Clinical Correlates of Apathy in Patients Recently Diagnosed with Parkinson's Disease: The ANIMO Study

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Key Words

Behavior • Parkinson's disease • Apathy • Nonmotor symptoms

Abstract

Objective: Little is known about apathy in the early stages of Parkinson's disease (PD). We determined the clinical correlates of apathy in a large representative sample of patients recently diagnosed with PD (ANIMO study). **Methods:** PD patients, diagnosed within 2 years of inclusion, were recruited in 102 outpatient clinics situated in 82 populations throughout Spain. Apathy was quantified using the Lille Apathy Rating Scale (LARS). Clinical comparisons and correlations were performed using nonparametric tests. Regression analyses were used to test the association of clinical variables with apathy. **Results:** We recruited 557 PD patients (60.3% men) with a mean age of 68.8 ± 9.7 years, and UPDRS motor score of 21.1 ± 10.8 . Apathy only was diagnosed in 186 (33.4%), and apathy and depression in 215 patients (38.6%). Patients with higher comorbidity (OR = 1.10, 95% CI 1.01–1.20, $p = 0.001$), motor impairment (OR = 1.07, 95% CI 1.03–1.10, $p < 0.0001$), and lower education (OR = 2.16, 95% CI 1.21–3.85, $p = 0.009$) had higher odds of having apathy, in contrast to

patients living in a rural environment (OR = 0.35, 95% CI 0.32–0.85, $p = 0.01$), and left predominant PD motor laterality (OR = 0.34, 95% CI 0.13–0.88, $p = 0.01$). LARS scores were significantly correlated with UPDRS motor scores ($r_s = 0.44$, $p < 0.001$), predominantly with axial score ($r_s = 0.43$, $p < 0.001$). **Conclusions:** In PD, apathy is a very common and disabling nonmotor symptom separable from depression. Patients living in a rural environment, with lower comorbidity and motor impairment, higher education background, and left predominant PD motor laterality are at lower risk of suffering from apathy.

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Introduction

Although Parkinson's disease (PD) is primarily a movement disorder, it is accompanied by various non-motor symptoms, including psychiatric and behavioral problems. Cross-sectional studies suggest that nonmotor symptoms, especially apathy, frequently go unrecognized by clinicians and remain untreated [1], with important clinical consequences for patients and their families [2]. This relative lack of attention is not justified, because ap-

athy is reported in 17–70% of PD patients [3], and has been associated with more severe cognitive dysfunction. In the clinical setting, apathy is characterized by lack of initiative and effort to perform everyday activities, lack of intellectual interest and initiative regarding personal or social issues, and indifference or flattening of affect [4]. Several authors have reported that apathy in PD can occur with or without depression, and may be associated with executive deficits, verbal memory impairment, bradyphrenia, and decreased global cognition [5].

Apathy is a topic that has only recently drawn scientific attention. Because little is known about the clinical correlates of apathy in patients recently diagnosed with PD, we conducted a national multicenter cross-sectional survey of apathy, designed to examine the clinical correlates of apathy in this group of patients.

Methods

General Study Design

The study was designed as a cross-sectional survey. There were no treatment interventions during the course of this study. The ANIMO (Spanish word for ‘good spirit’) Group was formed in 2007 by a group of Spanish neurologists with expertise in PD [6]. We sampled a series of patients from 102 Spanish PD outpatient clinics from October 2008 to June 2009. These outpatient clinics were situated in 82 populations throughout Spain, therefore representing a broad geographic sampling. We chose these PD outpatient clinics because they maintain a computer-based registry of PD patients. In these computer-based registries, basic demographic data of the PD patients (e.g. age, gender) and clinical variables were recorded. We asked the participant neurologists to recruit a minimum of 6 consecutive PD patients who were coming to their clinic and who met the following criteria: PD diagnosed according to the United Kingdom Parkinson’s Disease Society Brain Bank criteria [7], within 2 years of inclusion, and age ≥ 30 years. Patients with other types of parkinsonism were excluded, as were those with dementia according to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR) criteria [8]. A diagnosis of dementia was established on the basis of the medical history, an interview with the patient and a family member or caregiver, a general medical examination, results of laboratory tests, and diagnostic neuroimaging when needed. This study was approved by the Ethics Committee of ‘Complejo Asistencial Universitario’ in Burgos, Spain. All patients signed an informed consent before being enrolled.

In Person Evaluation

All assessments in each patient were performed on a single day by movement disorder neurologists. The presence and severity of motor impairment was assessed during the ‘on state’ using the motor subscale of the Unified Parkinson Disease Rating Scale (UPDRSm) [9], and the Hoehn and Yahr stage [10]. The UPDRSm provided the following scores: bradykinesia-rigidity score (sum of the bradykinesia plus rigidity items), tremor score (sum of the

postural and rest tremor items), axial score (sum of the gait, postural stability, facial expression, and speech items), and total score [11]. We also asked the neurologists to supply medical information related to these patients, including age, gender, educational level, marital status, environment (urban vs. rural area), employment status, and medications. Comorbidity was assessed using the Cumulative Illness Rating Scale-Geriatrics (CIRS-G) [12], in which higher scores are associated with greater comorbidity. Individuals received a clinical psychiatric interview [13], with current and past psychiatric diagnoses established according to the DSM-IV-TR using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders. Diagnoses of symptomatic depression included major depressive episode, minor depression, and dysthymia. Depressive disorders in full remission (asymptomatic) were classified as non-depressed.

Apathy was evaluated using the Lille Apathy Rating Scale (LARS) [14]. This physician-administered scale was developed to ascertain and quantify apathy in the month prior to the assessment. LARS has been validated in individuals with PD with and without dementia, and categorizes the severity of apathy into 1 of 4 categories (absent, mild, moderate and severe apathy) [14]. LARS is based on a structured interview and includes 33 items divided into 9 domains, including reduction in everyday productivity; lack of interest; lack of initiative; extinction of novelty seeking and motivation; blunting of emotional responses; lack of concern; poor social life, and extinction of self-awareness [14]. Standard validity indices showed that the LARS is sensitive and capable of distinguishing between apathy and depression [14]. Global LARS scores range from -36 to $+36$, with higher scores indicating greater apathy [14, 15]. Apathy was defined here as a score on the LARS ≥ -22 [14]. Missing LARS data were imputed by individual mean method if the missing data were $\leq 20\%$ of total.

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (version 19.0; IBM SPSS, Statistics). All tests were two-tailed and significance was accepted at the 5% level ($\alpha = 0.05$). None of the continuous variables were normally distributed, thus nonparametric tests (Mann-Whitney U test, Kruskal-Wallis test, Spearman’s rho) were used. Categorical variables were compared using the χ^2 and Cramer’s V tests. As most of the patients on dopaminergic agonists were receiving pramipexole, with fewer on ropinirole and rotigotine, these patients were considered as a single group (dopaminergic agonists). Patients were grouped according to the binary clinical diagnosis of apathy, in apathetic (LARS score ≥ -22), nonapathetic (LARS score < -22), and clinical diagnosis of depression. Based on the presence of apathy and coexisting depression, patients were classified into four clinical groups: apathy only, patients with apathy and depression, depression only and free of apathy or depression (FAD). For multinomial logistic regression analysis, adjusted models were developed in which we considered the four clinical groups as the dependent variable, and all variables that were significantly associated with apathy or depression in univariate analysis ($p < 0.10$) as predictor variables. These analyses generated odds ratio (OR) with 95% CI. A separate stepwise linear regression analysis was also conducted to examine the relationship between clinical and sociodemographic variables and LARS total score as the dependent variable.

Table 1. Clinical and demographic characteristics of cohort (n = 557)

Characteristics	
Mean age $\pm$ SD, years (median)	68.8 $\pm$ 9.7 (70.0)
Male gender	336 (60.3%)
Educational level	
Illiterate	38 (6.8%)
Primary studies	350 (62.8%)
Secondary or higher studies	167 (30.0%)
Unknown	2 (0.4%)
Geographical area	
Rural area	197 (35.3%)
Urban area	360 (64.6%)
Mean PD duration $\pm$ SD, years (median)	1.3 $\pm$ 0.6 (1)
Median Hoehn and Yahr stage (range)	1.5 (1–4)
Mean UPDRSm score $\pm$ SD (median)	21.1 $\pm$ 10.8 (19)
Depression	250 (44.8%)
Major depression	31 (12.4%)
Minor depression	161 (64.4%)
Dysthymia	58 (23.2%)
Mean LARS score $\pm$ SD (median)	-12.4 $\pm$ 14.4 (-16)
Dopaminergic agonists use	357 (64.1%)
Levodopa use	332 (59.6%)
Antidepressants use	235 (42.2%)

Frequency (%) is reported.

Results

Of the 677 PD patients who were deemed eligible for the study, 557 (82.3%) were finally chosen. The remaining 120 (17.7%) PD patients were excluded due to insufficient medical information (e.g. missing values on one or more UPDRS items). We compared the final sample of 557 cases to the 120 cases with insufficient medical information and they were similar in terms of age (68.8 $\pm$ 9.7 vs. 67.7 $\pm$ 9.4 years, Mann-Whitney, $p = 0.14$) and gender (336 [60.3%] vs. 67 [55.8%] men, χ^2 test, $p = 0.41$). Imputation for missing data of the LARS was carried out in 47 subjects (8.4% of the final sample). The 557 PD patients were recruited between March 2007 and January 2009.

Sociodemographic and clinical characteristics of patients are listed in table 1. One hundred and eighty-six patients (33.4%) were diagnosed with apathy only, 215 patients (38.6%) were diagnosed with apathy and depression, 35 patients (6.3%) were diagnosed with depression only, and 121 patients (21.7%) were FAD. Apathy was more frequently diagnosed as severe in patients diagnosed with minor depression compared to patients with major depression (χ^2 test, $p < 0.001$). Clinical and treatment characteristics are reported in table 2.

Table 2. Demographic and clinical characteristics comparison

	Apathy only (n = 186)	Apathy and de- pression (n = 215)	Depression only (n = 35)	No apathy or de- pression (n = 121)	p value
Mean age $\pm$ SD, years (median)	69.9 $\pm$ 9.6 (71.0)	69.8 $\pm$ 8.8 (71.0)	66.6 $\pm$ 9.0 (68.0)	66.0 $\pm$ 10.9 (67.0)	0.004
Male gender (%)	117 (62.9)	129 (60.0)	14 (40.0)	76 (62.8)	0.07
Secondary studies or higher (%)	46 (25.0)	54 (25.1)	19 (54.3)	48 (39.7)	<0.0001
Married or cohabitant (%)	137 (73.7)	144 (67.0)	26 (76.5)	95 (78.5)	0.12
Employee (%)	25 (13.4)	27 (12.6)	6 (17.1)	30 (24.8)	0.02
Urban area (%)	129 (69.4)	136 (63.3)	26 (74.3)	69 (57.0)	0.09
Mean UPDRSm score $\pm$ SD (median)	20.9 $\pm$ 9.8 (19.0)	24.8 $\pm$ 12.0 (24.0)	15.6 $\pm$ 9.1 (14.0)	16.5 $\pm$ 7.7 (15.0)	<0.0001
Mean LARS score $\pm$ SD (median)	-10.0 $\pm$ 8.8 (-12.0)	-3.1 $\pm$ 13.9 (-2.0)	-27.8 $\pm$ 3.4 (-27.0)	-27.8 $\pm$ 3.7 (-27.0)	<0.0001
PD laterality (%)					
Right	87 (46.8)	118 (54.9)	21 (60.0)	64 (52.9)	0.001
Left	77 (41.4)	57 (26.5)	12 (34.3)	50 (41.3)	
Both	22 (11.8)	40 (18.6)	2 (5.7)	7 (5.8)	
Dopaminergic agonists use (%)	119 (64.0)	147 (68.4)	22 (62.9)	69 (57.0)	0.22
Levodopa use (%)	114 (61.3)	141 (65.6)	21 (60.0)	56 (46.3)	0.006
Antidepressants use (%)	77 (41.4)	124 (57.7)	25 (71.4)	9 (7.4)	<0.0001
Mean CIRS-G score $\pm$ SD (median)	4.3 $\pm$ 3.4 (4.0)	5.1 $\pm$ 3.5 (4.0)	3.0 $\pm$ 2.6 (3.0)	3.4 $\pm$ 2.8 (3.0)	0.001

Kruskal-Wallis test and Cramer's V tests were used for comparisons.

In terms of apathy, LARS scores were significantly higher among patients on antidepressants compared to patients not taking antidepressants (-5.63 ± 15.12 vs. -17.35 ± 11.66 , Mann-Whitney test, $p < 0.0001$). As we can see from table 2, compared to other groups, patients diagnosed with apathy only were older, less educated, and with a trend toward having a higher proportion of males. Instead, patients diagnosed with apathy and depression had more severe motor and apathy impairment, higher comorbidity, higher use of levodopa, lower rate of employees, and higher proportion of patients classified as having symmetric PD. In contrast, patients diagnosed with depression only were predominantly women, had a higher education background, lower comorbidity, and higher proportion with predominant right PD. Finally, FAD patients had the lowest proportion of levodopa use, symmetric PD, the highest rate of employees and less severe motor impairment. In the multinomial logistic regression model (table 3), the following variables were included: age, gender, predominant motor PD laterality, education, rural versus urban environment, employment status, levodopa use and UPDRSm and CIRS-G scores, as the independent variables, and apathy and depression status as the dependent variable. Compared to the FAD group, higher scores of the UPDRSm and lower education were associated with higher odds of having apathy only, and apathy with depression. Instead, higher scores of comorbidity were associated with higher odds of having apathy and depression. On the contrary, rural environment and predominant left PD motor impairment were associated with lower odds of having apathy only, and apathy and depression, respectively. Males were associated with lower odds of having depression only.

In the stepwise linear regression, the following variables were included: age, gender, education, marital and employment status, UPDRSm score, predominant motor PD laterality, dopaminergic treatment, CIRS-G score, and clinical diagnosis as the independent variables and the LARS scores as the dependent variable. Forty-four percent of the variance of the LARS scores were explained by the clinical diagnosis of apathy and depression (standardized $\beta = 0.46$, $t = -13.83$, $p < 0.0001$), UPDRSm scores (standardized $\beta = 0.28$, $t = 9.03$, $p < 0.0001$), CIRS-G scores (standardized $\beta = 0.13$, $t = 3.73$, $p < 0.0001$), dopaminergic treatment (standardized $\beta = 0.07$, $t = 2.37$, $p = 0.01$), and marital status (standardized $\beta = 0.09$, $t = 2.83$, $p = 0.005$).

In univariate analysis, there were significant correlations between the LARS scores and UPDRSm scores ($r_s = 0.44$, $p < 0.001$), predominantly with the axial ($r_s = 0.43$, $p < 0.001$) and bradykinesia-rigidity ($r_s = 0.38$, $p < 0.001$) UPDRSm subscales, and moderate with the tremor UPDRS subscale ($r_s = 0.21$, $p < 0.001$). Axial and bradykinesia-rigidity-UPDRSm scores were significantly higher in patients with apathy and depression compared to patients with depression only and FAD (table 4).

Discussion

In this large multicenter nationwide cross-sectional study, we found a similar prevalence of apathy compared to other studies including incident PD and more advanced PD cases [5, 16–18]. The results of this study have several clinical implications. First, prior reports are inconsistent about the prevalence of apathy and frequent overlapping of apathy and depression [19, 20]. In our

Table 3. Odds of clinical and sociodemographic characteristics based on apathy and depression status (dependent variable)

	Apathy only (n = 186)		Apathy and depression (n = 215)		Depression only (n = 35)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
UPDRSm	1.04 (1.01–1.07)	0.005	1.07 (1.03–1.10)	<0.0001	–	
CIRS-G score	–		1.10 (1.01–1.20)	0.001	–	
Lower education	2.16 (1.21–3.85)	0.009	2.10 (1.17–3.76)	0.01	–	
Rural area	0.52 (0.32–0.85)	0.01	–		–	
PD laterality (left)	–		0.34 (0.13–0.88)	0.002	–	
Male gender	–		–		0.32 (0.14–0.73)	0.01

Adjusted for age, employment status, and levodopa use.

The reference category was the group of patients free of apathy and depression.

Table 4. UPDRS motor domains scores and apathy-depression status

	Axial mean $\pm$ SD (median)	Bradykinesia-rigidity mean $\pm$ SD (median)	Tremor mean $\pm$ SD (median)
Apathy only (n = 186)	4.17 $\pm$ 2.70 (4)	13.22 $\pm$ 6.67 (12.50)	3.51 $\pm$ 2.89 (3)
Apathy and depression (n = 215)	5.04 $\pm$ 3.24 (5)	15.60 $\pm$ 7.57 (15)	4.13 $\pm$ 3.54 (3)
Depression only (n = 35)	3.28 $\pm$ 3.07 (3)	10.08 $\pm$ 6.04 (9.00)	2.25 $\pm$ 1.99 (2)
No depression or apathy (n = 121)	2.77 $\pm$ 2.04 (3)	10.72 $\pm$ 5.45 (10)	3.04 $\pm$ 2.44 (3)
Comparison*, p value	<0.0001	<0.0001	0.007
* Kruskal-Wallis test.			

study, in agreement with another study [21], we found that apathy and depression may be separable in PD, and each nonmotor symptom is associated with distinctive clinical features. Interestingly, apathy was more severe when it coexisted with depression and in patients taking antidepressants.

Second, in contrast to depression, apathy was significantly associated with more severe motor symptoms in agreement with other studies [5, 17, 21]. This discrepancy with the literature associating depression and PD [22] is likely explained by the bias of the small size of this particular group in our study. Third, when the UPDRS (nontremor, axial and bradykinesia/rigidity items) was analyzed separately, nontremor dominant symmetric PD was associated with apathy and coexisting depression indicating most likely a more rapid disease progression [23, 24]. However, a practical disadvantage of the cross-sectional approach of our study is the fact that the diagnosis of 'symmetric PD' may change to other forms of parkinsonism during follow-up. Likewise, older patients were more frequently diagnosed with apathy. It has been reported that higher age at onset is the most important factor for predicting greater motor impairment and nonmotor symptoms [25]. Therefore, apathy may be a sign of disease progression in PD [5], but longitudinal studies are needed to investigate exact relationships.

Fourth, interestingly, we observed that patients with left predominant PD motor symptoms (representing right hemisphere pathology) had lower odds of having apathy and depression compared to predominant PD left hemisphere pathology. It is well known that the motor symptoms of PD are mainly due to progressive asymmetric degeneration of nigral dopaminergic neurons [26]. Since this is an observational study, we cannot preclude more conclusions, but it seems that the PD left hemisphere may be dominant in mood and apathy, in contrast

to previous findings, where apathy was a prominent feature of a dysfunction in the right prefrontal pathway [27].

Fifth, gender seems to influence depression in neurologic illness. We observed that depression was more frequent in females, in agreement with other studies [22]. Understanding how gender influences depression in neurologic illness and its response to treatment is a necessary step to improve the specificity of psychiatric treatment for depression [28]. Sixth, of note, we found that patients without apathy and depression remained employees. Likewise, living in a rural environment and higher education background were associated with lower odds of having apathy. The design of this study does not allow us to explain these results, but at least remarks the importance of the association of lifestyle, environment, and education with apathy. On the contrary, higher comorbidity influenced the manifestation of apathy and depression.

This study has several limitations. Although we excluded patients with dementia, we recognize that there is a lack of information regarding the cognitive status, especially mild executive dysfunction in our sample, which may have contributed to our results. Likewise, the design of our study did not enable us to establish the biochemical basis of apathy or depression. Reports in the literature suggest that apathy may be linked to ventral striatum and mesolimbic dopaminergic denervation [29]. As a matter of debate, dopaminergic treatments could potentially have a confounding effect on this aspect of the disease [4]. We found that apathy with or without associated depression was associated with a higher use of levodopa. This association may be likely due to the higher needs of dopaminergic medication in patients with more severe and predominant axial motor symptoms.

There are also certain factors that may confound the interpretation of our results, such as the confounding in-

fluence of depression on the performance of apathy rating scales. Concomitant apathy and depression was detected in 38.6% of our PD sample, and the LARS scores were worse when apathy coexisted with depression. Although we recognize it can be criticized, LARS has shown good discriminant validity between apathy and depression by the original developers of the scale [14]. In fact, in our study, apathy was not directly associated with the severity of depression according to the DSM-IV TR classification [8], and LARS scores were similar between the group of patients diagnosed with depression only, and the FAD group [14], indicating that depression did not significantly impact on LARS scores. Overall, this study involved the analysis of cross-sectional data which precludes conclusions about the direction of causality. In effect, we cannot establish if there was a sample selection bias (patients volunteered to participate in this study), which may have led to an underestimation of the prevalence of apathy in PD. However, we recruited a large representative cross-section of the community-dwelling population of nondemented Spanish patients recently diagnosed with PD patients. In Spain, healthcare is fully state-subsidized, and community-dwelling PD subjects are mostly seen by hospital-based and hospital-associated neurologists [30]. There is no doubt that the use of a cross-sectional design leaves us more susceptible to confounding variables; however, it also enables us to generate hypotheses that should be confirmed in further studies. This study also has several strengths. First, we attempted to adjust for the effects of many potential confounders and classified patients based on their apathy status and coexistence with depression. Second, as a matter of debate as well, we used modern statistical methods to deal with the challenge of missing data of the LARS [31]. People with worse apathy scores tend to be the persons with missing data. Hence excluding them would have provided artificially better mean scores. However, other authors have reported that the imputation of missing data can also result in biased conclusions [32]. Third, we determined the clinical correlates of apathy in a population of patients recently diagnosed with PD patients already on treatment. This avoided bias of treatment status on apathy status. Our results may therefore be extrapolated to the PD community to some degree.

In conclusion, apathy with or without coexisting depression is a common and disabling nonmotor symptom in patients recently diagnosed with PD. Patients with PD and lower education, living in a urban environment and with more severe motor impairment (especially axial signs) and comorbidity, are at risk of having apathy and

depression. Instead, women with PD are at higher risk of having depression. Further studies are required to investigate the efficacy of pharmacological and nonpharmacological treatments of these currently under-recognized aspects of PD.

Disclosure Statement

The authors declare that there are no conflicts of interest and no competing financial interests.

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