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ARTICLE

Presence or absence of cognitive complaints in Parkinson's disease: mood disorder or anosognosia?

Presença ou ausência de queixas cognitivas na doença de Parkinson: transtorno de humor ou anosognosia?

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ABSTRACT

We intended to evaluate whether non-demented Parkinsons's disease (PD) patients, with or without subjective cognitive complaint, demonstrate differences between them and in comparison to controls concerning cognitive performance and mood. We evaluated 77 subjects between 30 and 70 years, divided as follows: PD without cognitive complaints (n = 31), PD with cognitive complaints (n = 21) and controls (n = 25). We applied the following tests: SCOPA-Cog, Trail Making Test-B, Phonemic Fluency, Clock Drawing Test, Boston Naming Test, Neuropsychiatric Inventory, Hospital Anxiety and Depression Scale (HADS) and Beck Depression Inventory. PD without complaints presented lower total score on Scales for outcome of Parkinson's disease-cognition as compared to controls (p = 0.048). PD with complaints group showed higher scores on HADS (p = 0.011). PD without complaints group showed poorer cognitive performance compared to controls, but was similar to the PD with complaints group. Moreover, this group was different from the PD without complaints and control groups concerning mood.

Keywords: Parkinson disease; cognition; dementia; depression; anxiety.

RESUMO

Avaliar se pacientes com doença de Parkinson (DP) sem demência, com ou sem queixa cognitiva subjetiva, demonstram diferenças entre eles e comparativamente aos controles relativos a desempenho cognitivo e humor. Avaliados 77 indivíduos entre 30 e 70 anos: PD sem queixas cognitivas (n = 31), PD com queixas cognitivas (n = 21) e controles (n = 25). Testes aplicados: SCOPA-cognição, Trail Making Test-B, Fluência Fonêmica, Teste do Relógio, Teste Nominativo de Boston, Inventário Neuropsiquiátrico, Escala Hospitalar de Depressão e Ansiedade (HADS) e Inventário de Depressão de Beck. PD sem queixas apresentaram menor pontuação total na SCOPA-cognição, comparativamente aos controles (p = 0,048). Por outro lado, PD com queixas apresentaram maior pontuação no HADS (p = 0,011) em comparação aos controles. O grupo PD sem queixas mostrou pior desempenho cognitivo em comparação aos controles, mas foi semelhante ao PD com queixas. Este grupo foi diferente dos grupos PD sem queixas e controle em relação ao humor.

Palavras-chave: doença de Parkinson; cognição; demência; depressão; ansiedade.

Non-motor deficits have been recognized as important features of Parkinson's disease (PD) over the past years[1]. Among them, cognitive impairment, with or without definite dementia, is increasingly recognized and has meaningful clinical impact, being associated with higher risk of nursing home placement, caregiver burden, and higher morbidity and mortality[2]. The prevalence of PD associated dementia (PDD) ranges from 24 to 31%, with a lifelong risk of 83%(3). PDD is estimated to account for 3.6% of demented patients, with estimated prevalence of 0.2% in the population older than 65 years[3].

The characteristics of the cognitive impairment in PD can vary regarding affected domains, timing of onset, and rate of progression. The most frequently affected domains

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are: attention, frontal executive functions, visuospatial abilities, memory and language[4]. This heterogeneity of cognitive dysfunction is not surprising, given the distinct pattern of neuronal degeneration in PD[5]. The disease is pathologically defined by loss of dopaminergic cells in the substantia nigra and by the presence of Lewy bodies, mainly comprising alpha-synuclein, which is likely implied in the neuronal death in PD[6]. There are evidences of subcortical involvement in earlier stages of the disease, including noradrenergic neurons in the *locus ceruleus*, serotonergic neurons in the raphe dorsal nuclei, and cholinergic neurons in nuclei basalis of Meynert, which takes place since early stages of the disease[5]. Moreover, there is strong evidence that mesocortical dopaminergic system contributes to cognitive and behavioral disturbances[7].

In this heterogeneous context, studies have demonstrated distinct subgroups of PD patients in respect to cognitive deficits, some of them particularly vulnerable to convert to dementia[8]. Identifying patients with higher risk of dementia at earlier stages could be an opportunity for further interventions[9]. In line with this, it has recently been shown that subjective cognitive complaints (SCC) may harbor early dementia[10,11]. On the other hand, it has been also found that cognitive complaints in the absence of dementia might be attributed to an underlying mood disorder[12].

In this study, we intended to evaluate whether non-demented PD patients, with or without subjective cognitive complaint, demonstrate differences between them and in comparison to controls concerning cognitive performance and mood.

METHOD

Patients

We enrolled subjects in regular follow-up at the Movement Disorders Unit of Universidade Federal de Sao Paulo. The sample constituted of subjects with PD meeting the United Kingdom Brain Bank Criteria[13], with age between 30-70 years old, and stable doses of PD medications for at least 8 weeks. PD subjects were separated into two groups: with SCC (PD-C), and with no SCC (PD-NC). Control group was constituted of healthy volunteers, mainly non-related caregivers, with exception of one, who was a healthy sister of one PD subject, all without SCC. Subjective cognitive complaint was defined as the existence of any self-reported impairment in memory and/or attention. Complaints reported by spouses or caregivers were not taken into account.

Subjects were excluded if they had dementia, poor visual acuity, past medical history of brain injury, brain surgery, stroke or psychiatric illness. They were also excluded if there was current established major depression or in the last 6 months before the study, or in use of drugs that could potentially interfere in cognition (e.g.; anticholinergics, benzodiazepines).

Clinical and neuropsychological evaluation were done during the on – medication phase. Data were collected over 10 months. We initially screened 150 PD subjects, of whom 73 (48.6%) were excluded and 77 fulfilled the criteria for the study. All patients provided written informed consent to participate in the study.

Clinical protocol

PD subjects were submitted to a complete neurological examination, evaluation of PD motor symptoms with the Unified Parkinson's disease rating scale (UPDRS) part III[14], Hoehn and Yahr scale[15], and the Schwab and England scale[16]. Neuropsychological battery applied to all subjects included: Scales for outcome of Parkinson's disease - cognition (SCOPA-COG)[17,18], phonemic verbal fluency[19], Boston naming test (BNT)[20], neuropsychiatric inventory (NPI)[21], and the Hospital anxiety and depression scale (HADS)[22], all in validated Portuguese versions. Subjects were also assessed using clock drawing test (CDT)[23], trail-making-test part B (TMT)[24] and Beck depression inventory (BDI)[25]. Pfeffer scale was used in the screening visit to support the exclusion of subjects with dementia.

Statistical analysis

The outcome variables were analyzed with Kolmogorov-Smirnov test for normality of distribution. Student's T test for independent samples was used to analyze UPDRS motor score duration of the disease and levodopa equivalent dose, and Mann Whitney test for independent samples to compare the Hoehn & Yahr and Schwab England and ultimately the Pfeffer Scale scores in PD groups. To compare the performance in the TMT and gender we used Chi-square test.

Afterwards, ANOVA with Post Hoc Tukey was applied to compare the three groups regarding a age, years of education, phonemic fluency, SCOPA-COG (total score), HADS (total score and separated anxiety and depression items) and BDI. Kruskal-Wallis test was used to compare the three groups regarding NPI, Boston naming test, CDT and SCOPA-COG score in sub-items.

Finally, it was used ANOVA with covariate (HADS, HADS – depression and BDI) and comparisons using the Bonferroni's method, when needed, with the purpose of comparing the total and sub-items' score of SCOPA-COG, phonemic fluency, CDT and Boston naming test. In the same way, it was performed a controlled analysis for the UPDRS.

Data were expressed in tables as mean (m) ± standard deviation (sd), median (M), 95% confidence interval (CI) and p-values, with exception of performance in the TMT, which was expressed in absolute and relative frequency because of its categorical nature. It was established in 5% the alpha-level for rejection the null hypothesis.

Ethics

The study protocol has been approved by the ethics committee from the Universidade Federal de Sao Paulo (project number 32906/12).

RESULTS

We evaluated 150 patients, of which 77 were included in the study. The main reasons for exclusion were mood disorders (24%), use of benzodiazepines or biperiden (22.5%) in the PD group, and cognitive complaints (50%) in the control group.

Of the 77 patients included in the study, 49 were male and 28 female. We found no statistically significant differences in cognitive performance between males and females ($p > 0.05$).

Demographic information

Table 1 shows demographic information of the patients studied. There were no differences in age and level of education among the three groups. The PD-NC group showed significantly higher scores on the UPDRS than the PD-C group, but we found no significant differences in cognitive performance between these two groups after controlling the analysis for this variable.

Neuropsychological assessment

The PD-NC group showed lower scores on the Scales for Outcomes in Parkinson's Disease-Cognition (SCOPA-COG) as compared to control group ($p = 0.048$), but the scores of PD-C group were similar to those seen in all the other groups (Table 2).

In the fist-palm-side test ($p = 0.022$) and verbal semantic fluency test ($p = 0.045$) the PD-NC group also showed lower scores (2.00 and 3.61, respectively) than the control group (2.72 and 4.36, respectively). The same was seen in the CDT ($p = 0.023$) (Table 3).

After we conducted an ANOVA controlling for the covariates HADS, HADS-D and BDI scores, there were no longer differences ($p = 0.32$) in the word-list generation performance between the PD-C (mean = 1.24) and the control group (mean = 2.04). An analysis controlled for UPDRS scores did not change the results we previously obtained.

A comparison of the trail making test results showed nearly 57% errors in the PD-C group, 81% in the PD-NC group and 52% in the control group. Although 81% of the patients in the PD-NC group did not manage to complete the test task, the difference did not reach statistical significance ($p = 0.056$) when groups were compared.

Table 1. Clinical and demographic features of patients (mean ± SD).

Variable	PD-C (n = 21)	PD-NC (n = 31)	CG (n = 25)	p*
Age (years)	60.62 ± 8.40	60.74 ± 7.06	55.76 ± 8.69	0.06[b]
Education (years)	10.38 ± 4.87	7.48 ± 5.84	9.3 ± 4.00	0.11b[b]
Disease duration (years)	10.73 ± 5.67	9.74 ± 5.37	NA	0.54[a]
UPDRS	23.95 ± 9.08	30.29 ± 11.10	NA	0.02*[a]
HY	2.35 ± 0.56	2.38 ± 0.54	NA	0.79[c]
SE (%)	79 ± 13	80 ± 14	NA	0.77[c]
Pfeffer	0.95 ± 0.92	0.87 ± 1.2	NA	0.36[c]
Levodopa Equivalent dosage	704.76 ± 303.89	690.25 ± 325.46	NA	0.87[a]

SD: standard deviation; PD-C: PD with cognitive complaints; PD-NC: PD with no cognitive complaints; CG: control group. UPDRS: unified Parkinson's disease rating scale; HY: Hoehn Yahr; SE: Schwab & England;. a: Teste T de Student; b: ANOVA; c: Mann Whitney; NA: Non-aplicable; *p < 0,05.

Table 2. Comparison of groups concerning scores on scales for outcome of Parkinson's disease – cognition (SCOPA-COG).

Test	Group	mean ± SD	95%CI	p
SCOPA-COG	PD-C (n = 21)	20.38 ± 6.8	17.28–23.48	> 0.999
	PD-NC (n = 31)	18.35 ± 6.67	15.91–20.8	0.048*[b]
	CG (n = 25)	22.84 ± 5.27	20.66–25.02	NA

PD-C: PD with cognitive complaints; PD-NC: PD with no cognitive complaints; CG: control group. b: ANOVA with covariance; NA: Non-aplicable; *p < 0,05

Table 3. Comparison of groups concerning score on Boston naming test (BNT) and clock drawing test (CDT).

Test	Group	mean ± SD	95%CI	p
BNT	PD-C	13.71 ± 1.90	12.85–14.58	> 0.999
	PD-NC	13.23 ± 2.09	12.46–13.99	0.619
	CG	13.76 ± 1.42	13.17–14.35	NA
CDT	PD-C	11.24 ± 3.52	9.64–12.84	> 0.999
	PD-NC	10.74 ± 3.74	9.37–12.11	NA
	CG	13.16 ± 1.72	12.45–13.87	0.023*[a]

PD-C: PD with cognitive complaints; PD-NC: PD with no cognitive complaints; CG: control group; b: ANOVA with covariance; NA: Non-aplicable; *p < 0,05.

For all other cognitive tests, there was no significant difference in performance among the groups.

Regarding mood assessment, PD-C group showed higher scores on the HADS than the control group (p = 0.011). PD-C group also showed higher mean scores in the HADS depression subscale when compared to the PD-NC group (p = 0.004) and the control group (p = 0.001) (Table 4). PD-C group also had higher scores on the Beck depression inventory (p = 0.018) and the neuropsychiatric onventory (p = 0.012) when compared to the control group (Table 4).

DISCUSSION

In our study, patients with PD-NC had worse mean cognitive performance – assessed by the SCOPA-COG, fist-hand-palm sequence, verbal semantic fluency test and clock-drawing test – than controls. However, we found no differences in mean cognitive performance between PD-C and the control group.

This finding suggests that PD patients may have misperceptions of their cognitive impairment. As Seltzer[26] noted, patients with PD and Alzheimer's disease misperceive their cognitive deficits in multiple domains, which is associated with overall cognitive impairment and poor performance on tests assessing memory, attention and constructional ability. However, PD patients can have a better "insight" about their cognitive deficits when compared to patients with Alzheimer's disease, although they have poor perception of their functional and social deficits[27].

Leritz et al.[28] reported that PD patients had low perception of impairment in daily living activities, and they inferred that basal ganglia dysfunction might affect their "insight" about the severity of their condition.

Rosen[27] claimed that, although the underlying mechanisms of anosognosia are not yet clearly understood, neurotransmitter pathways in the brain's frontal lobes must be preserved so that, self-perception is intact. From a neuropathological viewpoint, PD is characterized by neuronal degeneration in the substantia nigra leading to dopamine depletion in the nigrostriatal dopaminergic projections. It, in turn, is associated with disruptions of subcortico-frontal circuits[29] which may cause anosognosia in these patients. Anosognosia is very common in patients with neurodegenerative conditions and significantly impact on function and quality of life of these patients and their caregivers[27].

According to Sitek et al.[30] it is a relevant aspect for patient follow-up since, misperception of one's own deficits in patients with PD has been associated to the development of dementia.

PD-C group had similar cognitive performance as compared to the other groups studied. On the other hand, mood disorders seem to be present in this group (PD-C) as compared to the other two groups.

Different from what Hong et al.[11], we could not find significant differences in comparison to PD-NC group. They have found that PD-C group had the poorest performance on phonemic and semantic fluency tests and backward digit span test. The reason for this conflicting results could be the longer disease duration (mean = 27 years) in Hong's patients as compared to ours (mean = 10 years). This finding may suggest that, as disease progresses, cognitive decline prevails over the misperceptions of these deficits.

The PD-C group had higher scores on the HADS, HADS-D, BDI and NPI, and that were significantly different compared to the control group. They also showed significantly higher HADS-D scores when compared to PD-NC group. These findings may be explained by the fact that patients with depressive symptoms are likely to overestimate their cognitive symptoms[30].

Table 4. Comparison of groups concerning mood assessment.

Test	Group	mean ± SD	CI 95%	p
HADS	PD-C	13.95 ± 7.11	10.72–17.19	0.011*[b]
	PD-NC	10.61 ± 6.05	8.39–12.83	0.45
	CG	8.64 ± 5.05	6.56–10.72	NA
HADS-A	PD-C	6.05 ± 3.38	4.51–7.6	0.39
	PD-NC	5.87 ± 3.98	4.41–7.33	0.42
	CG	4.68 ± 2.94	3.47–5.89	NA
HADS-D	PD-C	7.90 ± 4.44	5.88–9.92	0.001*[b]
	PD-NC	4.74 ± 2.92	3.67–5.81	0.667
	CG	3.96 ± 2.86	2.78–5.14	NA
BDI	PD-C	13.38 ± 7.62	9.91–16.85	0.018*[b]
	PD-NC	9.87 ± 7.76	7.03–12.72	0.428
	CG	7.48 ± 5.7	5.12–9.84	NA
NPI	PD-C	7.05 ± 7.88	3.46–10.64	0.012*[c]
	PD-NC	4.06 ± 3.83	2.66–5.47	0.523
	CG	2.56 ± 3.33	1.19–3.93	NA

SD: standard deviation; CI: confidence interval; HADS: hospital anxiety and depression scale; HADS-A: HADS subscale of anxiety; HADS-D: HADS subscale of depressive symptoms; BDI: Beck depression inventory; NPI: neuropsychiatric inventory. PD-C: PD with cognitive complaints; PD-NC: PD with no cognitive complaints; CG: control group; NA- Non-aplicable; b: ANOVA; c: Kruskal – Wallis test; *p < 0,05

This is consistent with Marino et al.[12] who concluded that PD patients with memory-related complaints showed mood disorders and that there was no relationship between subjective complaints and objective cognitive impairment.

Another hypothesis could be the impact of depressive symptoms on attention and memory. The poorer word-list generation performance of the PD-C group compared to the control group disappeared after controlling for HADS, HADS-D and BDI scores in the covariate analysis, i.e., when the impact of depressive symptoms assessed by these scales on cognitive performance was removed.

Our findings regarding the presence of depressive symptoms in the PD-C and PD-NC groups contrast with those reported by Hong et al.[11] who found no mood differences between these groups. This may be due to the smaller number of patients with PD (n = 35) of their study. Dujardin et al.[10] also found a greater rate of depressive symptoms in PD patients with cognitive complaints.

We should consider that our study has some limitations. Possibly, patients could misunderstand the meaning of attention or memory complaints. Another possible limitation was our small sample size since we had difficulty in recruiting patients who met study criteria.

Despite these limitations, the study findings and their comparison with literature data allow to further interpreting the significance of cognitive complaints in PD patients. They may vary not only with factors such as depressive symptoms, but also with disease progression.

This study showed that PD patients without cognitive complaints had worse cognitive performance as compared to controls, as measured by total score on the SCOPA-COG, fist-hand-palm sequence, verbal semantic fluency test and clock-drawing test. However, their cognitive performance was similar to that seen in the PD-C group.

PD subjects with cognitive complaints scored higher on HADS in comparison to controls and scored higher on items related to depressive symptoms on the HADS, when compared to PD-NC group.

In conclusion, our results suggest that cognitive complaints in PD patients could point to mood disorders instead of real cognitive impairment. On the other hand, the absence of cognitive complaints could be related to anosognosia.

These findings help better understanding the significance of subjective cognitive complaints in PD patients, but further investigations are warranted.

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