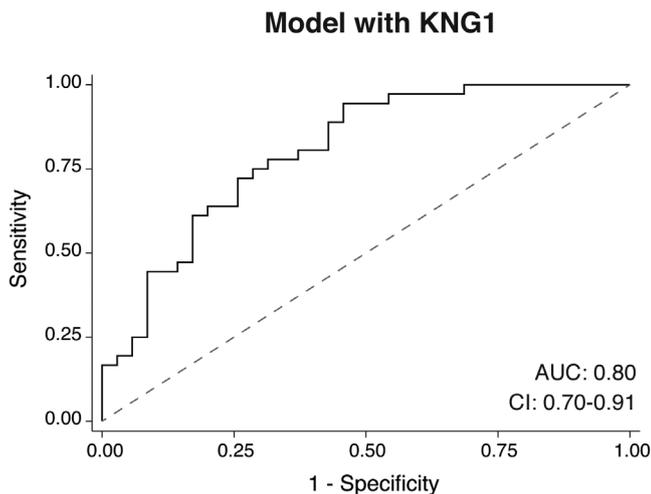
FIG. 2. ROC curve with 95% CI of multivariate logistic regression model including KNG1, predicting cognitive status as defined by RBANS total score. AUC, area under the curve.

With regard to differences among clinical sites, RBANS total score was highest in patients recruited in the French sites (median, 101; interquartile range [IQR]: 19), lowest in Stockholm (median, 84; IQR, 13), and intermediate in Bonn (median, 91; IQR, 13; $P = 0.002$), whereas KNG1 levels had an inverse pattern and were lowest in the French group (median, 496; IQR, 111), highest in the Swedish group (median, 684; IQR, 91), and intermediate in the German group (median, 570; IQR, 82; $P = 0.0001$; Supporting Information Fig. S2A,B). Distribution of KNG1 levels over RBANS total score quantiles by clinical site is shown in Supporting Information Fig. S3. When clinical site was added in the multivariate, linear regression model, a significant association with KNG1 was still apparent (B, −0.02; 95% CI: −0.04, −0.0007; $P = 0.04$).

KNG1 was also associated with MoCA total score in the multivariate logistic regression analysis (n = 71; B, −0.004; 95% CI: −0.009, −0.0002; $P = 0.04$), but not with MMSE total score (n = 71; B, −0.002; 95% CI: −0.004, 0.0008; $P = 0.2$).

Two additional antibodies targeting KNG1 were included in the bead-based assay (HPA001615 and HPA001616), and a strong correlation was noted between them and HPA001645 ($\rho = 0.95$ and 0.89, respectively; $P < 0.0001$). KNG1 was further investigated with ELISA in the subgroup of patients recruited in Stockholm (n = 28 of 29; no results were obtained in 1 patient), in order to validate the bead-based results. Spearman's rho (ρ) between the ELISA- and bead-based values were 0.72 ($P < 0.0001$), which further adds support for on-target binding. Separate, multivariate linear regression models were applied for each of the additional antibodies targeting KNG1, and a significant association was shown for HPA001615 (B, −0.012; 95% CI: −0.02, −0.005; $P = 0.002$) and HPA001616

(B, −0.033; 95% CI: −0.054, −0.012; $P = 0.003$), but not for the ELISA-based KNG1 levels (B, −0.003; 95% CI: −0.008, 0.001; $P = 0.1$), presumably because of the lower number of subjects included in this analysis.

KNG1 Associations With RBANS Domain-Specific Scores, Age, and CSF Tau and Beta-Amyloid$_{1-42}$ Levels

KNG1 measurements based on the bead-based assay correlated moderately with RBANS Attention Index ($\rho = -0.37$; $P = 0.002$), Visuospatial Index ($\rho = -0.31$; $P = 0.009$), Immediate ($\rho = -0.33$; $P = 0.006$), and Delayed Memory Index ($\rho = -0.36$; $P = 0.002$) and total score ($\rho = -0.42$; $P = 0.0003$). ELISA-based KNG1 measurements correlated also with RBANS Immediate ($\rho = -0.5$; $P = 0.008$) and Delayed Memory Index ($\rho = -0.46$; $P = 0.02$) and RBANS total score ($\rho = -0.34$; $P = 0.08$). No significant correlation was observed with RBANS Language Index. Age and CSF total tau, phospho-tau, and beta-amyloid$_{1-42}$ levels did not correlate with KNG1 measurements and did not differ between patients with low versus high RBANS total score (Fig. 1).

Discussion

In our study, CSF levels of KNG1 were associated with cognitive performance of PD patients without overt dementia. Increased CSF levels of KNG1 were associated with low RBANS and MoCA total score in PD patients, independent of sex, disease duration, and potential confounders including anxiety and hyposmia.

Because of alternative splicing, the gene encoding kininogen-1 produced low-molecular-weight kininogen and high-molecular-weight kininogen, where the latter is also known as kininogen-1. It is essential for blood coagulation through the intrinsic coagulation pathway and also constituent of the kallikrein-kinin system involved in proinflammatory reactions.[12] No studies have previously reported an association between KNG1 and PD. However, studies on Alzheimer's disease (AD) have shown that the contact system and complement are activated and the high-molecular-weight kininogen is cleaved in the CSF of patients with early-onset AD.[13] Consistently with the hypothesis of increased cleavage of KNG1 in the AD brain, low CSF levels of KNG1 were observed in AD patients compared to controls, in a proteomic study.[14] Also, beta-amyloid$_{1-42}$–induced activation of plasma protein factor XII and kallikrein-mediated KNG1 cleavage with release of proinflammatory bradykinin have previously been demonstrated in plasma of AD patients, representing a potential mechanism of inflammatory pathology.[15] A recently developed detection method of cleaved plasma KNG1 has been tested and further supported the theory

that decreased levels of intact KNG1 and increased levels of cleaved KNG1 in AD plasma are associated with dementia and neuritic plaque scores, and may be used as novel AD markers.[16] Finally, an antibody against high-molecular-weight kininogen has been developed and shown to block beta-amyloid–induced bradykinin release in human plasma, suggesting new treatment strategies against bradykinin-driven pathologies.[17] In our study, higher CSF levels of KNG1 (not distinguishing between intact and cleaved) were found in patients with low RBANS score. Our findings may be in line with previous AD research, assuming that higher levels of KNG1 in our patients with lower cognitive scores reflect cleaved KNG1, but further studies with assays that distinguish between intact and cleaved KNG1 are needed. To further assess our findings in relation to hallmarks of Alzheimer's pathology, we measured levels of total tau, phospho-tau, and beta-amyloid$_{1-42}$, and showed that they did not differ in patients with low versus high RBANS score, which, however, was expected in a nondemented cohort. On the other hand, KNG1 correlated significantly with the domains of immediate and delayed memory in RBANS subscores. Higher CSF levels of KNG1 were also associated with MoCA, but not with MMSE, total score. Previous studies have shown that MoCA has more adequate psychometric properties than MMSE for detection of PD-related mild cognitive impairment or dementia.[18,19]

The limitations of the study include the relatively small number of patients and absence of late-stage disease patients, facilitating further exploration of the results in different stages of disease severity and cognitive impairment. Also, AETIONOMY is a cross-sectional study, and future longitudinal prospective cohorts are necessary to determine the nature of the associations reported here. Nonetheless, our results are based on a very well-described cohort of patients, with demographic, environmental, and clinical characteristics well in accordance with larger cohorts, and CSF levels of KNG1 are validated with several antibodies. Our sample comprises patients recruited and evaluated in several sites by different examiners. However, all investigators are movement disorders specialists in expert centers, and significant variability in patient evaluation should rather lead to underestimation of the effect size of observed associations. Common SOP has been used in all sites to secure similar conditions of sample processing, and proteomic studies were performed in one site.

In conclusion, we present the results of a high-throughput antibody-based proteomic approach for the analysis of CSF markers related to early signs of cognitive impairment in PD. We found that KNG1 levels in CSF were altered in PD patients with RBANS total score of low average level or less. Furthermore, longitudinal studies with serial cognitive assessments and lumbar punctures are necessary to further explore the nature of KNG1 levels to detect cognitive decline and predict dementia development. It will also be interesting to learn more about the interplay of KNG1 with synuclein pathology in the PD brain. ●

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

GBA-Related Parkinson's Disease: Dissection of Genotype–Phenotype Correlates in a Large Italian Cohort

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ABSTRACT: Background: Variants in *GBA* are the most common genetic risk factor for Parkinson's disease (PD). The impact of different variants on the PD clinical spectrum is still unclear.
Objectives: We determined the frequency of *GBA*-related PD in Italy and correlated *GBA* variants with motor and nonmotor features and their occurrence over time.
Methods: Sanger sequencing of the whole *GBA* gene was performed. Variants were classified as mild, severe, complex, and risk. β-glucocerebrosidase activity was measured. The Kaplan-Meier method and Cox proportional hazard regression models were performed.
Results: Among 874 patients with PD, 36 variants were detected in 14.3%, including 20.4% early onset. Patients with GBA-PD had earlier and more frequent occurrence of several nonmotor symptoms. Patients with severe and complex GBA-PD had the highest burden of symptoms and a higher risk of hallucinations and cognitive impairment. Complex GBA-PD had the lowest β-glucocerebrosidase activity.
Conclusions: GBA-PD is highly prevalent in Italy. Different types of mutations underlie distinct phenotypic profiles. © 2020 International Parkinson and Movement Disorder Society

Key Words: dementia; GBA; genotype–phenotype correlates; impulsive–compulsive behavior; Parkinson's disease