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Short communication

Caregiver report of apathy predicts dementia in Parkinson's disease

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ABSTRACT

Introduction: Apathy is a common, troublesome symptom in Parkinson's disease (PD). However, little is known about its relationship with long-term cognition. We sought to determine if a caregiver-reported apathy measure predicts the development of PD dementia.
Methods: Non-demented PD patients were recruited as part of a longitudinal study of cognition. Demographics, medications, Dementia Rating Scale-2, Unified Parkinson's Disease Rating Scale, Geriatric Depression Scale and the Neuropsychiatric Inventory-Questionnaire (NPI-Q) ratings were obtained. Apathy was defined as an NPI-Q apathy score $\geq$1. Participants were evaluated annually with cognitive and functional assessments until the end of the study period or a physician consensus diagnosis of dementia was assigned. Cox proportional hazard models were used to assess the effects of baseline apathy on dementia development while controlling for other clinical and demographic factors.
Results: Of 132 PD patients 12.1% (N = 16) scored in the apathetic range at baseline. A total of 19.6% (N = 26) individuals developed dementia over the course of the study, 8 of whom (30.8% of future dementia patients) had baseline apathy. In bivariate analyses baseline apathy, older age, and worse cognitive, motor, and depressive symptom scores predicted the development of dementia. In a multivariate analysis the predictive effects of baseline apathy were still significant (HR = 3.56; 95% CI = 1.09 −11.62; p = 0.04).
Conclusions: A simple, caregiver-reported measure of apathy is an independent predictor of progression to dementia in PD. This highlights the importance of apathy as a clinical characteristic of PD and could prove useful for the prediction of future dementia.

1. Introduction

Apathy is typically characterized by indifference, loss of interest, and lack of motivation [1]. It is a common and disabling feature in Parkinson's disease (PD), with reported prevalence rates that range from 14 to 60% [2,3]. In cross-sectional studies, apathy has been associated with a variety of undesirable consequences in patients, such as poor cognitive performance and dementia [4,5]. While these findings support the association between apathy and global cognition, little is known about the role of apathy as a risk marker or predictor of future Parkinson's disease dementia (PDD).

There are several established risk factors for PDD, including older age, greater motor severity and hallucinations [6]. Unfortunately, few longitudinal studies of apathy in PD currently exist. Dujardin and colleagues studied 20 apathetic and 20 non-apathetic PD patients over 18 months and found that apathetic patients had significantly greater cognitive decline as measured by multiple neuropsychiatric batteries compared with non-apathetic patients [7]. We sought to study if apathy as measured by a single caregiver-reported item predicted conversion to clinically diagnosed dementia in a longitudinal cohort study.

2. Methods

2.1. Ethics

This study was approved by the University of Pennsylvania Institutional Review Board and written informed consent was obtained from all participants.

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2.2. Participants

Participants were patients enrolled in the University of Pennsylvania Morris K. Udall Center for Excellence in Parkinson's Disease Research cohort. Udall cohort participants were included in this study if they had a diagnosis of idiopathic PD based on UK Brain Bank criteria, a caregiver or study partner, at least one post-baseline study visit, and did not have baseline dementia. Participants were evaluated by a trained research assistant annually for the first four years and biannually thereafter. At each evaluation patients were administered questionnaires, and underwent a cognitive and motor examination.

2.3. Measures

All patients received both global and domain specific cognitive tests. Global cognitive tests included the Dementia Rating Scale-2 (DRS-2) for all participants and the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) for subsets. Functional ability was assessed using the Schwab and England scale and the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory. In addition, we administered the 15-item Geriatric Depression Scale (GDS-15) and the Unified Parkinson's Disease Rating Scale (UPDRS). Dopaminergic medication was included in the analysis as a levodopa equivalency daily dose (LED).

2.4. Assessment of apathy

Apathetic symptoms were assessed by the caregiver or study partner using the apathy item of the Neuropsychiatry Inventory-Questionnaire (NPI-Q). The apathy item asks, "Does the patient seem less interested in his/her usual activities or in the activities and plans of others?" If the response is yes, the caregiver is then asked to quantify how severe this symptoms is (1 = mild; 2 = moderate; 3 = severe). A composite score is calculated as presence of apathy X severity (range 0–3). We defined apathy based on any presence of apathy (composite score $\geq$ 1). While the standard cutoff for the NPI-Q is $\geq$ 2, we chose a cutoff of 1 to capture all apathetic symptoms.

2.5. Dementia diagnosis

Dementia was diagnosed by experts (either movement disorder specialists or a psychiatrist with specialist knowledge of PD). At each visit two physicians evaluated patient data and classified each participant as normal cognition, mild cognitive impairment (MCI) or dementia based upon cognitive and functional testing according to the MDS task force recommendations for classification of MCI and dementia in PD. Inter-rater agreement between physician teams was outstanding (Kappa = 0.80, 95% CI 0.70–0.90).

2.6. Analysis

Baseline clinical characteristics were examined using summary statistics. Means were used to describe normally distributed items and medians were used for items with skewed distributions. We categorized subjects as apathetic or non-apathetic using an NPI-Q cutoff of 1. T-tests (normal data) and Wilcoxon rank sum tests (skewed data) were used to examine baseline clinical, cognitive and behavioral associations between apathetic and non-apathetic subjects. Time to dementia was calculated using Kaplan–Meier survival estimates. Log rank tests were used to examine associations between clinical, demographic, cognitive, and behavioral measures and time to dementia. All reported p-values are two-sided, and we used a standard cut-off of 0.05 for significance.

We used Cox proportional hazard models to determine whether baseline apathy was associated with time to dementia when controlling for demographic and clinical characteristics that were hypothesized to be associated with apathy and/or dementia.

We ran four models to ascertain separately the effects of baseline cognitive impairment as measured by a clinical diagnosis of MCI, the two brief cognitive screening measures, and the DRS-2 on the relationship between apathy and development of dementia. All models included covariates that were either an established risk factor for PDD (e.g. hallucinations) or had a p-value < 0.15 in bivariate analysis comparing the covariate and dementia. Model 1 did not adjust for baseline cognitive differences between patients. Model 2 repeated the analysis including overall baseline DRS-2 score. In model 3 we measured cognition using clinical screening measures (either the MoCA or MMSE). Model 4 excluded participants given a consensus diagnosis of "MCI" at baseline and controlled for overall DRS-2 score. We could not control for hallucinations in this model since no one with hallucinations developed dementia.

3. Results

3.1. Baseline sample characteristics

Of 314 Udall participants 232 met the study criteria. Due to missing data an additional 100 people were excluded, leaving 132 participants in our final sample. Excluded participants did not differ significantly in terms of major clinical or demographic factors.

Participants in the final sample were an average of 69.4 (SD 7.8) years old, had a median Hoehn and Yahr stage of 2.0 (IQR 2.0-2.5), and a median disease duration of 7 years (IQR 4-11). 68.9% (N = 91) of participants were male. The median LED of the sample was 600.0 mg (IQR 375.0-930.3).

At baseline, 12.1% (N = 16) had an NPI score $\geq$ 1 and of those, only 3.1% (N = 4) had an NPI score $\geq$ 2. For subsequent analyses, we categorized all subjects with an NPI score $\geq$1 in the apathetic group. Patients who were apathetic had significantly worse cognition at baseline by DRS (median DRS-2 131.0 vs. 139.0; p < 0.01) than those who were non-apathetic. They did not differ in other major clinical characteristics.

3.2. Survival analysis

The cohort was followed for an average of 3.13 years (range 0.84–6.02). Average follow up time was 2.06 years (range 0.84–4.26) for those with baseline apathy and 3.28 years (range 0.90–6.02) for those without baseline apathy. A total of 19.7% participants became demented over the course of the study. 50.0% (N = 8/16) of the apathetic patients and 15.5% (N = 18/116) of the non-apathetic patients developed dementia during follow-up. Average time to dementia was 1.7 years for individuals with baseline apathy and 3.0 years for non-apathetic individuals. Patients with baseline apathy developed dementia at a faster rate than those without apathy (HR = 7.23, 95% CI = 3.03–17.25; p < 0.01) (Fig. 1).

Participants who developed dementia were also significantly older (mean age 73.3 vs. 68.5; p < 0.01), had significantly higher LED (median dosage in milligrams 820 vs. 600; p = 0.004), and had significantly worse motor, (mean UPDRS III 28.2 vs. 18.5; p < 0.01), cognitive (median DRS-2 131.0 vs. 139.0; p < 0.01) and depression (median GDS 3.5 vs 1.0; p < 0.01) scores at baseline than those who did not become demented.

Next, we performed Cox proportional hazards model including age, education, gender, disease duration, apathy, UPDRS-III motor score, GDS score, hallucinations, LED, and antidepressant use as covariates to determine the independent effect of apathy on dementia rates. Presence of apathy, worse motor scores, higher LED,

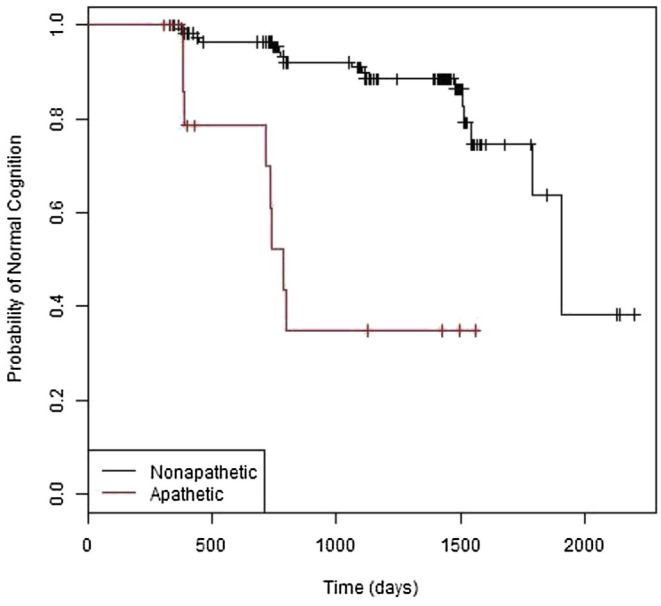

Fig. 1. Kaplan Meier curves showing time to dementia between apathetic and non-apathetic patients.