Depression and Disability in Parkinson's Disease

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The relationship between depression and disability in idiopathic Parkinson's disease (PD) was examined in 31 outpatients. Thirteen percent had current major depression (MD), 10% dysthymia, and 32% a lifetime history of MD. Depression was significantly related to both illness severity and functional impairment. Male patients with early-onset PD (before age 55) had more mood and anxiety disorders than late-onset male patients. Patients with right-sided PD had significantly more depressive symptoms than those with left-sided PD. On multiple regression analyses, depression predicted impaired social, role, and physical functioning for men (but not for women), independent of the impact of illness severity. The results suggest that treatment of depression may improve function; however, findings of gender differences will require replication.

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Depression is common in patients with Parkinson's disease (PD), with reported prevalence rates ranging from 4% to 70%.[1–5] It is not clear whether depression represents a psychological reaction to severe physical illness or occurs as a direct physiological dimension of PD. Several investigators report that the prevalence of depression in patients with PD is not different from rates in patients with chronic medical illnesses.[3,4,6] Others maintain that the depression is a biological aspect of PD and thus is more common than in non-CNS illnesses. These investigators also report that severity of depression is not highly correlated with severity of motor impairment in PD.[1,7]

The purpose of this study was to determine the prevalence of mood and anxiety disorders in patients with PD and the extent to which depressive symptoms are associated with illness severity and impairment of function. Multiple regression techniques were used to test two hypotheses. The first hypothesis asserts that depression contributes to impairment in function independently of the impact of illness severity. The second hypothesis asserts that the severity of PD, when considered apart from the effect on impairment in function, does not explain the severity of depression.

Previous investigators have reported that depressive symptoms are more prevalent and more severe in patients with early-onset and right-sided (left brain) PD.[8]

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This study examined these issues, as well as gender, to determine the extent to which these previously reported relationships exist in patients at Emory University Medical Center.

METHODS

Subjects

Thirty-one patients, 14 female and 17 male, participated in the study. Each had a diagnosis of idiopathic PD and was an outpatient visiting one of two board-certified neurologists (J.J. and R.W.) at the Emory University Movement Disorders Clinic (EUMDC). Patients with dementia were excluded.

The mean age of the subjects at the time of the interview was 65 years, ranging from 28 to 83. The mean age of onset of PD was 57 years, ranging from 24 to 79. The mean number of years since the onset of PD was 7.7 years, ranging from 1 to 33 years.

Procedures

The patients in this study represent a sample of PD patients scheduled for regular follow-up visits at the EUMDC with either J.J. or R.W. Patients waiting to see their neurologists on a day of evaluation were asked if they would be interviewed by a research assistant (J.K.) after seeing their doctors. There were no refusals.

Measures

Several measures were used to determine the presence and severity of depression in patients with PD. A modification of the Structured Clinical Interview for DSM-III-R[9] (SCID) was used to diagnose the current and lifetime prevalence of mood and anxiety disorders. This instrument, however, excludes symptoms "due to a physical condition" and becomes problematic for patients with many physical illnesses because clinicians may not be able to make this distinction reliably.[10,11] For example, it may not be possible to decide in a reliable and valid way whether to attribute the etiology of psychomotor retardation to the physical illness (PD) or consider it a symptom of depression.[12,13] Therefore, in this study we used an inclusive approach, in which all symptoms reported by patients were assessed whether or not the symptoms may have been secondary to a physical disorder.[11] Interestingly, this has now become the diagnostic approach to this problem under DSM-IV guidelines.[14] DSM-IV further indicates that a mood disorder should be considered "secondary to a general medical condition" if it is judged to be the direct physiological consequence of the general medical disorder. For the purposes of this study, however, conditions otherwise meeting criteria for major depression (MD) were not excluded even if they might be better considered secondary mood disorders.

The Hamilton Rating Scale for Depression[15] (Ham-D) and the Geriatric Depression Scale[16] (GDS) were used to determine the severity of depressive symptoms. Although a trained research assistant (J.K.) administered all psychiatric measures in the study, individual ratings and diagnoses were decided for each patient in diagnostic conference with the senior author (S.A.C.).

Several measures were used to assess function, disability, activities of daily living (ADL), and severity of illness: 1) the 20-item Medical Outcome Study–Short Form[17] (MOS), with its functional subscales for physical (MOS-PF), role (MOS-RF), and social function (MOS-SF), was self-administered by patients; 2) the Schwab and England Activities of Daily Living Scale[18] (SE), which measured physical disability due to impaired ADL specific for patients with PD, was completed by the study neurologists; and 3) the Hoehn and Yahr Staging Scale[19] (HY) was used by the neurologists to assess the stage and severity of the PD.

RESULTS

Prevalence of Psychiatric Disorders in PD

Current psychiatric diagnoses included DSM-III-R mood disorders in 29.1% of our patients (12.9% MD, 9.7% dysthymia, and 6.5% hypomania). An additional 6.5% had generalized anxiety disorder. None of the patients in our sample met criteria for bipolar disorder or for current panic disorder or phobias. Lifetime rates were 32.3% for MD experienced at some point in life, 6.5% for a simple phobia in the past, 3.2% for past panic disorder, and 3.2% for previous obsessive-compulsive disorder.

Tables 1 and 2 list specific MD symptoms reported on the SCID by patients who met criteria for current or lifetime MD. Table 1 indicates that 3 of the 4 patients met criteria for current MD even after excluding symptoms likely to be caused by the PD (psychomotor retardation and fatigue).[13] Excluding these PD-related symptoms would change the rate of current MD from 12.9% to 9.7%. Table 2 indicates that 4 of the 7 patients meeting inclusive criteria for lifetime MD would not meet diagnostic criteria if psychomotor retardation and fatigue were excluded. Using this diagnostic approach would change the overall prevalence rate of lifetime MD from 32.3% to 19.3%.

TABLE 1. Symptom pattern of 4 patients meeting inclusive criteria for current major depression

Symptom	Patient #1	#2	#3	#4
Depressed mood	X	X	X	X
Anhedonia	X	X	X	X
Psychomotor retardation			X	X
Fatigue	X	X	X	X
Sleep disorder			X	X
Appetite disturbance			X	
Low self-esteem or guilt	X	X	X	X
Trouble concentrating		X	X	X
Hopelessness/suicidal ideation	X	X	X	
Total symptoms	5	6	9	7

Note: A total of 5 symptoms is required for the diagnosis of major depression. One of the 5 must be depressed mood or anhedonia. Note that Patient #1 would not be diagnosed with major depression if fatigue were not counted toward the diagnosis. Patients #2, #3, and #4 would remain diagnosed even after psychomotor retardation and fatigue were excluded.

TABLE 2. Symptom pattern of 7 patients meeting inclusive criteria for lifetime major depression

Symptom	Patient #5	#6	#7	#8	#9	#10	#11
Depressed mood	X	X	X	X		X	X
Anhedonia	X	X	X	X	X	X	X
Psychomotor retardation		X	X	X	X	X	X
Fatigue	X	X		X	X	X	X
Sleep disorder	X	X		X	X		X
Appetite disturbance	X			X	X	X	X
Low self-esteem or guilt	X				X	X	
Trouble concentrating			X			X	X
Hopelessness/suicidal ideation			X				
Total symptoms	6	5	5	6	6	7	7

Note: Patients #6, #7, #8, and #9 would no longer be diagnosed with major depression if symptoms of psychomotor retardation and fatigue were not counted toward the diagnosis of major depression.

Depressive Symptoms: Association With Age at Onset, Gender, and Laterality

The men in our sample were significantly younger (mean = 59.2 vs. 71.6; $t = -2.86$, df = 28, $P = 0.009$) and had an earlier age of onset (mean = 51.5 vs. 64.2, $t = -2.65$, df = 28, $P = 0.02$) than the women. However, there were no differences between genders in depression, disability, illness duration, or illness severity.

Calculation of the relationship between psychiatric diagnosis and early onset (before age 55) versus late onset revealed that men (but not women) with early-onset PD were more likely to have mood disorders ($\chi^2 = 4.29$, df = 1, $P = 0.04$) or anxiety disorders ($\chi^2 = 4.29$, df = 1, $P = 0.04$) than men with late-onset disease (55 or older). Seventy-one percent of early-onset men (5 of 7) had diagnoses of MD, dysthymia, or anxiety disorder, compared with only 2 of 8 male patients (25%) with late-onset PD ($\chi^2 = 3.23$, df = 1, $P = 0.08$). These relationships between age at onset and depression did not hold true for women.

Consideration of symptom laterality revealed a pattern suggesting that patients with right-sided PD (left brain) were likely to suffer from more significant depressive symptoms. This was true for symptoms indicated on Ham-D ($r = 0.40$, $P < 0.05$), but not GDS.

Depression, Functional Impairment, Impaired ADL, and Illness Severity

Depression was associated with functional impairment, impaired ADL, and illness severity. Functional impairment, as assessed by the physical, role, and social functioning subscales of the MOS, was negatively correlated with Ham-D ($r = -0.46$, $P < 0.01$; $r = -0.39$, $P < 0.05$; and $r = -0.56$, $P < 0.01$, respectively). Similar significant relationships were found among all of these functional scales and GDS (all $P < 0.05$).

Impaired ADL (as measured on SE) was negatively correlated with both depression scales (Ham-D: $r = -0.44$, $P < 0.01$; GDS: $r = -0.40$, $P < 0.05$).

Illness severity (HY) was associated with depression as assessed by the Ham-D (Spearman rank-order correlation, $r = 0.36$, $P < 0.03$), but not the GDS. Severity of disease (HY) was strongly associated with physical disability (SE: $r = 0.81$, $P < 0.0005$) and all measures of functional impairment (MOS-PF: $r = -0.65$, $P < 0.0005$; MOS-RF: $r = -0.66$, $P < 0.0005$; MOS-SF: $r = -0.49$, $P < 0.005$; Spearman rank-order correlations).

Regression Analyses

Hypothesis One: Depression contributes to impairment in function independently of the impact of the severity of underlying disease. Although the results described above indicated that illness severity, functional impairment, impaired ADL, and depression were related, the strength and nature of these complex interrelationships were not clear from correlation analyses alone. Therefore, regression analyses, using simultaneous entry of predictors, were employed.

The principal hypothesis underlying this investigation was that depression contributes to disability, over and above the contribution of physical illness to impairment in function. Multiple regression analysis was used to test this hypothesis because it allows examination of the contribution of specific independent variables (depressive symptoms) to a dependent variable (function), holding constant the impact of another independent variable (illness severity). Thus, a series of simultaneous analyses was performed in which various measures of

disability were used as dependent functional variables (social function, MOS-SF; role function, MOS-RF; physical function, MOS-PF; and activities of daily living, SE). The independent variables in these analyses were physical illness severity (HY) and two measures of depression (Ham-D, GDS).

Because the men and women in our sample had significantly different ages at onset, which may have affected other relationships among depression, illness severity, and disability, we performed multiple regression analyses on separate subsamples of men and women.

For women alone, depression, as measured by Ham-D or GDS, did not contribute significantly to functional impairment, as measured by SE, MOS-SF, MOS-RF, and MOS-PF. In the male subsample, however, depression, measured by Ham-D or GDS, was significantly and repeatedly associated with impaired function in three of the four measures. Table 3 lists the beta weights for each independent variable, showing that depressive symptoms (measured by either Ham-D or GDS) explained a significant proportion (17%–53%) of variance in functional outcome for social, role, and physical functioning of the men, even after we controlled for the impact of illness severity. Between 65% and 82% of the total variation in outcome in these three functional variables was explained by the combination of illness severity and depression for the men in our sample. Depression did not contribute independently to neurologists' assessments of impairment in ADL (measured by SE) after accounting for the impact of illness severity.

Hypothesis Two: Illness severity, considered apart from the effect of impairment in function, does not account for the severity of depressive symptoms in PD. Because some observers argue that the physical limitations of PD may constitute "a good reason" for depression, multiple regression techniques were used to determine the effect of physical illness on depressive symptoms after controlling for functional impairment.

Because separate analyses for the men and women yielded similar results, the subsamples were combined. Although illness severity was weakly correlated with depression (as measured by the Ham-D, but not the GDS), this correlation became nonsignificant when measures of functional impairment were added to the regression analyses.

TABLE 3. The relationship of illness severity and depression to impairment in function in male patients with PD (n = 15): results of simultaneous multiple regression, reported as beta weights and percentages of variance explained

Dependent Variable	Disease Severity[a] β Wt.	%	Depression β Wt.	%	Total % of Variance Explained
	Impact of Depression as Measured by Ham-D				
Social function[b]	−0.54*	29	−0.55	30	65
Role function[c]	−0.65**	42	−0.50	25	74
Physical function[d]	−0.67	45	−0.41	17	66
Activities of daily living[e]	−0.78***	61	NS		73
	Impact of Depression as Measured by GDS				
Social function[b]	−0.39*	15	−0.73**	53	74
Role function[c]	−0.54**	29	−0.67**	45	82
Physical function[d]	−0.56*	31	−0.57	32	69
Activities of daily living[e]	−0.66**	44	NS		73

Note: ß wt. = beta weight; Ham-D = Hamilton Rating Scale for Depression; NS = not significant; GDS = Geriatric Depression Scale.
[a]Hoehn and Yahr Staging Scale.
[b]Medical Outcome Study (MOS), social function subscale.
[c]MOS, role subscale.
[d]MOS, physical subscale.
[e]Schwab and England Activities of Daily Living Scale.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

DISCUSSION

Two hypotheses were developed and tested in this study to evaluate the relationships among illness severity, functional impairment, and depression. The theoretical model underlying this research asserts that depression in PD is *not* best understood as a natural psychological reaction to the physical impairment associated with PD. Rather, depression in this view is primarily a core physiological aspect of PD. A hypothesis was therefore proposed that the severity of physical illness, after associated disability was controlled for, would not account for the severity of depressive symptoms (hypothesis two). A related hypothesis proposed that depression leads to excess functional impairment, over and above the disability caused by the physical disease (hypothesis one).

This study supported both hypotheses. The weak association of illness severity with depression (as measured by Ham-D but not GDS) became nonsignificant after we controlled for functional impairment. In addition, the hypotheses regarding the impact of depression on disability received very strong support for our subsample of men, but not for women. In men, depression (measured by either GDS or Ham-D) was strongly associated with impaired physical, role, and social functioning, even after we controlled for the impact on illness severity.

Although regression analyses cannot prove causality,

these results suggest that, for men at least, depression is strongly associated with excess functional disability in PD. Furthermore, these findings raise the important possibility that treatment of the depression might alleviate some of this excess disability. A study by Borson et al.[20] in a group of patients with chronic obstructive pulmonary disease showed that improvement in depression was associated with improved functioning.

At this point, we cannot offer an explanation for the finding that depression did not seem to affect disability in our subsample of female PD patients, although it may be related to the later onset of their disease. Future research in larger patient samples may clarify this question.

This study replicated several previous findings regarding depression in patients with PD.[1,5,21] Consistent with previous reports[1,4] was our finding that an earlier age at onset of PD in men, but not women, was associated with more anxiety and depressive disorders. The small sample size precludes definitive generalization regarding gender differences but again emphasizes the need for further investigation of the associations among gender, age at onset, and psychiatric problems. As noted in previous work,[1] patients with right-sided PD scored higher on measures of depression. Interestingly, other studies in patients with traumatic brain injury[22,23] and stroke[24] reported similar associations between left brain pathology and depression.

Current mood disorders were common in this population (29.1%) but were somewhat lower than the rate of approximately 40% reported in some recent studies.[1,5,21] Similarly, we found a rate of 6.5% of current anxiety disorders, below the rates of 15% and 38% reported in two previous studies.[25,26] Because these two studies and our own were small and were selected from convenience rather than random samples, these prevalence rates should be considered provisional pending further studies in larger, random samples.

These results must be considered preliminary for several reasons. The university-based sample in this study not only was small, but also may differ from the general population of PD patients in income, occupation, or degree of impairment. Future investigators may wish to use larger samples. Furthermore, the relationship of depression to disability may differ in early stages versus later stages of PD. The Hoehn and Yahr Scale may also be a less desirable measure of severity than the Unified Parkinson's Disease Rating Scale, which could be considered for use in future studies. Finally, the age at onset of depression itself may precede the onset of PD in some patients, and this issue should be examined as well.

From the standpoint of implementation of criteria for the diagnosis of MD, the inclusive approach to diagnosis led to a prevalence of both current (12.9%) and lifetime (32.3%) MD considerably higher than would have been found if physical symptoms common in PD (psychomotor retardation and fatigue) were excluded (9.7% and 19.3%, respectively). In contrast to these findings, several other studies in stroke,[27] chronic fatigue,[28,29] rheumatoid arthritis,[28] and diabetes[30] reported prevalence rates of depression that do *not* differ markedly depending on the diagnostic approach used. However, a study in Alzheimer's patients[31] did report considerable differences in prevalence rates of MD depending on whether patients were diagnosed by using an inclusive approach (14%) as opposed to an approach excluding symptoms common to Alzheimer's patients (4%).[31] Progress in clarifying the diagnosis of depression in patients with physical illness will require studies validating different diagnostic approaches by use of external criteria such as social impairment, disability, biological markers of depression, and, most important, response to treatment.[32] Such data can eventually lead to identification of the most accurate diagnostic approach to depression in patients with general medical illnesses.

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