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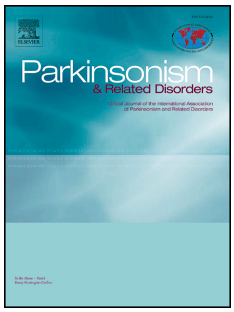

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Cardiovascular autonomic function and MCI in Parkinson's disease.

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Abstract

Introduction: dysautonomic dysfunction and cognitive impairment represent the most disabling non-motor features of Parkinson's Disease (PD). Recent evidences suggest the association between Orthostatic Hypotension (OH) and PD-Dementia. However, little is known on the interactions between cardiovascular dysautonomia and Mild Cognitive Impairment (MCI). We aimed to evaluate the association between cardiovascular dysautonomia and MCI in patients with PD.

Methods: non-demented PD patients belonging to the PACOS cohort underwent a comprehensive instrumental neurovegetative assessment including the study of both parasympathetic and sympathetic function (30:15 ratio, Expiratory-Inspiratory ratio [E-I] and presence of Orthostatic Hypotension [OH]). Diagnosis of MCI was made according to the MDS criteria level II.

Results: we enrolled 185 PD patients of whom 102 (55.1%) were men, mean age was 64.6 ± 9.7 years, mean disease duration of 5.6 ± 5.5 years with a mean UPDRS-ME score of 31.7 ± 10.9. MCI was diagnosed in 79 (42.7%) patients. OH was recorded in 52 (28.1%) patients, altered 30:15 ratio was recorded in 39 (24.1%) patients and an altered E-I ratio was found in 24 (19.1%) patients. Presence of MCI was associated with an altered 30:15 ratio (adjOR 2.83; 95%CI 1.25-6.40) but not with an altered E-I ratio, while OH was associated only with the amnestic MCI subgroup (OR 2.43; 95% CI 1.05-5.06).

Conclusion: in our study sample, MCI was mainly associated with parasympathetic dysfunction in PD.

Introduction

Dysautonomic dysfunction and cognitive impairment represent the most disabling non-motor features of Parkinson's Disease (PD). Cognitive impairment in PD ranges from Mild Cognitive Impairment (MCI) to Parkinson's Disease Dementia (PDD) and it can be present even in the early phase of the disease, with up to 30% of the patients presenting MCI at the time of diagnosis [1].

Recent evidences suggest a possible association between cardiovascular autonomic dysfunction and cognitive impairment in PD, and in particular Orthostatic Hypotension (OH) has been demonstrated to be associated with PDD [2]. Two mechanisms have been hypothesized in order to explain the possible role of OH in the development of cognitive impairment: the influence of frequent blood drops on vascular damage to cortical brain areas or the presence of a more widespread neurodegeneration characterized by the presence of cognitive impairment and OH [2].

Nevertheless, the possible relationship between the different components of cardiovascular autonomic function and PD-MCI have not been elucidated, except for one study focusing on OH that found no association with PD-MCI [3].

The main objective of the present study was to evaluate the possible relationship between cardiovascular dysautonomia and MCI in a large cohort of PD patients. This study is part of The PArkinson's disease COgnitive impairment Study (PACOS) a study involving two centers located in south Italy (Sicily), aimed at evaluating frequency, clinical features and biomarkers associated with MCI in a large hospital-based cohort of PD patients [1].

Materials and methods

Study population

Patients affected by PD were retrospectively selected from the Neurologic Unit of the "Policlinico Vittorio Emanuele" in Catania, and the Memory and Parkinson's Disease Center of the "Policlinico Paolo Giaccone" in Palermo, during a 6-year period (2011–2016).

A sample of 185 PD patients from the original cohort of the PACOS study [1] was included in the present study based on the following criteria: a comprehensive neuropsychological and neurovegetative assessment to detect cardiac autonomic function. All patients underwent a neurological examination including the administration of the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr scale (HY) and a neuropsychological evaluation as detailed elsewhere [1,4]. Patients were classified in PD with Normal Cognition (PD-NC) or PD-MCI according to the MDS Level II criteria [5]. Furthermore, patients with MCI have been classified in amnestic MCI single domain (aMCIsd) and multiple domain (aMCImd) or non-amnestic MCI single domain (naMCIsd) and multiple domain (naMCImd). The overall burden of dopaminergic drugs was evaluated with the total daily Levodopa Equivalent Dose (LED) [6]. All participants provided written informed consent prior to entering the study, which was approved by the local medical Ethics Committee and in accordance with the Declaration of Helsinki.

Cardiac autonomic function assessment

All the evaluations have been performed in fasting patients between 8 am and 9 am. Patients in dopaminergic therapy were assessed in their "practical OFF" motor status after an overnight washout. Heart rate response to deep breathing tested both afferent and efferent vagal pathways by evaluating the maximal heart rate variability (R-R interval) during the manoeuvre. It was expressed as the mean Expiratory-Inspiratory (E-I) ratio of the maximal and minimal heart rate obtained in 6 consecutive respiratory cycles [7]. Heart rate response to standing tested the cardioacceleration response to exercise and the subsequent baroreflex-mediated heart rate response by computing the 30:15 ratio (R-R interval at beat 30 seconds/R-R interval at beat 15 seconds) [7]. Both E-I and

30:15 ratio parameters for single subjects were considered abnormal according to age-dependent values (DANTEST, Medeia Inc.). Baseline blood pressure has been recorded at least five minutes after reaching the supine position. Using an automated sphygmomanometer, three measurements with a 1 minute interval have been used to assess the average baseline pressure and, when assuming the standing position, at 30, 60, 120 and 180 seconds. The presence of OH was based on the detection of a systolic and diastolic blood pressure reduction of at least 20 and 10 mm Hg respectively, within 3 minutes of standing [8].

Statistical analysis

The data were analyzed using STATA 12.1 software packages. In order to evaluate the possible predictors of MCI, an unconditional multivariate logistic regression analysis was performed. Parameters associated with the outcome at the univariate analysis with a threshold of $p = 0.10$ were included in the model. Age at baseline and sex were considered as *a priori* confounders. The model was manually constructed using the likelihood ratio test (LRT). Patients have been stratified in short disease duration (≤5 years) or long disease duration (>5 years). A subgroup analysis has been performed to analyse the association between the neurovegetative tests and the different MCI phenotypes.

Results

From the PACOS cohort consisting of 659 non-demented PD patients, 185 PD patients (102 men; mean age 64.6 ± 9.7 years) underwent a complete cardiac autonomic function assessment and were included in the analysis.

At the time of the enrolment, PD patients presented a mean disease duration of 5.6 ± 5.5 years, a mean UPDRS-ME score of 31.7 ± 10.9, a mean HY stage of 2.2 ± 0.7, and a mean LED of

355.0 ± 434.0. Among them 27 (14.6%) reported a history of diabetes and 66 (35.7%) a history of hypertension (Table 1).

When stratified according to the 5 years of disease duration 113 patients (61.1%) had a disease duration ≤5 years, while 72 (38.9%) had a longer disease duration. Out of the 185 non-demented PD patients 79 (42.7%) fulfilled the diagnosis of PD-MCI. Concerning the MCI subtype, the majority had multidomain MCI (39 [49.4%] were naMCImd and 25 [31.6%] aMCImd), while only few presented a single domain MCI (10 [12.7 %] were naMCIsd and 5 [6.3 %] aMCIsd). Prevalence of MCI in this sample was close to that recorded in the entire PACOS cohort (39.6%) [1].

Regarding cardiac autonomic parameters, OH was recorded in 52 (28.1%) patients, being significantly more frequent in patients with long disease duration *versus* those with a short duration (59.6% and 40.4%, respectively; p<0.001). Altered 30:15 ratio was recorded in 39 (24.1%) patients, with no significant difference between short *versus* long disease duration (29.5% and 21.0% respectively). An altered E-I ratio was found in 24 patients (19.1%), without any significant difference between short *versus* long disease duration (18.8% and 19.6% respectively).

At univariate analysis, the presence of MCI was significantly and positively associated with male sex, disease duration, age, age at onset, and 30:15 ratio test, while a significant negative association was found with educational level (Table 2). After multivariate analysis, adjusting by sex, age, disease duration and education, the presence of altered 30:15 ratio was associated with an almost three times increased risk of MCI (adj OR 2.83; 95%CI 1.25-6.40; p-value 0.01) as shown in table 2. Frequency of altered 30:15 ratio was not significantly different among patients with and without OH (33.3% vs 20.5% respectively; p = 0.09). Similar results were obtained when analysis has been conducted excluding patients with diabetes and hypertension, as well as when both diabetes and hypertension were included in the multivariate model.

When patients were divided according to an amnestic or a non amnestic MCI phenotype, 49 (62.0%) patients were classified as naMCI, while 30 (38%) had aMCI. Demographic characteristics of the two groups were comparable except for a slightly higher prevalence of men (86.7% versus 53.1%) in the aMCI group. At the univariate analysis an altered 30:15 and the presence of OH were significantly associated with aMCI with, respectively an OR of 3.49 (95% CI 1.36-8.94; p=0.009) and an OR of 2.43 (95% CI 1.05-5.06; p=0.037).

Discussion

The nature and the pathophysiological processes leading patients with PD to develop cognitive impairment are still unclear. Recently, a great effort has been spent in investigating potential biomarkers that may allow to stratify PD patients according to their risk of progressing to dementia, because of the increased disease burden and possible treatment strategies. Among evaluated biomarkers, the presence of MCI represents one of the strongest predictor of a future development of dementia [9]. Furthermore, there is a growing body of evidence that associates the presence of cardiovascular dysautonomia, especially OH, with cognitive impairment and dementia [2,10]. However, cardiovascular dysautonomia may be present even in the earliest phases of PD, involving the parasympathetic function with [11] or without [12] concurrent sympathetic dysfunction.

At multivariate analysis we found an association between a test that assesses the cardiovascular parasympathetic function (30:15 ratio) and PD-MCI (OR 2.83). Differently from data reported on PDD, OH was not associated with PD-MCI in the whole sample, but a significant association was found only when analysis was restricted to aMCI.

Based on available literature, only another study has evaluated the association between OH and PD-MCI, finding also no association [3]. Our results are in agreement with this report even if

different methodologies have been used. In this previous study, in fact, the researchers tested only OH and supine hypertension and applied a broader definition of MCI, while in our study autonomic function has been investigated by a set of standardized neurophysiological measurements and the diagnosis of MCI has been made according to MDS criteria Level II.

Even if we have not a clear explanation for the restricted association between OH and the subgroup of aMCI, it could be hypothesized that aMCI and PDD may share the same pathological background as compared to naMCI. Some studies have suggested a high risk of progression from aMCI to PDD with respect to naMCI, but literature data are still controversial [13].

To the best of our knowledge, this is the first study that has evaluated the association between cardiovascular autonomic functions and PD-MCI. The presence of an altered parasympathetic function in MCI has been already described in subjects with MCI due to Alzheimer's Disease [14]. In these patients, it has been in fact suggested that reduced acetylcholine levels may affect both cognitive function and parasympathetic nervous system whose main neurotransmitter is represented by acetylcholine [14]. There is still uncertainty in literature regarding the role of cholinergic neurons in PD patients brain [15]. However it has been demonstrated that progressive degeneration of structures such as the nucleus basalis of Meynert and the dorsal motor nucleus of the vagus, the former implicated in cognitive performances and the latter in parasympathetic function, are part of the pathological processes underlying PD. According to Braak's hypothesis, both these structures may be involved in the pathologic distribution of alpha-synuclein pathology, impairing the cholinergic projections that regulate cognition and autonomic function at different disease stages [16].

We are aware that some limits should be taken into account in interpreting our data. Due to the hospital-based design a possible selection bias cannot entirely ruled out. Indeed the possibility of more severe cases attending the two hospital centers involved in the study cannot be excluded, even if baseline characteristics of the PACOS cohort are comparable with the majority of published

studies [1,17]. Furthermore, concerning the neurovegetative assessment, we are aware that the restricted number of parameters evaluated (only two tests that primarily assess the parasympathetic function and just one for the sympathetic function) could limit the accuracy of our findings, thus caution must be taken in speculating the type of cardiovascular autonomic dysfunction found in PD-MCI. Moreover the interpretation of obtained results is limited by the cross-sectional study design, which does not allow to assess any kind of causal relationship, but only the presence of associations. Accordingly, prospective studies are needed in order to evaluate the progression of MCI and cardiovascular dysautonomia in PD patients.

Author roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

CEC: 1A, 1B, 1C, 2A, 2B, 2C, 3A.

LR:1A, 1B, 1C, 2A, 2B, 2C, 3A.

GD: 1C, 3B.

RM: 1A, 1B, 1C, 3B.

GM: 1B, 1C, 2C, 3A, 3B.

GS: 1C, 3B.

AL:1A, 1B, 1C, 2C, 3B.

CT: 1A, 1B, 1C.

LG: 1B, 1C, 3B.

RB: 1A, 1B, 3B.

MD: 1A, 1B, 3B.

MZ: 3B.

AN: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.

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Table 1: demographic and clinical characteristics of the study sample

	PD-NC **N= 106**	**PD-MCI** **N = 79**	**Total** **N=185**
Sex, Men (%)	50 (47.2)	52 (65.8)	102 (55.1)
Age (mean ± SD)	63.6 ± 10.6	66.0 ± 8.1	64.6 ± 9.7
Age at onset (mean ± SD)	58.7 ± 10.5	59.4 ± 10.3	59.0 ± 10.4
Disease duration, years (mean ± SD)	4.9 ± 4.9	6.5 ± 6.1	5.6 ± 5.5
Educational level (mean ± SD)	10.7 ± 4.4	8.3 ± 4.7	9.6 ± 4.7
UPDRS-ME (mean ± SD)	30.4 ± 10.5	33.4 ± 11.4	31.7 ± 10.9
Hoehn and Yahr Score (mean ± SD)	2.2 ± 0.6	2.3 ± 0.7	2.2 ± 0.7
LED (mean ± SD)	293.9 ± 393.4	436.2 ± 473.1	355.0 ± 434.0
MMSE (mean ± SD)	27.7 ± 1.9	26.8 ± 1.8	27.3 ± 1.9
Diabetes	11 (10.4)	16 (20.2)	27 (14.6)
Hypertension	38 (35.9)	28 (35.4)	66 (35.7)
Cardiac autonomic functions			
OH	28(26.4)	24(30.4)	52(28.1)
E-I	16(19.7)	8(17.8)	24(19.0)
30:15	18(18.4)	21(32.8)	39 (24.1)

Abbreviations: PD-NC, Parkinson's Disease with normal cognition; MCI, Mild Cognitive Impairment; UPDRS-ME, Unified Parkinson's Disease Rating Scale, Motor Examination; LED, Levodopa Equivalent Daily Dose; MMSE, Mini-Mental State Examination; OH, Orthostatic hypotension; E-I, Expiratory-Inspiratory ratio.

Table 2. Univariate and multivariate analysis.

	Univariate analysis			***Multivariate analysis***		
	OR	**95%CI**	**p-value**	**AdjORs**	**95%CI**	**p-value**
Sex, men	2.15	1.18-3.93	**0.01**	3.47	1.63-6.40	**0.001**
Age*	1.02	0.99-1.05	0.1	1.01	0.98-1.05	0.3
Age at onset*	1.00	0.98-1.03	0.7	/	/	/
Disease duration*	1.05	1.00-1.11	**0.05**	1.04	0.97-1.11	0.3
Educational level*	0.89	0.83-0.95	**0.001**	0.84	0.77-0.92	**<0.0001**
UPDRS-ME ≤ 20 *(median)*	1.05	1.00-1.05	0.07	/	/	/
Hoehn-Yahr Score	1.34	0.85-1.06	0.2	/	/	/
LED*	1.00	1.00-1.001	**0.03**	/	/	/
Cardiac autonomic functions						
OH	1.21	0.64-2.31	0.5	/	/	/
E-I	0.89	0.34-2.25	0.8	/	/	/
30:15	2.17	1.04-4.50	**0.04**	2.83	1.25-6.40	**0.01**

Abbreviations: *continuous variables; AdjORs = ORs have been adjusted by sex, age, education considered as *a priori* confounders; UPDRS-ME, Unified Parkinson's Disease Rating Scale Motor Examination; LED, Levodopa Equivalent Daily Dose; OH, Orthostatic hypotension; E-I, Expiratory-Inspiratory ratio.

- **MCI seems to be associated with cardiovascular autonomic dysfunction in PD.**
- **OH is present in almost one third of PD patients**
- **OH is more frequent in patients with amnestic MCI**