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Clinical Correlates of Depressive Symptoms in Familial Parkinson's Disease

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Abstract

Depression is one of the most common nonmotor complications of Parkinson's disease (PD) and has a major impact on quality of life. Although several clinical factors have been associated with depression in PD, the relationship between depression and stage of illness as well as between depression and degree of disability remains controversial. We have collected clinical data on 1,378 PD cases from 632 families, using the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II (activities of daily living) & III (motor), the Mini-Mental State Exam, the Geriatric Depression Scale (GDS), and the Blessed Functional Activity Scale (Blessed). Analyses were performed using the 840 individuals with verified PD and without evidence of cognitive decline. Logistic regression was used to identify study variables that individually and collectively best predicted the presence of depressive symptoms (GDS ≥ 10). After correcting for multiple tests, depressive symptoms were significantly associated with Hoehn and Yahr stage and other clinical measures but not with any genetic variant (*parkin*, *LRRK2*, *APOE*). The Blessed score, education, presence of a first degree relative with signs of depression, and UPDRS Part II were found to best predict depressive symptomatology ($R^2 = 0.33$; $P = 4 \times 10^{-48}$). Contrary to several reports, the results from this large study indicate that stage of illness, motor impairment, and functional disability are strongly correlated with depressive symptoms.

Keywords

Parkinson's disease; depression; Hoehn and Yahr stage; association; activities of daily living

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Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting more than 1% of individuals older than 55 years of age and more than 3% of those older than 75 years of age.¹ In 1817, James Parkinson noted depression as a comorbidity of PD,² and depression has since been reported to occur in 25 to 50% of individuals with PD.^{3–5}

Many of the risk factors for depression identified in studies of the general population have also been reported to be risk factors for depression in individuals with PD. These factors include female gender, family history of depression, and comorbid somatic disease.^{6,7} A strong correlation between depression and dementia has been reported not only in the general population but also in PD patients^{4,8–10}; however, other risk factors for depression that are specific to individuals with PD have not been consistently replicated. For example, some reports have found depression to be more common among those with early onset as compared with late onset of disease^{11–13}; however, this association has not been found in other studies.^{14–16} Some studies have found correlations between depression and stage of illness, motor impairment, and/or disability,^{4,13,15,17} whereas others either have not replicated these associations^{18,19} or have only found a correlation with scales of activities of daily living (ADL).¹⁶ Depression has also been associated with bradykinesia/rigidity-predominant PD when compared with tremor-predominant PD.^{20,21}

Both environmental and genetic factors are believed to predispose individuals to PD and much about the etiology of PD remains to be learned; however, over the last 10 years, mutations in five genes have been shown to cause parkinsonism. Mutations in *PRKN* and *LRRK2* appear to be the most common. It is not yet known if depression is more common in subsets of PD patients with particular genetic mutations.

The primary purpose of this study was to determine in this large sample of well characterized PD patients the clinical correlates of depressive symptoms. In addition, given the availability of molecular testing results in this sample, we have also examined whether depressive symptoms are more common in PD patients with either mutations in *PRKN* or *LRRK2* or patients with the *APOE4* allele.

PATIENTS AND METHODS

Subject Recruitment and Assessment

As part of an ongoing effort to identify susceptibility genes for PD, we have recruited families ascertained through a pair of siblings, both of whom were reported to have PD. Any additional affected and available individuals in a family were also recruited. At the time of these analyses, 1,378 individuals with PD from 632 multiplex PD families have been recruited. All available affected individuals were seen by a movement disorder specialist at one of 59 Parkinson Study Group sites located throughout North America. Each participant completed a uniform clinical assessment that included the Unified Parkinson's Disease Rating Scale (UPDRS)²² Parts II (ADL) & III (Motor Exam), Schwab and England score, Hoehn and Yahr stage, the Mini-Mental State Examination (MMSE),²³ the Geriatric Depression Scale (GDS),²⁴ and the Blessed Functional Activity Scale (Blessed).²⁵ In addition, a diagnostic checklist with inclusion criteria consisting of clinical features highly associated with autopsy-confirmed PD and exclusion criteria highly associated with non-PD pathological diagnoses was used to classify individuals as having either verified PD (*n* = 929) or nonverified PD (*n* = 450).²⁶ Appropriate written informed consent approved by each individual institution's institutional review board was completed by all participants.

Because depression may be a risk factor for dementia²⁷ and because self report of depressive symptomatology could be less accurate in cognitively impaired individuals, we excluded those subjects with an MMSE score below an education-specific cutoff (lower limits of normal: 21

for middle school, 23 for high school, and 24 for college/graduate school attainment).^{28,29} Because of the potential amelioration of depressive symptoms due to pharmacological treatment, all participants who reported that they were taking medication specifically for depression were removed from the initial analyses (mean GDS score: 12.3, range: 4–29). The primary analytic sample included 840 nondemented subjects who met criteria for verified PD and were not known to be treated for depression. Since this is a family-based sample, secondary analyses were limited to only the first nondemented, verified PD subject in each of the 541 families that contained at least one such individual to minimize bias toward genetic association.

Molecular Analysis

All subjects in this study were screened for the G2019S mutation in the *LRRK2* gene.³⁰ Of the 840 nondemented individuals with verified PD, 34 were found to be carriers of a G2019S mutation. Six additional mutations in *LRRK2* have been found, with each observed in only a single family.^{31,32} In addition, the 313 nondemented participants with verified PD whose symptoms began before age 50 years or whose family had a positive LOD score in the region on chromosome six where the *PRKN* gene is located were screened for mutations in *PRKN* using both sequencing and gene dosage analysis.^{33,34} Of these 313 individuals, 25 were found to have a single *PRKN* mutation and 41 were found to have two *PRKN* mutations. *APOE* was assayed regardless of age of onset or any other factor.²⁹ Of the 475 individuals assayed, 99 carried an E4 allele (21%).

Measures and Statistical Analyses

In addition to the UPDRS Part II score and the UPDRS Part III score, two additional clinical measures were computed from the items of the UPDRS. The tremor subscore was calculated as the sum of the base-line tremor score (from UPDRS Part II, maximum 4 points) and the sum of the rest and action tremor scores (from UPDRS Part III, maximum 28 points).²¹ The postural instability gait disturbance (PIGD) subscore was computed as the sum of the UPDRS Part II falling, freezing, and walking scores and UPDRS Part III gait and postural stability scores (all with a maximum of 4 points each). The ratio of the tremor subscore and PIGD subscore was used to classify individuals as either tremor-dominant (ratio ≥ 1.5 ; $n = 335$) or PIGD-dominant (ratio ≤ 1.0 ; $n = 430$).^{20,21} The individuals in the intermediate range ($n = 71$) did not fall into either classification.

The Geriatric Depression Scale (GDS), a 30-item self-reported index of depressive symptomatology, was obtained from all study participants. The GDS has been validated with the Structured Clinical Interview for DSM-IV³⁵ as a measure of depression in individuals with PD.^{36–38} Although there is not complete agreement regarding the optimal thresholds to utilize for classification of depressive symptoms, the consensus from these studies indicates that a cutoff of 9/10 provides excellent sensitivity and specificity. We have therefore partitioned out data into two categories: little to no depression symptomatology ($0 \leq \text{GDS} \leq 9$) and mild to marked depression symptomatology ($10 \leq \text{GDS} \leq 30$). A family history of depression was not collected as part of this study. However, as all affected individuals had at least one other family member present in the study (with a full examination), a proxy could be defined by the presence of a first degree relative with a GDS score greater than or equal to 10.

The primary hypothesis of this study was that depressive symptoms in PD patients are associated with disability and stage of illness. To test this hypothesis we used the Hoehn and Yahr staging system as well as several secondary measures including: (1) the motor subscore of the UPDRS (0–108 with 0 being completely normal), (2) cognitive performance, as determined by the MMSE (0–30 with 30 being best performance), and (3) ADL as assessed by the UPDRS Part II (0–52 with 0 being completely normal), the Blessed (0–29 with 0 being

completely normal), and the Schwab and England score (0–100 with 100 being completely independent).

Analyses were also performed to assess whether there was a difference in frequency of depressive symptoms in those subjects with a mutation in either *LRRK2* or *PRKN*. Similarly, analyses were designed to test whether the *APOE4* allele was significantly associated with depressive symptoms.

The relationship between study measures and the two tiers of depression was analyzed using logistic regression. In addition, stepwise logistic regression was performed to identify study variables that collectively best predicted depression classification. All statistical analyses were performed using the SAS/STAT 9.1 software package. A Bonferroni correction was applied to reduce Type I error (19 tests required an alpha of 0.0026).

We then repeated the analysis including those subjects who had been removed from the primary analysis because they were undergoing pharmacological treatment explicitly for depression. As treatment could affect GDS score, these subjects being treated for depression were coded as having depressive symptomatology. Analyses were then performed to test for an association between depressive symptomatology and the clinical measures listed earlier.

RESULTS

The mean age at exam for the 840 affected individuals used in this sample was 68.8 ± 9.6 years (range: 36–91). The mean age of onset was 60.1 ± 12.1 years (range: 21–84; median: 62; interquartile range: 15), making the mean duration of PD 8.7 ± 7.6 years (range: 0–50). The sample was 95% Caucasian and 3% Hispanic, with 2% self reporting another ethnicity. The average number of years of education was 13.8 ± 4.0 , and 60% of the cases were male. Estimates of this demographic information remained robust when computed using only one individual from each family.

After correcting for multiple comparisons, depressive symptomatology was significantly associated ($P < 0.001$) with many clinical measures of disability (Table 1), including Hoehn and Yahr stage (see Fig. 1), MMSE and UPDRS Part III (motor) score. The PIGD subscore derived from the UPDRS was highly associated with depressive symptomatology, whereas the tremor subscore was not. The Blessed score and the UPDRS Part II (ADL) score were the two factors most significantly associated with depression classification, followed closely by the PIGD subscore. Given the evidence in the literature supporting an association of depression with either early or late onset PD, we dichotomized the sample with those who had an onset at or before age 60¹³ considered earlier onset and the remainder grouped as later onset. After correcting for multiple comparisons, neither early onset of PD nor late onset of PD was significantly associated with depressive classification ($P = 0.03$).

Of those factors previously reported to be associated with depressive symptoms in the general population, only lower education and family history of depression were significantly associated with depressive symptoms in this PD population; two other factors associated in the general population, age and gender, were not significant predictors of depression classification in this sample (Table 1). Analyzing only the proband from each family yielded similar results as compared with analyses employing the full sample of all individuals with verified PD. The same factors (Blessed, education, presence of greater depressive symptomatology in first degree relatives, Hoehn and Yahr, Schwab and England examiner's score, UPDRS Parts II&III, MMSE) remained significant ($P < 0.002$). There was no association between depressive symptoms and the presence of an *APOE4* allele or a mutation in either *LRRK2* or *PRKN* (Table 2). When those individuals undergoing pharmacological treatment for depression were included in the analyses and coded as having depressive symptomatology, all tests of

association between depression classification and the genetic variants became even less significant. All significant associations with clinical measures of disability, however, remained significant after Bonferroni correction ($\alpha = 0.0026$).

Stepwise regression analysis was employed to identify which of those variables significant in univariate analyses best predicted depression classification (Table 3). The final model included Blessed score, education, UPDRS Part II, presence of greater depressive symptomatology in first degree relatives (at least one first degree relative examined within the study that had a GDS ≥ 10), and MMSE ($R^2 = 0.33$; $P = 4 \times 10^{-48}$). When only the probands were analyzed, the same factors entered the model in the same order ($R^2 = 0.33$; $P = 2 \times 10^{-30}$).

DISCUSSION

This large study of familial PD was used to rigorously test which clinical measures are associated with the presence of depressive symptoms comorbid with PD. Contrary to several smaller studies,^{16,18,19} our results demonstrate a strong positive association between depressive symptoms and stage of illness, motor impairment, and disability.

The UPDRS motor score, and particularly the PIGD subscore, were strongly associated with depressive symptoms as measured by the GDS. It has been suggested that there are two forms of PD: one dominated by tremor and characterized by slow progression and another more dominated by PIGD symptoms that progresses more rapidly and is associated with cognitive decline and a more severe phenotype.^{20,21} However, given the evidence that tremor symptoms do not necessarily worsen with time and tend to progress independently of the more correlated cardinal signs of bradykinesia, rigidity, gait, and balance,³⁹ the PIGD subscore acts as quantitative proxy for disease stage. With the ratio of tremor subscore to PIGD subscore being used to classify individuals as tremor-predominant and PIGD-predominant, it is not surprising that the PIGD subtype has previously been shown to have more severe symptoms of cognitive decline and rapid disease progression.

Significant associations between depression classification and Hoehn and Yahr stage, cognitive impairment based on MMSE, and two measures assessing the ADL (Blessed and UPDRS Part II), all indicate that depressive symptoms are associated with a more severe phenotype. Individuals showing early signs of dementia were removed from the sample to ensure that their cognitive decline did not confound other measures of disability. Therefore, it is notable that MMSE score remains significantly associated with depressive symptoms even within this narrowed range.

We found no evidence that mutations in *PRKN* and *LRRK2* are associated with depressive symptomatology; however, our sample of mutation positive individuals was limited. Similarly, we found no significant evidence that inheriting an *APOE4* allele affected the risk of depressive symptoms, an association which has been suggested in some studies of Alzheimer disease, 40 but not others.⁴¹ This is not surprising as those showing signs of cognitive decline were removed from analyses. As individuals in this study were screened for depression at different stages of disease, it is possible that these genetic studies could be confounded by these different stages. However, even when analyses were limited to the largest subgroup (Hoehn and Yahr = 2.0; $n = 356$), the genetic associations remained nonsignificant.

A limitation of this study is its cross-sectional nature, a limitation it shares with most other studies seeking factors contributing to the risk of depression in PD. A longitudinal study would be better able to test the importance of the rate of decline and the importance of “on”/“off” fluctuations on depressive symptoms. Another limitation of this study was the absence of a detailed personal and family history of depression; however, the proxy used in this study, depressive symptoms in a first degree relative, was significantly associated with depression

classification. Finally, although the sample was recruited requiring a sibling pair with PD, a number of families have a more extensive family history of PD. Therefore, while possible, we believe it is unlikely that the results of this study would be limited to familial PD defined as siblings with PD; rather, we believe the results of this study also inform us regarding the relationship between depressive symptomatology and stage of illness, motor impairment, functional disability, and cognition in patients with a family history of PD that extends beyond a sibling with disease.

The GDS was used to measure depressive symptoms instead of the Structured Clinical Interview for DSM-IV-TR (SCID). Four studies have now validated the GDS against the SCID.^{36–38,42} Each study found the GDS to have high sensitivity and specificity; however, each also found a different optimal cutoff value to maximize these measures. One of these studies found the GDS to have the highest sum of sensitivity and specificity when compared with the 17-item Hamilton Depression Rating Scale, the Beck Depression Inventory-I, the Center for Epidemiologic Studies of Depression Rating Scale Revised, and the Patient Health Questionnaire-9.⁴² The use of any dimensional scale to categorize individuals, however, is likely to lead to more heterogeneity than would a pure categorical diagnosis. Categorical diagnoses, by definition, provide some uniformity among subgroups, as they all meet some minimum criteria.

Although the genetic variants we have genotyped so far do not appear to influence the development of depressive symptoms, it is possible that future studies might identify genetic variants that can help us more clearly understand why some individuals develop depression concomitant with PD whereas others do not. Regardless of the cause, depression has a major impact on quality of life, and the diagnosis, treatment, and continual monitoring of depression should be standard of care for individuals with PD.

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APPENDIX

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FIG. 1.
Relationship between depressive symptomatology and Hoehn and Yahr stage.

TABLE 1

Results of univariate analyses to identify significant predictors of depression symptomatology

	No depression symptomatology [*]	Depression symptomatology [*]	P-value
N	525	315	
Age at exam	68.8	68.8	0.91
Age at onset	60.6	59.2	0.10
Disease duration (yr)	8.2	9.5	0.02
Onset <60 yr	43.2%	51.0%	0.03
Male	60.0%	60.6%	0.86
Parent with PD	31.4%	28.2%	0.34
1° relative with GDS ≥ 10	36.0%	51.8%	8 × 10⁻⁶
Previous smoker	41.9%	44.0%	0.56
Education (yr)	14.2	13.1	8 × 10⁻⁵
MMSE score	28.1	27.6	0.002
Hoehn and Yahr stage	2.3	2.6	1 × 10⁻⁷
Blessed Functionality score	2.2	5.1	1 × 10⁻³⁰
Schwab and England (Examiner)	85.0	76.6	5 × 10⁻¹⁴
UPDRS Part II (ADL) score	10.5	15.2	2 × 10⁻²⁰
UPDRS Part III (Motor) score	24.2	28.9	1 × 10⁻⁷
Tremor score	4.1	4.4	0.25
PIGD score	3.5	5.4	1 × 10⁻¹³
Tremor dominant	45.0%	31.6%	0.0002
PIGD dominant	47.1%	59.4%	0.0005

Items set in bold exceed a Bonferroni correction of alpha = 0.0026.

* Depression classification is based on GDS score: few to no depressive symptoms ($0 \leq \text{GDS} \leq 9$), mild to marked depressive symptoms ($10 \leq \text{GDS} \leq 30$).

TABLE 2

Comparison of raw GDS score among independent (one per family) carriers and noncarriers of genetic variants related to PD

Genetic variant*	Percentage of carriers with depressive symptomatology (%)	Percentage of noncarriers with depressive symptomatology (%)	P-value
<i>LRRK2</i> G2019S mutation	4.4	4.2	0.90
Any <i>LRRK2</i> mutation	5.7	4.7	0.65
Homozygous <i>PRKN</i> mutation	9.3	10.2	0.82
Heterozygous <i>PRKN</i>	6.6	9.8	0.37
<i>APOE4</i> polymorphism	20.0	26.5	0.18

* Tests for association with genetic data were performed using only one individual per family (n = 537).

TABLE 3

Results of stepwise logistic regression for depression classification

	Odds ratio (95% CI)	P-value
Blessed Functionality score	1.38 (1.28, 1.48)	1×10^{-19}
UPDRS Part II (ADL) score	1.06 (1.03, 1.09)	3×10^{-5}
First degree relative with GDS ≥ 10	1.84 (1.32, 2.55)	0.0003
Education (yr)	0.93 (0.89, 0.97)	0.001
MMSE score	1.10 (1.01, 1.20)	0.03