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Comorbid conditions associated with Parkinson's disease: A longitudinal and comparative study with Alzheimer disease and control subjects

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ABSTRACT

Background and objective: To study what comorbid conditions were present at baseline and 3 years later in a cohort of Spanish Parkinson's disease (PD) patients, to compare comorbidity with both Alzheimer's disease (AD) and control groups and to analyze the role of comorbidity as predictor of mortality.
Methods: One hundred and forty-seven non-demented PD patients (57.1% males; 70.9 ± 8.6 years old) were included in this 36 months follow-up (2012–2015), monocenter, evaluation study. The International Classification of Diseases, Tenth Revision (ICD-10), Charlson Index (CI), Comorbidity-Polypharmacy Score (CPS) and Elixhauser Comorbidity Measure (ECM) were used to assess comorbidity at baseline and at 3 years. Forty-four AD patients and 44 control subjects were included as comparator groups.
Results: Total number of comorbidities (ICD-10) and polypharmacy at baseline were higher in PD and AD patients than controls (4.4 ± 2.3 vs 5.2 ± 2.4 vs 3.4 ± 1.9 [$p = 0.001$] and 81.6% vs 75% vs 56.8% [$p = 0.003$], respectively). Diseases of the circulatory system (ICD-10/chapter-IX) and endocrine, nutritional and metabolic diseases (ICD-10/chapter-IV) were the most frequent in all groups. There was a significant increase in comorbidity (mean, +1.6 ± 2.8) in all groups ($p < 0.0001$) without differences between them. Seventeen patients died and 8 cases were did not follow-up. Comorbidity was a predictor of death in PD patients after adjust for other covariates (including age, sex, disease duration, disease stage, motor status and non-motor symptoms): ICD-10 (total number of comorbidities), hazard ratio 1.285 (95% confidence interval, 1.047–1.577; $p = 0.017$); CI, hazard ratio 1.462 (95% confidence interval, 1.045–2.047; $p = 0.027$).
Conclusions: Comorbidity is frequent in PD patients, increases significantly over time and predicts mortality.

1. Introduction

Parkinson's disease (PD), the second most common neurodegenerative disease after Alzheimer's disease (AD), is a progressive neurodegenerative disorder causing motor and non-motor symptoms that result in disability, loss of patient autonomy and caregiver burden [1]. PD patients frequently take many anti-parkinsonian drugs (levodopa, dopamine agonists, MAO-B inhibitors, COMT inhibitors, anticholinergic drugs, etc.) for improving motor symptoms and also other medications (analgesics, acetylcholinesterase inhibitors, anxiolytic, antipsychotic or antidepressant agents, etc.) for some other symptoms related to their disease such as pain, anxiety, depression, fatigue, apathy, dementia, psychosis, gastrointestinal symptoms, urinary symptoms or sleep problems [2,3]. The occurrence of these symptoms and conditions in persons with PD are well described. There is less certainty regarding the extent to which persons with and without PD differ with respect to a broader spectrum of comorbid conditions. Some previous studies have demonstrated that polypharmacy and comorbidity are frequent in PD patients and that the excess morbidity and mortality observed for persons with PD are consistent with recognized PD sequelae [4–6]. It is also critical for understanding the extent to which the excess disability and mortality observed in persons with PD are likely to be reduced by treatment specific for PD [7]. In view of this, the management of PD and therapeutic decisions should take into account other disabling comorbidities and all medications received. In real practice, quality of life and patient autonomy are conditioned by all comorbidities, not only PD. Therefore, for these reasons it is necessary to know what comorbid conditions are frequent in PD patients and how these change over time.

Abbreviations: AD, Alzheimer disease; ADLS, Schwab & England Activities of Daily Living Scale; BDI, Beck Depression Inventory; CI, Charlson Index; CPS, Comorbidity-Polypharmacy Score; ECM, Elixhauser Comorbidity Measure; H&Y, Hoehn & Yahr; ICD-10, International Classification of Diseases, Tenth Revision; NMSS, Non-Motor Symptoms Scale; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

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The aim of the present study was to know which comorbid conditions were present at baseline and 3 years later in a cohort of Spanish PD patients. Secondary objectives included comparing comorbidity with both AD and control groups and to analyze the role of comorbidity as predictor of mortality.

2. Material and methods

One hundred and forty-seven non-demented PD patients (57.1% males; 70.9 ± 8.6 years old) from a cohort previously studied in detail in 2012 [8,9] were included in this 36 month follow-up, longitudinal-retrospective, single, evaluation study.

Baseline assessment included motor dysfunction (ON-state Hoehn & Yahr [H&Y]/Unified Parkinson's Disease Rating Scale [UPDRS] part III and motor complications [UPDRS part IV]), mood (Beck Depression Inventory [BDI]), non-motor symptoms (Non-Motor Symptoms Scale [NMSS]), disability (Schwab & England Activities of Daily Living Scale [ADLS]), quality of life (39-item Parkinson's disease Quality of Life Questionnaire Summary Index [PDQ-39SI]), socio-demographic variables and other disease-related variables [8,9]. All the patients were examined in the morning, 1–2 h after taking their medications.

The International Classification of Diseases, Tenth Revision (ICD-10) [10], Charlson Index (CI) [11], Comorbidity-Polypharmacy Score (CPS) [12] and Elixhauser Comorbidity Measure (ECM) [13] were used to asses comorbidity at baseline (visit 1, V1; between May 11 and December 24, 2012 depending on the case) and at 3 years (visit 2, V2). In a first step, the information about comorbidity (ICD-10, CI, CPS, ECM) at V1 and V2 was recorded retrospectively by four investigators (DSG, ESC, IER, TdDF) in March 2016. All data were collected from our electronic medical record system (IANUS), a very complete system that provides information about all medical visits in all departments, hospitalizations, diagnoses reported, complementary studies or treatments received from 2006 [14]. In a second step, comorbidity was assessed in two comparator groups, 44 CE patients and 44 control subjects, at V1 (2012) and V2 (2015) using the same method by nine investigators (DSG, ESC, IER, TdDF, CTG, AAD, DNA, MLF, MBT) in May 2016. Finally, one evaluator (DSG) reviewed all the information collected. Parkinson's disease was recorded in ICD-10 as G20 (Chapter-VI/disease of the nervous system). Alzheimer's disease was recorded in ICD-10 as F00 (Chapter-V/mental and behavioural disorders). A control subject was defined as a subject who was evaluated in external consults of our department of Neurology and who was discharged on the first and/or second evaluation. The inclusion of controls was consecutive according to definition. Polypharmacy was defined according to WHO definition (taking over 3 chronic drugs) [15].

The study (COMORBIDA-PD, COMORBID conditions Associated with Parkinson's Disease; DSG-PAK-2015-01) was approved by the local ethics committee. All participants signed an informed consent form. This consent form was signed by a caregiver or family member of the patient when necessary (i.e., AD patients).

Data were processed using SPSS 21.0 for Windows. Proportions between groups were compared using the chi-square test. Continuous variables are expressed as the mean ± SD or median and quartiles, depending on whether they were normally distributed. Relationships between variables were evaluated using the Student's *t*-test, the Mann-Whitney *U* test, Spearman's or Pearson's correlation coefficient as appropriate (distribution for variables was verified by one-sample Kolmogorov-Smirnov test). Correlations were considered weak for coefficient values ≤0.40, moderate for values between 0.40 and 0.59 and strong for values ≥0.60 [16]. Changes between comorbidity at baseline and at 3 years were analyzed with Wilcoxon's rank sum test. Predictors of mortality were estimated through multiple linear regression analyses (Cox Regression model). Values of $p < 0.05$ were considered significant.

3. Results

One hundred and forty-seven PD patients, 44 CE patients and 44 control subjects were included in the analysis at baseline. Over 3 years of follow-up, 17 PD patients (11.5%) died and 8 cases were lost, so 122 PD patients were included in the analysis for comparison of changes in comorbidity between V1 and V2. Six AD patients (13.6%) and one control subject (0.2%) died. Two AD patients were lost. Results of the clinical and socio-demographic variables of the cohort of PD patients and both comparator groups at baseline are shown in Table 1.

Total number of comorbidities (ICD-10) and polypharmacy at baseline were higher in PD and AD patients than controls (4.4 ± 2.3 vs 5.2 ± 2.4 vs 3.4 ± 1.9 [$p = 0.001$] and 81.6% vs 75% vs 56.8% [$p = 0.003$], respectively) (Table 2). Only CI was significantly higher in AD patients compared to PD patients (1.6 ± 0.9 vs 0.6 ± 1.1; $p < 0.0001$). However, the number of pills taken per day was significantly higher in PD compared to AD group (8.4 ± 3.7 vs 5.2 ± 2.7; $p < 0.0001$). Diseases of the circulatory system (ICD-10/chapter-IX) and endocrine, nutritional and metabolic diseases (ICD-10/chapter-IV) were the most frequent in all groups (Table 2). According to ECM, hypertension was the most frequent comorbidity in all groups, being present at baseline in 42.2% of PD patients, 54.5% of AD patients and 40.9% of controls (Supplementary material/Table1).

There were no differences in comorbidity frequency (total number of comorbidities according to ICD-10) or comorbidity severity (CI) between men and women. Both variables correlated weakly with age ($r = 0.215$ [$p = 0.009$] and $r = 0.286$ [$p = 0.009$], respectively). Significantly, younger PD patients (<65 years old; mean age 57.3 ± 6.65; $n = 27$) had lower comorbidity than PD patients ≥65 years old (ICD-10 total number of comorbidities [3.37 ± 1.82 vs 4.69 ± 2.35; $p = 0.007$]; Charlson Index [0.18 ± 0.48 vs 0.76 ± 1.20; $p = 0.015$]), with diseases of the ICD-10/chapters IV, XIII and IX being the most frequent ones (51.9%, 48.1% and 44.4%, respectively) in this subgroup and 33% of

Table 1
Clinical and sociodemographic data of PD patients ($n = 147$), AD patients ($n = 44$) and control subjects ($n = 44$) at baseline (2012). Three PD patients of the 150 from the cohort previously studied in detail [6,7] were excluded because they were diagnosed with Parkinson plus syndrome "a posteriori" (1 case of supranuclear progressive palsy and two cases of multiple system atrophy). At baseline, 18 AD patients (40.9%) showed mild AD, 16 (36.4%) showed moderate AD and 10 (22.7%) showed advanced AD, with the mean time from diagnosis being 34.4 ± 36.0 months.

	PD patients ($n = 147$)	AD patients ($n = 44$)	Controls ($n = 44$)
Age	70.9 ± 8.6 (40–84)	70.5 ± 3.4	70.7 ± 2.6
Males (%)	57.1	38.6	31.8
Disease duration (years)	6.8 ± 4.8 (0.5–32)		
Hoehn&Yahr-ON	2 ± 0.6 (1–4)		
UPDRS-III-ON	16.3 ± 9.1 (2–62)		
UPDRS-IV	2.6 ± 2.5 (0 − 10)		
Motor fluctuations (%)	34		
Dyskinesia (%)	32		
Levodopa (%)	86.4		
Dopamine agonist (%)	46.3		
COMT inhibitor (%)	36.7		
MAO-B inhibitor (%)	33.3		
Amantadine (%)	6.8		
Anticholinergic drug (%)	1.4		
L-dopa eq. daily dose (mg)	639.4 ± 473.6 (0–2134)		
NMSS (0–360)[a]	67.2 ± 53.3 (0–318)		
BDI (0–63)[b]	12.7 ± 8.8 (0–43)		
ADLS (0 − 100)	73.4 ± 21.6 (10 − 100)		
PDQ-39SI (0–100)	30.1 ± 20.8 (0–84.6)		
PQ-10 (0–10)[c]	6.1 ± 1.8 (1 − 10)		

ADLS, Activities of Daily Living Score; BDI, Beck Depression Inventory; NMSS, Non-motor Symptoms Scale; PDQ-39SI, 39-item Parkinson's disease Quality of Life Questionnaire Summary Index score; UPDRS, Unified Parkinson's Disease Rating Scale (part III, motor examination; part IV, motor complications).

[a] 16 patients did not respond to item 25, and 18 did not respond to item 26.

[b] $n = 146$.

[c] $n = 108$.