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ORIGINAL COMMUNICATION

Cardiovascular autonomic neuropathy and falls in Parkinson disease: a prospective cohort study

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Abstract

Background Falls represent one of the main complications of Parkinson's disease (PD), significantly lowering quality of life. Cardiovascular autonomic neuropathy (cAN) is one of the key contributing factors to PD-associated falls. However, a direct quantification of its impact on the risk of falling in PD is still lacking. In this 12-month prospective study, we sought to evaluate the association between cAN and falls.

Methods Fifty consecutive patients were evaluated with a standardized battery of autonomic testing, Unified Parkinson's Disease Rating Scale, push and release (P&R) test, timed up and go test, freezing of gait (FOG) questionnaire, Montreal cognitive assessment (MoCA). Dyskinesia severity and presence of REM sleep behavioral disorder (RBD) were additionally considered. Patients were followed-up for 12 months.

Results We observed a 38% prevalence of cAN. At baseline, 36% of patients reported at least one fall in the previous 6 months. This figure increased to 56% over the follow-up. After adjusting for age, disease duration, axial symptoms, MoCA and dopaminergic treatment, cAN was significantly associated with a 15-fold (OR 15.194) higher probability of falls; orthostatic hypotension (OH), the most common expression of cAN, with a 10-fold probability (OR 10.702). In addition P&R test (OR 14.021), RBD (OR 5.470) and FOG (OR 1.450) were independently associated with greater probability of falls.

Conclusions cAN, including but not limited to OH, is a strong independent predictor of falls in PD. Future research endeavors clarifying to what extent pharmacological and non-pharmacological treatments targeting autonomic dysfunctions might reduce the risk of falls are warranted.

Keywords Parkinson disease · Autonomic neuropathy · Falls · Orthostatic hypotension · RBD

Introduction

Falls represent a key determinant of functional disability in Parkinson's disease (PD) [1], with a major impact on patients' mobility and quality of life [2] and an increased risk of mortality due to both direct and indirect complications, such as head trauma, fractures, and prolonged post-traumatic hospitalizations [3].

Cardiovascular autonomic neuropathy (cAN) including, but not limited to, orthostatic hypotension (OH), is a possible cause of falls in PD. Approximately, 30–50% of PD patients have cAN [4]. However, the clinical impact of this potentially disabling PD complication remains poorly quantified and incompletely understood.

A large number of additional factors have also been associated with falls in PD including history of previous falls, older age, executive dysfunction, attention deficits, freezing

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of gait, disabling dyskinesia, and PD severity, in particular axial symptoms [1, 5–7].

This 12-month prospective cohort study aims to evaluate the association between falls and cAN adjusting for potential confounding factors such as age, disease duration, motor symptoms severity, cognitive impairment and dopaminergic treatment. Our main objective was to quantify the impact of cAN on falls, considered as one of the major causes of morbidity and mortality in PD.

Methods

Study population

A cohort of 50 consecutively selected PD patients was enrolled from the Movement Disorder Center of Turin University Hospital between March 2017 and May 2017. Inclusion criteria were idiopathic PD, meeting UK PD Brain Bank criteria [8]; age between 30 and 85 years old; and stable doses of dopaminergic treatment for at least 4 weeks prior to enrollment.

Exclusion criteria were diabetes mellitus or other diseases potentially associated with cAN [9]; cardiac arrhythmia; treatment with antihypertensive drugs and/or any therapy with an effect on blood pressure (BP), such as alpha-adrenergic antagonists for prostate disorders; and any atypical features lowering the diagnostic certainty of PD.

Patients underwent a battery of clinical and autonomic assessments at baseline. Follow-up visits were conducted at 6 and 12 months recording the number of falls, defined as per the definition of the World Health Organization (WHO), as "an event which results in a person coming to rest inadvertently on the ground or floor or other lower level".

The local institutional review board (Comitato Etico Interaziendale Città della Salute e della Scienza di Torino; Protocol n° 0050175/CEI-715) approved the study and all participants provided written informed consent.

Clinical evaluations

Motor severity was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) [10], calculating the UPDRS-III axial subscore by the sum of items 18, 27–30 [11]. The push and release (P&R) test [12] was used to assess postural stability, the timed up and go (TUG) test [13] to assess mobility and gait, the freezing of gait (FOG) questionnaire (FOGQ; 0–24, higher is worse) [14] to assess the severity of freezing episodes, the Montreal cognitive assessment (MoCA; 0–30, lower is worse) [15] to assess cognition, the UPDRS item 33 (Dyskinesia severity) to evaluate the severity of dyskinesia, and the "single question screen" [16] to ascertain rapid eye movement sleep behavior disorder (RBD).

Dopaminergic medications were logged, calculating the levodopa equivalent daily doses (LEDD) as per a validated conversion table [17].

Autonomic evaluations

All patients were evaluated in the morning during their best ON state, defined as a period of perceived maximal efficacy of dopaminergic medications, at least 3 h after the last meal. We used a standardized battery of autonomic tests (DAN Test Microlab, Padua, Italy) [18] consisting of heart rate variability (HRV) and blood pressure (BP) assessment during deep breathing, Valsalva maneuver, and laying to standing. Examinations were performed in a silent room, maintained at ambient temperature (23 °C–26 °C).

Deep breathing

The R–R interval was continuously recorded while the subject was asked to breathe deeply and evenly at 6 breaths/min. Expiratory–inspiratory HRV was calculated from the maximum and minimum R–R interval during five consecutive breathing cycles.

Valsalva maneuver

The subject was asked to sit quietly and then blow into a mouthpiece attached to an aneroid pressure gauge at a pressure of 40 mmHg, holding the breath for 15 s. The Valsalva ratio was calculated as the ratio between the longest R–R interval (shortly after the maneuver) and the shortest R–R interval (during the strain period). BP changes were analysed during the four phases of the Valsalva manoeuvre, namely (I) onset of strain, (II) continued strain, (III) release, and (IV) recovery.

Laying to standing

The subject was asked to lie for at least 10 min and then stand up as quickly as possible and remain upright quietly for 5 min. The 30:15 ratio was calculated as the ratio between the longest R–R interval (around the 30th beat after standing) and the shortest R–R interval (around the 15th beat after standing). BP was monitored during the entire duration of the test using both a beat-to-beat BP monitor (Finapres; Finapres Medical Systems B.V., The Netherlands) and confirmed by manual sphygmomanometer BP recordings after 1, 3, and 5 min of standing.

After adjusting for age, the cardiovascular autonomic tests were scored as follows:

Cardio-vagal index: 0 = normal; 1 = reduction in deep-breathing HR variability < 50%; 2 = reduction in the deep-breathing HR variability > 50% or reduced baroreflex sensitivity index; 3 = reduction in deep-breathing HR variability > 50% and reduced baroreflex sensitivity index.

Adrenergic index: 0 = normal; 1 = reduced late phase II and/or mildly increased BP recovery time (5–6 s) and/or absent phase IV during the Valsalva maneuver; 2 = moderately increased BP recovery time (7–10 s) during the Valsalva maneuver; 3 = Markedly increased BP recovery time (> 10 s) and/or absent late phase II and phase IV during the Valsalva maneuver; 4 = above plus OH.

cAN was defined as a moderate–severe alteration in at least one cardio-vagal and one adrenergic test, with a total autonomic score ≥ 4 [18].

OH was defined as a reduction of systolic BP ≥ 20 mmHg or diastolic BP ≥ 10 mmHg within 3 minutes of standing [19].

Outcome measures and statistical analyses

Sample size calculation

We used published data reporting an average rate of 60.5% of PD patients falling at least once [1], and an average rate of 30% of PD patients having cAN [4]. Using these data, we estimated that a sample size of 34 patients would have sufficed to detect significant differences in PD patients with and without cAN, with 80% power at the 5% level of significance [20]. The recruitment goal was set at 50 patients, accounting for a 15% rate of drop-out or tests with insufficient technical quality for accurate interpretation.

Primary endpoint was the presence of cAN and its association with falls. Clinical and demographic characteristics were summarized as mean ± standard deviation or percentages, as appropriate. A binary logistic regression was used to estimate the impact (Odds Ratio, OR) of cAN and OH (independent variables) on falls (dependent variable), adjusting for age, disease duration, UPDRS-III axial scores, MoCA scores and total LEDD. Secondary endpoints included history of falls, TUG, P&R test, FOGQ, RBD, and dyskinesia. A binary logistic regression was used to estimate the impact (OR) of the above-mentioned clinical characteristics on falls during follow-up, adjusting for age, disease duration, UPDRS-III axial scores, MoCA scores and total LEDD at baseline. Analyses were performed both in the whole sample and in the subgroup of patients without a previous history of falls. The Hosmer and Lemeshow's goodness-of-fit test was applied. Comparisons between groups were analyzed by means of Mann–Whitney non-parametric test or Fisher's exact test, as appropriate. All the analyses were performed with SPSS 24.0 for Macintosh using two-tailed p values with a level of significance of 0.05.

RESULTS

Patients

The cohort consisted of 50 consecutive PD patients (34 males/16 females), with disease duration ranging from 1 to 25 years (8.23 ± 5.13 years) and age from 45 to 80 years (65.06 ± 9.15 years) (Table 1). All patients were treated with dopaminergic therapy. Two patients (4%) were treated with bilateral subthalamic nucleus deep brain stimulation and four patients (8%) with levodopa–carbidopa intestinal gel infusion.

Baseline evaluation

There was a 38% prevalence of cAN ($n = 19/50$ patients) and a 34% prevalence of OH ($n = 17/50$ patients) at baseline. Age, disease duration, UPDRS-III and LEDD were significantly higher in patients with cAN, while MoCA score was significantly lower in patients with cAN (Table 1).

Association between falls and autonomic dysfunction.

During the 12-month follow-up, 56% of patients (28/50) had at least one fall, 42.9% (12/28) of which reported their first fall during the observational study period. The remaining 57.1% (16/28) were already classified as fallers at baseline.

After adjusting for age, disease duration, axial symptoms, MoCA score and total LEDD, there was a 15.2 greater ratio of falls in patients with cAN (OR 15.194; 95% CI 2.288–34.205; $p = 0.011$) and a 10.7 greater ratio of falls in patients with OH (OR 10.702; 95% CI 1.455–29.270; $p = 0.020$) (Fig. 1).

These data were confirmed after excluding patients who already had a history of falls at baseline, with 24.1 and 15.2 greater ratio of falls, respectively, for cAN (OR 24.104; 95% CI 2.259–38.654; $p = 0.016$) and OH (OR 15.226; 95% CI 1.818–32.678; $p = 0.019$) (Fig. 2).

Association between falls and other clinical features

After adjusting for age, disease duration, axial symptoms, MoCA score and LEDD, there was an independent association between falls and the following: previous history of falls (OR 15.549; 95% CI 2.058–36.571; $p = 0.017$;), postural instability at the P&R test (OR 14.021; 95% CI 1.521–35.526; $p = 0.017$), RBD (OR 5.470; 95% CI 1.133–26.410; $p = 0.034$) and FOGQ (OR 1.450; 95% CI

Table 1 Baseline clinical and demographic characteristics

	Total (*n* = 50)	Patients with cardiovascular **autonomic neuropathy (*n* = 19)**	Patients without cardiovascular autonomic neuropathy **(*n* = 31)**	*p* value
Sex (men/women)	34/16	12/7	22/9	0.394
Age (years)	65.06 ± 9.13 (45–80)	68.58 ± 8.40 (45–80)	62.90 ± 9.01 (46–80)	0.026
Disease duration (years)	8.23 ± 5.13 (2–25)	12.00 ± 5.56 (4–25)	5.92 ± 3.16 (2–16)	0.001
TOTAL LEDD (mg/day)	736 ± 386 (250–1944)	921 ± 473 (300–1944)	610 ± 253 (250–1255)	0.023
L-DOPA LEDD (mg/day)	567 ± 427 (0-1824)	799 ± 510 (0-1824)	409 ± 269 (0-1075)	0.006
DA-LEDD (mg/day)	134 ± 138 (0-480)	102 ± 136 (0-480)	156 ± 138 (0-450)	0.153
UPDRS-III	21.20 ± 15.93 (2–72)	28.21 ± 12.53 (8–48)	16.90 ± 16.43 (2–72)	0.001
Axial subscore	4.64 ± 4.30 (0–16)	6.74 ± 4.48 (0–14)	3.35 ± 3.69 (0–16)	0.005
Patients with dyskinesia	8 (16.0%)	3 (15.8%)	5 (16.1%)	0.630
Timed up and go test (sec)	14.08 ± 6.407 (8–30)	15.24 ± 5.08 (11–25)	13.37 ± 6.04 (8–30)	0.189
Falls at push and release test	19 (38.0%)	10 (52.6%)	9 (29.0%)	0.086
MoCA	25.68 ± 4.42 (9–30)	23.91 ± 4.54 (14–29)	26.76 ± 4.38 (9–30)	0.045
Patients with cognitive impairment	31 (62.0%)	12 (63.2%)	19 (61.3%)	0.569
FOG questionnaire	5.92 ± 5.62 (0–19)	6.58 ± 5.06 (1–15)	5.51 ± 5.39 (0–19)	0.254
Patients with RBD	21 (42.0%)	11 (57.9%)	10 (32.3%)	0.069
Patients with OH	17 (34.0%)	11 (57.9%)	6 (19.4%)	0.394
Patients with falls	18 (36.0%)	9 (47.4%)	9 (29.0%)	0.157

Results are reported as average values ± standard deviation (minimum–maximum) or in percentage. *P* value: difference between patients with vs. without Cardiovascular Autonomic Neuropathy

DA dopamine-agonists, *FOG* freezing of gait, *LEDD* levodopa equivalent daily dose, *MoCA* Montreal cognitive assessment, *OH* orthostatic hypotension, *RBD* rapid eye movement sleep behavior disorder, *UPDRS* unified Parkinson's disease rating scale

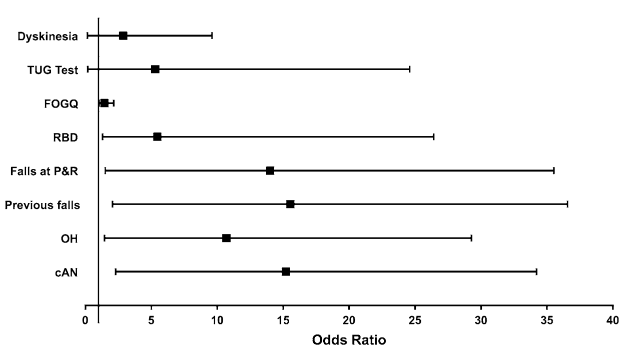

Fig. 1 Factors associated with falls in the entire study cohort. Cardiovascular autonomic neuropathy (cAN), orthostatic hypotension (OH), history of previous falls, positivity of push and release (P&R) test, REM sleep behavior disorder (RBD), and freezing of gait questionnaire (FOGQ) score were associated with risk of falls. *TUG* timed up and go

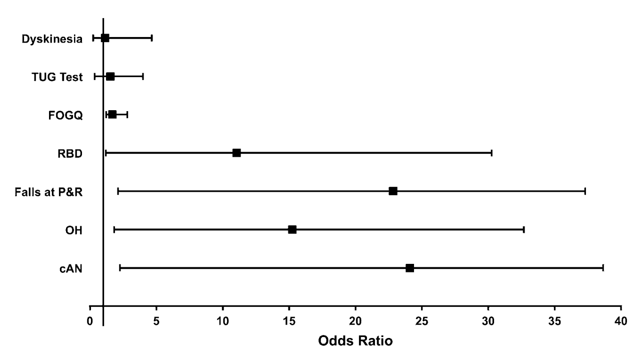

Fig. 2 Factors associated with falls in patients without previous history of falls. Cardiovascular autonomic neuropathy (cAN), orthostatic hypotension (OH), positivity of push and release (P&R) test, REM sleep behavior disorder (RBD) and freezing of gait questionnaire (FOGQ) score were associated with risk of falls in patients without history of previous falls. *TUG* Timed up and go

1.050–2.151; $p = 0.044$). No significant associations were found with the TUG test ($p = 0.389$) and the severity of dyskinesia ($p = 0.471$) (Fig. 1).

These data were confirmed after excluding patients who already had a history of falls at baseline, with a 22.8 greater OR of falls in patients with postural instability at the P&R test (OR 22.832; 95% CI 2.109–37.304; $p = 0.020$), 11 greater OR of falls in patients with RBD (OR 11.056; 95% CI 1.189–30.249; $p = 0.038$), 1.7 greater OR of falls in patients with higher score at the FOGQ (OR 1.690; 95% CI 1.219–2.817; $p = 0.040$). The TUG test ($p = 0.495$) and dyskinesia ($p = 0.699$) continued not to remain associated with falls (Fig. 2).

Discussion

We observed that cAN, as detected by autonomic testing, is independently associated with a 15-fold odds ratio of falls, even after adjusting for age, disease duration, severity of axial symptoms, cognitive impairment, and dopaminergic treatment. The sensitivity of autonomic testing was greater than the simple measurement of orthostatic blood pressure at the laying-to-standing test and, more importantly, significantly superior than every other factor associated with falls in PD, namely history of previous falls, postural instability at the P&R test, freezing of gait, and RBD.

Our data prove relevant when considering that dysautonomia affects up to 30–50% of patients with PD [4], and may occur early in the disease course [21]. However, to what extent cAN may represent an endophenotypic marker of severe disease subtype, associated with greater cognitive impairment and mortality rate [22, 23] and lower quality of life [24], and to what extent it may cause clinical disability by itself, remains to be clarified.

While the association between OH and falls is well recognized as the result of a transient cerebral hypoperfusion due to blood pooling in the lower limbs [5, 25, 26], several evidences suggest a more complex interplaying between postural instability and dysautonomia, that is a complex neuro-mediated disorder not only limited to OH, but also including vasovagal syncope, situational syncope, carotid sinus syndrome, and postprandial hypotension [27, 28].

Our data also confirmed that a positive history of falls is an independent predictor of future falls [1, 5, 6], as well as postural instability at the P&R test [29], FOG severity [5], and RBD. This last finding, in particular, highlights the intimate connection between sleep dysfunction, dysautonomia, and postural instability, as already observed by Romenets et al. [30] who reported a strong association between RBD, falls and systolic BP fall at the laying-to-standing test. To date, few cross-sectional studies evaluated the association between RBD and falls, with conflicting results [30–32]. The only published longitudinal study [33] showed negative results. Therefore, our prospective study is the first one providing evidence that RBD is an independent predictor of falls.

From a pathophysiological standpoint, there is a large overlap in structures involved in OH, RBD, and falls. A cholinergic impairment has been demonstrated both in OH [34] and RBD [35], with an involvement of the pedunculopontine nucleus, which is a critical structure involved in gait and postural stability [36]. Moreover, thalamic and neocortical cholinergic deficits have been associated with RBD and falls [37]. Altogether, these findings confirm the link between cholinergic dysfunction and OH, RBD, and postural stability.

The strength of our conclusions, on the other hand, should be tempered by several limitations. First, the relatively small sample size, which may have influenced the statistical power for some analyses. Second, we did not consider the different causes of falls (i.e., related to or accompanied by syncope, orthostatism, freezing, dual-task, postural instability). Third, we adhered to the widely used definition of PD-associated OH, which relies on a BP drop of 20 mmHg (systolic) or 10 mmHg (diastolic), although other authors suggested a more conservative cutoff of 30 mmHg (systolic) and 15 mmHg (diastolic) [38]. Fourth, RBD was evaluated by the "single question screen" [16], without polysomnographic confirmation.

In sum, our study demonstrated for the first time that cAN, including but not limited to OH, is a strong, independent predictor of falls in PD and, therefore, deserves clinical attention and appropriate therapeutic management. Future research endeavors will need to clarify to what extent early pharmacological and non-pharmacological treatments may reduce falls in PD patients with cAN.

Author Contributions AR: conception and design of the study; acquisition, analysis and interpretation of data; writing of the first draft and review and critique of the manuscript. MZ: conception and design of the study; analysis and interpretation of data; writing of the first draft and review and critique of the manuscript. AM: design of the study; analysis and interpretation of data; review and critique of the manuscript. DC: design of the study; analysis and interpretation of data; review and critique of the manuscript. MS: design of the study; acquisition and interpretation of data; review and critique of the manuscript. EM: design of the study; acquisition and interpretation of data; review and critique of the manuscript. ACA: design of the study; acquisition and interpretation of data; review and critique of the manuscript. FV: design of the study; acquisition and interpretation of data; review and critique of the manuscript. SM: design of the study; analysis and interpretation of data; review and critique of the manuscript. LL: conception and design of the study; analysis and interpretation of data; review and critique of the manuscript. All the co-authors listed above gave their final approval of this manuscript version.

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Compliance with ethical standards

Conflicts of interest Dr Romagnolo has received grant support and speaker honoraria from AbbVie, speaker honoraria from Chiesi Farmaceutici and travel grants from Medtronic, Lusofarmaco and UCB Pharma. Dr Zibetti has received speaker's honoraria from Medtronic, Chiesi Farmaceutici, UCB Pharma, and AbbVie. Dr Merola is supported by NIH (KL2 TR001426) and has received speaker honoraria from CSL Behring, Abbvie, and Cynapsus Therapeutics. He has received grant support from Lundbeck. Dr Canova reports no disclosures. Dr Sarchioto reports no disclosures Dr Montanaro reports no disclosures. Dr Artusi reports no disclosures. Dr Vallelonga reports no disclosures. Dr Maule reports no disclosures. Dr Lopiano has received honoraria for lecturing and travel grants from Medtronic, UCB Pharma and AbbVie.

Data access and responsibility statement A. Romagnolo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical standard The authors declare that they acted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The local institutional review board (Comitato Etico Interaziendale Città della Salute e della Scienza di Torino; Protocol n° 0050175/CEI-715) approved the study and all participants provided written informed consent.

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