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Research Report

# The Degree of Cardiovascular Autonomic Dysfunction is not Different in *GBA*-Related and Idiopathic Parkinson's Disease Patients: A Case-Control Instrumental Evaluation

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**Abstract**.
**Background:** Increased prevalence of cardiovascular autonomic failure might play a key role on Parkinson's disease (PD) progression of glucocerebrosidase gene (*GBA*)-mutated patients, determining a malignant phenotype of disease in these patients.
**Objective:** To objectively characterize, for the first time, the cardiovascular autonomic profile of *GBA*-mutated patients compared to idiopathic PD patients by means of cardiovascular reflex tests (CRTs).
**Methods:** This is a case-control (1 : 2) study on PD patients belonging to well-characterized prospective cohorts. For each PD patient carrying *GBA* variants, two idiopathic PD patients, matched for sex and disease duration at CRTs, were selected. Patients recruited in these cohorts underwent a complete clinical and instrumental evaluation including specific autonomic questionnaires, CRTs and extensive genetic analysis.
**Results:** A total of 23 *GBA*-PD patients (19 males, disease duration 7.7 years) were included and matched with 46 non-mutated PD controls. *GBA*-mutated patients were younger than controls ($59.9 \pm 8.1$ vs. $64.3 \pm 7.2$ years, $p = 0.0257$) and showed a more severe phenotype. Despite *GBA*-mutated patients reported more frequently symptoms suggestive of orthostatic hypotension (OH) than non-mutated patients (39.1% vs 6.5%, $p = 0.001$), the degree of cardiovascular autonomic dysfunction, when instrumentally assessed, did not differ between the two groups, showing the same prevalence of neurogenic OH, delayed OH and cardiovascular reflex impairment (pathological Valsalva maneuver).

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**Conclusions:** *GBA*-PD patients did not show different instrumental cardiovascular autonomic pattern than non-mutated PD. Our findings suggested that symptoms suggestive of OH should be promptly investigated by clinicians to confirm their nature and improve patient care and management.

Keywords: Parkinson's disease, cardiovascular autonomic failure, glucocerebrosidase (GBA) gene mutations, orthostatic hypotension, autonomic dysfunction, case-control study

## INTRODUCTION

The glucocerebrosidase (*GBA*) gene is the most relevant genetic risk factor in the Parkinson's disease (PD) pathogenesis and can influence its clinical course [1]. The *GBA* gene (OMIM*606463) encodes the lysosomal enzyme glucocerebrosidase (GCase), which plays a crucial role in maintaining glycosphingolipid homeostasis [2]. While biallelic pathogenic variants of the gene are associated with Gaucher's syndrome, it is now well-established that monoallelic variants act as risk factor for PD. Indeed, currently heterozygous *GBA* variants are identified in approximately 10% of PD patients worldwide [1]. In a large Italian multicenter study, *GBA* variants were detected in 14.3% of unselected PD patients and in 20.4% of those with early onset [3].

*GBA* pathogenic variant not only increase the risk of developing PD but can also influence the disease phenotype, as, according to existing literature, *GBA*-mutated PD patients have an earlier disease onset, more prevalent non-motor features and a greater risk of cognitive decline than non-mutated PD [4, 5].

Orthostatic hypotension (OH) is one of the non-motor features of PD, and is defined as a sustained reduction of at least 20 mmHg of systolic blood pressure (SBP) and/or 10 mmHg of diastolic blood pressure (DBP) within 3 min of standing or head-up tilt test (HUTT) [6]. OH is the cardinal clinical sign of cardiovascular autonomic failure (i.e., neurogenic OH, nOH), but it may be also due to other factors like medications or dehydration. In PD, OH strongly correlated with reduced survival, as well as with an increased risk of dementia, falls and postural instability [7].

To date, some studies reported prevalence of non-motor symptoms in *GBA*-mutated patients [3, 5, 8], but only a few specifically focused on cardiovascular autonomic failure with conflicting results [5, 8–12]. Most of these studies investigated the presence of symptoms suggestive of OH only by history taking or questionnaires [5, 8, 9, 11], two studies investigating OH by means objective measurement of blood pressure (BP) or HUTT but without differentiate OH from nOH [10, 12].

Increased prevalence of cardiovascular autonomic failure might play a key role on disease progression of *GBA*-mutated patients, determining a malignant phenotype of PD in these patients. In present study we aimed to objectively characterize, for the first time, the cardiovascular autonomic profile of *GBA*-mutated patients compared to idiopathic PD patients by means of cardiovascular reflex tests (CRTs), which represent the gold standard for this purpose [13]. Specific autonomic questionnaires and other clinical investigations were also collected to define in depth the phenotype associated with the presence or absence of cardiovascular autonomic failure.

## MATERIALS AND METHODS

This is a case-control study on PD patients belonging to well-characterized prospective cohorts recruited in our Tertiary Centre: 1st cohort: PD patients included in the Bologna motor and non-motor prospective study on parkinsonism at onset (BoProPark) [14]; 2nd cohort: PD patients included in the prospective cohort of patients with advanced PD screened for device-aided therapies (mainly deep brain stimulation and levodopa/carbidopa intestinal gel infusion).

Patients recruited in these two cohorts underwent a complete clinical and instrumental evaluation including brain MRI, neuropsychological evaluation, psychiatric evaluation, all-night video-polysomnography (VPSG), CRTs and the levodopa response test assessed by the improvement in part III of the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [15]. All patients included in these two cohorts were screened for the major PD-related genes (Supplementary Table 1). For the cohort of patients screened for device-aided therapies only the clinical and instrumental features gathered during the screening inpatients program were considered (data obtained after surgery were not considered).

We retrospectively included all PD patients with pathogenic/likely pathogenic *GBA* variants identified by the genetic analysis who underwent complete CRTs during the disease course.

For each PD patient carrying these variants, two PD patients without pathogenic variants and/or rearrangements in the major PD-related genes (Supplementary Table 1), matched for sex and disease duration at CRTs, were selected.

Clinical data were collected from the medical records in a standardized fashion by a single clinician and entered into an *ad hoc* database for statistical analysis.

Clinical and instrumental features gathered at the time of CRTs were considered.

The following demographic and clinical data were collected: sex, age at CRTs, disease duration at CRTs, disease duration at the last follow-up, predominant phenotype, presence of freezing of gait (FOG), presence of postural instability in OFF medications, levodopa equivalent daily dose (LEDD) [16], symptoms suggestive of OH (dizziness, visual disturbances, neck pain during standing, etc.), occurrence of syncope, urinary frequency/urgency, nocturia, urinary incontinence, hallucination, impulse control disorders.

The levodopa challenge was performed in the morning, using the patient's regular morning dose of levodopa, after a 12 h washout of antiparkinsonian drugs. During levodopa challenge, the MDS-UPDRS- III [15] was calculated in ON and OFF medications conditions along with levodopa response, as follows: [("OFF" medications MDS-UPDRS III score – "ON" medications MDS-UPDRS III score)/ "OFF" medications MDS-UPDRS III score] $\times 100$. Levodopa-induced somnolence and Hohn & Yahr (HY) stage [17] were also collected.

In the cohort of patients screened for device-aided therapies for advanced PD, MDS-UPDRS I, II and IV [15] were systematically collected.

An extensive neuropsychological evaluation was performed including Mini-Mental State Examination [18] and the Brief Mental Deterioration Battery along with its final results [19, 20]. Mild Cognitive Impairment in PD (PD-MCI) was defined according to the Movement Disorder Society Task Force guidelines [21].

*Autonomic evaluation*

The Scale for Outcomes in Parkinson's Disease – Autonomic (SCOPA-AUT) questionnaire [22] was gathered in both cohorts. The SCOPA-AUT is a self-report questionnaire of 25 items evaluating the autonomic functions. Each item consists of a single question assessing the frequency of the symptom in the previous month, with four response options (0 = never; 1 = sometimes; 2 = regularly; 3 = often). Total score for each domain is calculated by summing the corresponding item scores.

In the cohort of patients screened for device-aided therapies for advanced PD, Composite Autonomic Symptom Score-31 (COMPASS-31) scale [23] was systematically performed. COMPASS 31 is a self-assessment instrument including 31 items assessing six domains of autonomic functions: orthostatic intolerance, 4 items; vasomotor, 3 items; secretomotor, 4 items; gastrointestinal, 12 items; bladder, 3 items; pupillomotor, 5 items. The scoring system consists in calculating the raw domain scores which are derived by adding the points obtained for the questions comprised in each domain. The final domain scores are generated by multiplying the raw score with a weight index. The total score is the sum of all domain scores and ranges from 0 (normal) to 100 (the worst condition).

CRTs were performed in the morning, starting at 8 : 00 a.m. for all subjects, in a temperature-controlled clinical investigation room ($23 \pm 1^{\circ}$C), according to standardized procedures [24, 25]. Subjects had been drug-free overnight and those on prolonged-release dopaminergic agents discontinued them for the necessary amount of time to allow proper washout. Subjects were allowed to have a light breakfast avoiding coffee and tea and refraining from smoking. Before starting CRTs, a standing test was performed by the specialized technician attending the laboratory, who also enquired about symptoms of OH during this test. CRTs were performed under audio and video-polygraphic monitoring (ANScovery Modular System, SparkBio Srl, Bologna, Italy). The following parameters were monitored continuously: beat to beat BP (Finometer Midi, Finapres Medical Systems, Amsterdam, The Netherlands), EKG, oronasal and abdominal breathing. The ANScovery software was used to visualize, store, and analyze the data, providing a final report. After 30 min of supine rest, the following tests were performed: HUTT: 10 min at 65°; Valsalva maneuver (VM): forced expiratory pressure of 40 mmHg maintained for 15 s; deep breathing (DB): 6 breaths/min; cold face (CF): cold stimulus on forehead for 1 min; sustained handgrip tests (HG): 1/3 of maximal effort for 5 min. An adequate period of rest was allowed to reach basal BP and

heart rate (HR) values in-between investigations. A specialized technician and an external device tutor monitor guided and supported subjects during the execution. The correct execution was checked automatically by an electronic device and by a specialized technician.

The following parameters were calculated: 1) basal SBP, DBP and HR as the mean value of the last 5 min of supine rest preceding HUTT; 2) response to HUTT as the difference ($\Delta$) between SBP, DBP and HR values at 3 and 10 min compared to basal; 3) Valsalva ratio (VR) = HR phase II/HR phase IV of VM (pathological if VR < 1.25); 4) presence of SBP recovery in late phase II of VM ($\Delta$ SBP IIb-IIa) = max SBP late phase II – min SBP early phase II (pathological if $\Delta$ SBP IIb-IIa < 2 mmHg); 5) presence of overshoot in phase IV of VM = max SBP phase IV (within 20 s after the strain release) – mean basal SBP; 6) Pressure recovery time (PRT) = time for SBP to recover from phase III back to basal [26]; 7) IE during DB: average of the 10 shortest RR intervals during inspiration/average of the 10 longest RR during expiration; 8) sinus arrhythmia during DB ($\Delta$IE) = average of the 10 shortest R-R intervals during inspiration - average of the 10 longest R-R during expiration (pathological $\Delta$IE during DB if $\Delta$IE < 9); 9) response to CF as $\Delta$ compared to basal values of SBP, DBP and HR within 1 min of cold stimulus; 10) response to HG as $\Delta$ compared to basal values of SBP, DBP and HR after 5 min of isometric effort.

Pathological VM was defined in the absence of overshoot in phase IV. OH was defined according to consensus criteria [6] and, when associated with absence of overshoot at the VM, was classified as nOH, while as non-nOH in case of normal VM.

Supine hypertension was defined as SBP $\geq$140 mmHg and/or DBP $\geq$90 mmHg, measured after at least 5 min of rest in the supine position [27].

*Genetic analysis*

All patients included in the study underwent next-generation sequencing (NGS) using a targeted panel comprising 19 genes associated with PD and parkinsonism (Supplementary Table 1). Exon rearrangements were assessed via Multiplex-Ligation Probe Amplification (MLPA) using Salsa MLPA Probemix P051-D2 or P052 Parkinson (MRC-Holland, Amsterdam, Netherlands), following the manufacturer's instructions. Furthermore, to prevent false negatives for *GBA* variants resulting from reads misalignment on the *GBAP1* pseudogene, we applied an *ad hoc* NGS amplicon-based method using long-range PCR. The entire *GBA* gene was initially amplified using a single LR-PCR (6kb) and subsequently sequenced using NGS methods. A customized bioinformatics pipeline, which included the masking of the pseudogene *GBAP1*, was also applied. Identified variants were validated by Sanger sequencing through the amplification of the gene in three overlapping fragments using specific primer pairs for *GBA* only, avoiding the pseudogene [28]. Variants were classified into 5 classes (mild, severe, complex, risk, and unknown) as previously reported [29].

*Ethics statement*

The study was conducted in agreement with the principles of good clinical practice. Study protocols were approved by the Local Ethics Committee of the local health service of Bologna, Italy (Cod. CE: 09070 and 18005). All patients gave their written informed consent to study participation.

*Statistical analysis*

The normality of the distribution of the continuous parameters was checked with the Skewness-Kurtosis test, and variables were expressed as the mean $\pm$ SD or median and interquartile range (IQR) when appropriate. We performed the *t* test or Wilcoxon rank-sum test to compare continuous variables, as appropriate. Categorical variables were described by their absolute or relative frequencies and compared by use of the $\chi^2$ test. A value of $p < 0.05$ (2 sided) was considered significant. Statistical analyses were performed with STATA statistical software, version 17.0.

## RESULTS

*Clinical and instrumental data*

A total of 23 PD patients with pathogenic/likely pathogenic *GBA* variants (Supplementary Table 2) at the genetic analysis were included (19 males and 4 females, disease duration at CRTs = 7.7 $\pm$ 3.1 years). Among *GBA*-PD subjects, 5 (21.7%) patients carried severe variants, 6 (26.1%) mild variants and 8 risk alleles (34.8%). In 4 (17.4%) patients, the severity of the variants could not be assessed (unknown variants) (Supplementary Table 2).

These 23 patients were matched with 46 non-mutated PD controls. *GBA*-mutated patients were younger than controls (59.9 $\pm$ 8.1 vs. 64.3 $\pm$ 7.2

Table 1
Demographic and clinical characteristics of the study sample

| | Total PD sample 69 | *GBA*-mutated group 23 | Non-mutated group 46 | *p* |
|---|---|---|---|---|
| **Sex** | | | | |
| Male, *n* (%) | 57 (82.6) | 19 (82.6) | 38 (82.6) | 1.000 |
| Female, *n* (%) | 12 (17.4) | 4 (17.4) | 8 (17.4) | |
| **Age, y** | 62.8 ± 7.7 | 59.9 ± 8.1 | 64.3 ± 7.2 | **0.0257** |
| **Disease duration at CRTs, y** | 7.7 ± 3.2 | 7.7 ± 3.1 | 7.7 ± 3.3 | 1.000 |
| **Disease duration at last follow-up**, *y* | 11.7 ± 3.6 | 11.1 ± 4.1 | 12.0 ± 3.4 | 0.315 |
| **Died** | | | | |
| Yes, *n* (%) | 5 (7.3) | 0 (0.0) | 5 (10.9) | 0.101 |
| No, *n* (%) | 64 (92.7) | 23 (100.0) | 41 (89.1) | |
| **Clinical features** | | | | |
| Phenotype | | | | 0.494 |
| Tremor-dominant, *n* (%) | 31 (44.9) | 9 (39.1) | 22 (47.8) | |
| Akinetic-rigid-dominant, *n* (%) | 38 (55.1) | 14 (60.9) | 24 (52.2) | |
| FOG, *n* (%) | 26 (37.7) | 10 (43.5) | 16 (34.8) | 0.482 |
| Postural Instability in OFF medications, *n* (%) | 15 (21.7) | 6 (26.1) | 9 (19.6) | 0.536 |
| Symptoms suggestive of OH, *n* (%) | 12 (17.4) | 9 (39.1) | 3 (6.5) | **0.001** |
| Syncope, *n* (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1.000 |
| Urinary Urgency / Frequency, *n* (%) | 44 (63.8) | 13 (56.5) | 31 (37.4) | 0.376 |
| Nocturia, *n* (%) | 28 (40.6) | 12 (52.2) | 16 (34.8) | 0.165 |
| Urinary Incontinence, *n* (%) | 12 (17.4) | 4 (17.4) | 8 (17.4) | 1.000 |
| Hallucination, *n* (%) | 1 (1.45) | 1 (4.4) | 0 (0.0) | 0.154 |
| Impulse Control Disorder, *n* (%) | 12 (17.4) | 5 (21.7) | 7 (15.2) | 0.500 |
| **LEDD**, *mg* | 725 (505–990) | 725 (500–990) | 722.5 (505–1040) | 0.846 |
| **Sleep disorders** | | | | |
| Clinical history of RBD, *n* (%) | 32 (46.4) | 12 (52.2) | 20 (43.5) | 0.495 |
| VPSG-confirmed RBD[1], *n* (%) | 25 (36.2) | 9 (39.1) | 16 (34.8) | 0.700 |
| Habitual snoring, *n* (%) | 30 (43.5) | 8 (34.8) | 22 (47.8) | 0.492 |
| OSAS (apnea-hypopnea episodes per hour of sleep > 10), *n* (%) | 6 (8.7) | 2 (8.7) | 4 (8.7) | 1.000 |
| **Levodopa challenge** | | | | |
| OFF MDS-UPDRS III | 41.8 ± 16.1 | 45.1 ± 17.5 | 40.2 ± 13.6 | 0.248 |
| ON MDS-UPDRS III | 23.6 ± 9.6 | 23.5 ± 9.8 | 23.6 ± 9.5 | 0.966 |
| Levodopa response, % | 46.2 ± 14.5 | 46.6 ± 16.6 | 45.9 ± 13.4 | 0.865 |
| Levodopa-related somnolence, *n* (%) | 9 (13.0) | 9 (39.1) | 0 (0.0) | **< 0.001** |
| **Scales** | | | | |
| HY | 2 (2–2.5) | 2 (2–2.5) | 2 (2–2.5) | 0.257 |
| MDS-UPDRS I[2] | 9.7 ± 4.1 | 9.7 ± 3.8 | 9.7 ± 4.3 | 0.963 |
| MDS-UPDRS II[2] | 13.6 ± 5.0 | 13.8 ± 4.5 | 13.4 ± 5.3 | 0.839 |
| MDS-UPDRS IV[2] | 7 (4.0–9.5) | 8 (3.5–9) | 6.5 (4.0–10) | 0.890 |
| COMPASS-31 scale score[2] | | | | |
| Orthostatic | 0 (0–12) | 4 (0–16) | 0 (0–0) | 0.058 |
| Vasomotor | 0 (0–1.8) | 0 (0–0) | 0 (0–2) | 0.3115 |
| Secretomotor | 2.1 (0–4.3) | 0 (0–4.3) | 2.1 (0–4.3) | 0.469 |
| Gastrointestinal | 5.4 (3.4–8.0) | 4.5 (0.9–7.1) | 6.2 (4.0–8.0) | 0.3857 |
| Bladder | 0.6 (0–2.2) | 1.1 (0–3.3) | 0 (0–2.2) | 0.272 |
| Pupillomotor | 1.0 (0.0–2.0) | 1.0 (1.0–3.0) | 1.0 (0.0–2.0) | 0.163 |
| Total score | 14.6 (8.2–21.2) | 16.9 (8.4–25.8) | 14.1 (8.0–20.0) | 0.548 |
| SCOPA-AUT | 13.5 (9.0–19.0) | 14.0 (10.0–17.0) | 13.0 (8.0–19.0) | 0.536 |

Data are expressed as mean ± standard deviation or median (interquartile range). [1]54 patients underwent VPSG; [2] Performed only in the cohort of patients screened for device-aided therapies for advanced PD ($n = 63/69$); COMPASS-31, Composite Autonomic Symptom Score-31; CRTs, Cardiovascular Reflex Tests; FOG, Freezing of gait; *GBA*, glucocerebrosidase gene; HY, Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorders Society—Unified Parkinson's Disease Rating Scale; *n*, sample size; OH, Orthostatic hypotension; OSAS, Obstructive Sleep Apnea Syndrome; PD, Parkinson's disease; RBD, REM sleep behavior disorder; SCOPA-AUT, Scale for Outcomes in Parkinson's Disease – Autonomic; VPSG, all-night video-polysomnography; *y*, years. Statistically significant *p*-values are denoted in bold ($p$ value $\leq 0.05$).

years, $p = 0.0257$). Comparisons between groups are shown in Table 1. The *GBA* group more frequently reported symptoms suggestive of OH (39.1% vs 6.5%, $p = 0.001$), when compared to the non-

mutated PD group, but without reporting syncope during disease duration. There were no other differences in other clinical features and LEDD. However, *GBA*-mutated patients showed more frequently akinetic-rigid phenotype, FOG, postural instability in OFF medications, urinary urgency/frequency and nocturia than non-mutated PD, without reaching a significance.

Concerning sleep disorders, history of RBD was reported by 32 (46.4%) of 69 patients. Overall, 54 patients underwent VPSG. Among the 32 patients reporting history of RBD, VPSG was performed in 29 patients and RBD was confirmed in 25 patients. Prevalence of both history of RBD and VPSG-confirmed RBD was similar between groups. All patients reporting habitual snoring underwent VPSG. There were no differences in snoring and OSAS (apnea-hypopnea episodes per hour of sleep $>10$) prevalence between groups (Table 1).

At levodopa challenge test, no differences between groups in MDS-UPDRS III score in OFF and ON conditions or levodopa response were found. However, a high occurrence of levodopa-induced somnolence was documented in *GBA* patients and not in the control group (39.1% vs. 0.0%, $p<0.001$).

Comparing scale scores between groups, no differences were found in HY, MDS-UPDRS I, MDS-UPDRS II, and MDS-UPDRS IV.

The scores of the neuropsychological evaluation were within normal limit without differences between groups (Supplementary Table 3). The *GBA*-mutated group showed a longer time of execution of Stroop test than the non-mutated group, but without reaching significance. Moreover, despite not statistically significant, a higher percentage of PD-MCI was diagnosed among *GBA* patients respect to non-mutated PD patients (26.1% vs. 17.4%, $p=0.318$).

*Autonomic questionnaires and testing*

The total score of SCOPA-AUT and COMPASS-31 were similar between groups. Concerning analysis of single domains, the *GBA*-mutated patients showed higher score in orthostatic domain at COMPASS-31 scale but without reaching a significance (Table 1).

Results of CRTs are reported in Table 2. OH was documented in 6/69 (8.7%) patients of the study sample, 1/23 (4.4%) of the *GBA*-mutated group and 5/46 (10.9%) of the non-mutated group. Among these, nOH (i.e., associated with absence of overshoot at VM) was found in 3/69 (4.4%) patients (one *GBA*-mutated subject and two non-mutated subjects) while non-nOH (i.e., associated with a normal VM) was found in 3/69 (4.4%) patients (three non-mutated subjects).

Delayed OH was found in 4/69 (5.8%) patients, 1/23 (4.4%) in the *GBA*-mutated group and 3/46 (6.5%) in the non-mutated group. In two patients delayed OH was associated with a pathological VM (two non-mutated subjects) and in two patients with a normal VM (one *GBA*-mutated patient and one non-mutated patient). No differences were found between groups in presence of OH, nOH, non-nOH, and delayed OH (Table 2). Hypertension in supine position was documented in 27/69 (39.1%) of patients, without difference between *GBA*-mutated and non-mutated groups (34.8% vs. 41.3%, $p=0.601$). Only in two patients supine hypertension was associated with nOH (one *GBA*-mutated patient and one non-mutated patient).

Overall, 13/69 (18.8%) patients had a pathological VM (absence of overshoot), 4 (17.4%) in the *GBA*-mutated group and 9 (19.6%) in the non-mutated group ($p=0.960$); 10/13 (14.5%) patients had pathological VM without OH, without differences between *GBA*-mutated and non-mutated groups. Furthermore, two patients had pathological VM with delayed OH. Concerning pathological VR, no difference was found between *GBA* group and controls (13.0% vs. 19.6%, $p=0.601$) (Table 2). Nine patients showed pathological SBP IIb – SBP II despite normal overshoot, this characteristic was more prevalent in the non-mutated group than in *GBA*-mutated one, but without reaching a significance (17.4% vs. 4.4% respectively, $p=0.129$). PRT, index of adrenergic failure, was similar between the two groups. Prevalence of abnormal $\Delta$IE at DB test was 36.2% and did not significantly differ between groups (26.1% in *GBA*-group vs. 41.3% in non-mutated group, $p=0.215$). Concerning cardiovascular reflex test parameters, no differences between groups were found.

## DISCUSSION

This case-control study describes the cardiovascular autonomic profile by means of CRTs of *GBA*-mutated patients compared with matched non-mutated PD patients (1 *GBA*-mutated: 2 non-mutated PD patients).

The main finding of the study is that, despite *GBA*-mutated patients reported symptoms suggestive of OH more frequently than non-mutated patients, the degree of cardiovascular autonomic dysfunction,

Table 2
Cardiovascular reflex test parameters obtained during the first diagnostic workup in the study sample

| | Total PD sample 69 | *GBA*-mutated group 23 | Non-mutated group 46 | *p* |
|---|---|---|---|---|
| **HUTT** | | | | |
| Supine Hypertension, *n* (%) | 27 (39.1) | 8 (34.8) | 19 (41.3) | 0.601 |
| OH, *n* (%) | 6 (8.7) | 1 (4.4) | 5 (10.9) | 0.365 |
| nOH, *n* (%) | 3 (4.4) | 1 (4.4) | 2 (4.4) | 0.273 |
| Non-nOH, *n* (%) | 3 (4.4) | 0 (0.0) | 3 (6.5) | |
| Delayed OH, *n* (%) | 4 (5.8) | 1 (4.4) | 3 (6.5) | 0.716 |
| Delayed OH with pathological[1] VM, *n* (%) | 2 (2.9) | 0 (0.0) | 2 (4.4) | 0.248 |
| Delayed OH with normal VM, *n* (%) | 2 (2.9) | 1 (4.4) | 1 (2.2) | |
| Supine rest SBP, mmHg | 137.8 ± 23.6 | 138.0 ± 19.9 | 137.7 ± 25.5 | 0.966 |
| Supine rest DBP, mmHg | 74.7 ± 9.3 | 74.4 ± 8.9 | 74.8 ± 9.6 | 0.871 |
| Supine rest HR, bpm | 68.2 ± 12.7 | 69.1 ± 12.8 | 67.8 ± 12.8 | 0.677 |
| Δ 3min SBP, mmHg | –3.6 ± 13.2 | –2.7 ± 12.2 | –4.0 ± 13.8 | 0.693 |
| Δ 3min DBP, mmHg | 4.1 ± 7.3 | 5.0 ± 7.2 | 3.7 ± 7.3 | 0.487 |
| Δ 3min HR, bpm | 11.4 ± 7.4 | 12.1 ± 7.8 | 11.0 ± 7.2 | 0.569 |
| **Valsalva Manoeuvre** | | | | |
| Overshoot, mmHg | 17.6 ± 13.4 | 16.7 ± 12.8 | 18.0 ± 13.8 | 0.755 |
| Pathological[1] VM, *n* (%) | 13 (18.8) | 4 (17.4) | 9 (19.6) | 0.960 |
| Pathological[1] VM with OH, *n* (%) | 3 (4.4) | 1 (4.4) | 2 (4.4) | 0.913 |
| Pathological[1] VM without OH, *n* (%) | 10 (14.5) | 3 (13.0) | 7 (15.2) | |
| Pathological[1] VM with delayed OH, *n* (%) | 2 (2.9) | 0 (0.0) | 2 (4.4) | 0.255 |
| VR < 1.25, *n* (%) | 12 (17.4) | 3 (13.0) | 9 (19.6) | 0.601 |
| Δ SBP IIb-IIa, mmHg | 4.0 (0.0–10.0) | 3.0 (0.0–12.0) | 5.5 (0.0–10.0) | 0.793 |
| Pathological Δ SBP IIb-IIa[2], *n* (%) | 21 (30.4) | 5 (21.7) | 16 (34.8) | 0.369 |
| Pathological Δ SBP IIb-IIa[2] without pathological VM[1], *n* (%) | 9 (13.0) | 1 (4.4) | 8 (17.4) | 0.129 |
| PRT, msec | 2963 (2032–4868) | 2873 (1990–3344) | 3471 (2053–5800) | 0.215 |
| **Deep breathing** | | | | |
| IE | 1.20 ± 0.15 | 1.23 ± 0.19 | 1.19 ± 0.13 | 0.411 |
| ΔIE, bpm | 12.0 (7.0–16.0) | 12.0 (8.0–17.0) | 10.0 (7.0–15.0) | 0.339 |
| Pathological ΔIE during DB[3], *n* (%) | 25 (36.2) | 6 (26.1) | 19 (41.3) | 0.215 |
| **Cold Face** | | | | |
| Δ SBP, mmHg | 19.0 (11.0–25.0) | 14.0 (7.0–25.0) | 19.0 (12.0–24.5) | 0.394 |
| Δ DBP, mmHg | 9.0 (5.0–14.0) | 8.0 (4.0–13.0) | 9.5 (7.0–14.0) | 0.351 |
| Δ HR, bpm | –4.0 (–8.0 – –2.0) | –4.0 (–8.0 – –2.0) | –4.0 (–8.0 – –2.0) | 0.937 |
| **Handgrip** | | | | |
| HG Δ SBP, mmHg | 22.3 ± 9.9 | 23.6 ± 11.7 | 21.8 ± 9.0 | 0.504 |
| HG Δ DBP, mmHg | 13.2 ± 6.6 | 12.9 ± 6.2 | 13.3 ± 6.9 | 0.849 |
| HG Δ HR, bpm | 13.7 ± 7.5 | 14.3 ± 8.3 | 13.5 ± 7.2 | 0.697 |

Data are expressed as mean ± standard deviation or median (interquartile range). Δ, change compared to basal values; ΔHR, change in heart rate; [1]Pathological VM, Absence of overshoot at Valsalva Maneuver; [2]Pathological Δ SBP IIb-IIa, Δ SBP IIb-IIa < 2 mmHg; [3]Pathological ΔIE during DB, ΔIE < 9; bpm, beats per minute; DB, deep breathing; DBP, diastolic blood pressure; *GBA*, glucocerebrosidase gene; HG, handgrip; HR, heart rate; HUTT, head-up tilt test; SBP, systolic blood pressure; PD, Parkinson's disease; PRT, pressure recovery time; VM, Valsalva Maneuver; VR, Valsalva ratio; IE, average of the 10 shortest RR intervals during inspiration/ average of the 10 longest RR during expiration. Statistically significant *p*-values are denoted in bold ($p$ value $\leq 0.05$).

when instrumentally assessed with gold standard evaluation, i.e. standardized CRTs, did not differ between the two groups, showing the same prevalence of nOH, delayed OH and cardiovascular reflex impairment (pathological VM). Indeed, according to consensus criteria, diagnosis of OH required objective measurement [6].

The discrepancy between clinical history of symptoms suggestive of OH and CRTs results may be due to different causes. First, questionnaires investigating OH symptoms could be useful for OH screening but are not recommended for diagnosis, and inconsistency between questionnaires and objective evaluation has been frequently observed [13, 30, 31]. Second, the presence of OH could be over- or underestimated when based only on clinical history. On one side, different symptoms (fatigue, instability, somnolence, transient OH) may be interpreted as OH on history taking, and, on the other side, a proportion of patients are asymptomatic despite substantial SBP falls and low orthostatic BP [32]. Third, orthostatic dizziness could be also related to the dysfunction of

vestibulo-sympathetic reflex, which includes multiple pathways stimulated by vestibular activation and associated with sympathetic or parasympathetic outflows, resulting in respiratory and cardiovascular (BP and HR) changes [33, 34]. This dysfunction was not instrumentally evaluated in the present study. Finally, levodopa could play a role in causing or worsening hypotension in both supine and orthostatic conditions. However, a recent study showed a higher risk of developing levodopa-induced OH and orthostatic symptoms in patients with an underlying cardiovascular autonomic dysfunction [35], and in the present study no difference emerged in rate of cardiovascular autonomic dysfunction between *GBA*-mutated and non-mutated PD patients.

Overall, our findings suggested that symptoms suggestive of OH should be promptly investigated by clinicians to confirm their nature and improve patient care and management.

In literature, different studies reported a more prominent subjective autonomic dysfunction in *GBA*-mutated patients compared to non-mutated PD. A higher prevalence of sexual dysfunction and constipation was reported in the first group in one study [8]. One recent multicenter Italian study on large PD sample compared autonomic symptoms including OH, urge- incontinence, erectile dysfunctions (in males), profuse sweating, and tachycardia between *GBA*-mutated and non-mutated PD patients showing higher rate of these symptoms in the first group [63/117 (53.8%) vs. 267/618 (43.2%), $p = 0.0338$] [3]. Another study found that carriers showed more frequently nonmotor symptoms (such as cognitive dysfunction, psychosis, and OH) as well as non-levodopa responsive motor symptoms (such as dysphagia and freezing of gait) [5]. Cross-sectional analysis of clinical features and of neuroimaging (brain perfusion and DAT density) strengthen the hypothesis of a more extensive brain synucleinopathy in *GBA* carriers, suggesting the involvement not only of neocortical areas (increasing the risk for dementia and psychosis), but also of subcortical regions and even the spinal cord (increasing the risk for OH) [5].

Concerning only symptoms suggestive of OH or prevalence of OH, few studies focused on this topic, reporting conflictual and inconclusive results. Disagreement in results may be a consequence of differences in design (retrospective vs. prospective studies, cohort vs. case-control studies), sample size, population characteristics, disease duration (< 5 years in some studies and > 10 years in others), method used to assess OH (clinical history, questionnaires, BP measurements or HUTT) and OH definition (OH vs. nOH).

Only one study, focusing on cognitive impairment in *GBA*-mutated patients, detected OH prevalence by means of HUTT showing no difference between groups [1/5 (20.0%) in carriers vs. 21/117 (17.9%) in non-carriers, $p = 0.93$) [10]. These findings are in line with our results, although were performed in a smaller sample of *GBA* patients and did not differentiate the neurogenic or non-neurogenic nature of OH.

In 3 studies the presence of symptoms suggestive of OH was based on history taking: in the first study on one large PD cohort, no difference in OH prevalence was found between 34 *GBA*-PD and 843 idiopathic PD (26.5 vs 26.2%, $p = 0.907$) [8]; in the second study, comparing 34 *GBA* mutation-positive and 113 *GBA* mutation-negative PD patients, no difference in rate of OH was found [5/34 (14.7%) vs. 21/113 (18.6%), $p = 0.798$] [11]; in the third study data on 2764 PD patients were retrospectively collected and a higher prevalence of OH at the last follow-up was found in carriers than in non-carriers [12/65 (18.5%) vs. 89/840 (10.6%), respectively] with an adjusted odd ratio of 2.61 (95% CI: 1.3–5.2, $p = 0.007$) [5].

One study evaluated autonomic symptoms though items 9–12 scores (orthostatic, urinary, sexual, and bowel function) of the Unified Multiple System Atrophy Rating Scale. In this study, on 20 *GBA*-PD and 20 sporadic PD, the severity of orthostatic symptoms item was more prominent in the first group than in the second one [1.00 (0–3) vs. 0.00 (0–1), $p = 0.001$] [9].

Systematic measurements of BP were carried out in a prospective analysis of 33 *GBA*-PD and 313 idiopathic PD patients: SBP upon changing from the supine to the upright position dropped more strongly in *GBA*-PD compared to idiopathic PD patients while DBP and HR did not differ between groups [12].

The cardiovascular pattern on CRTs showed no difference between *GBA*-mutated and non-mutated PD in our study. One recent study evaluating the cardiovascular autonomic control, through the analysis of Heart Rate Variability (HRV), at rest and during orthostatic challenge, in 15 idiopathic PD, 15 *GBA*-PD and 15 healthy controls, found a greater impairment of the parasympathetic component in the *GBA*-PD group [36]. However, this study analyzed only HRV in supine position and during active standing without evaluation of the cardiovascular responses to VM, DB and HUTT [13]. According to the Consensus Statement on Electrodiagnostic

assessment of the autonomic nervous system [13], HRV alone is not adequate to evaluate an impairment of the sympathetic and parasympathetic nervous systems.

Disease duration could influence results in cardiovascular dysautonomia. In our study, the disease duration was $7.7 \pm 3.2$ years and *GBA*-mutated patients were matched with non-mutated patients.

Case-control or cohort studies with longer mean disease duration (10–12 years) reported higher OH prevalence or severity [5, 9], while one study with shorter mean disease duration (4 years) did not find a difference between groups [8]. In line with this hypothesis, the study on HRV in 15 *GBA*-PD and 15 idiopathic PD showed that cardiovascular autonomic dysfunction in PD patients was associated with longer disease duration [36].

Another factor that could play a role in *GBA* disease severity and progression is the type of *GBA* variants. The clinical diagnoses in *GBA*-mutated patients ranged from PD to a phenotype characteristic of Lewy bodies dementia, and single cases with atypical manifestations similar to multiple system atrophy were also reported [37, 38].

Three clinical types of Gaucher Disease, a lysosomal storage disorder, are reported: non-neuropathic (type I); acute neuropathic (type II); and chronic neuropathic (type III). Accordingly, *GBA* mutations have been categorized as mild or severe: mild mutations are those that cause Gaucher Disease type I, and severe mutations are those causing Gaucher Disease types II and III [39]. Concerning genotype-phenotype correlations, mutations causing a more severe Gaucher Disease phenotype (e.g., p.L444P) seem to be associated with an increased PD risk, earlier age at onset, and greater cognitive dysfunction compared to less severe mutations (e.g., p.N370S) [40, 41].

This genotype-phenotype correlations could influence also autonomic involvement (with severe and complex variants resulting in worse cardiovascular regulation than mild and risk ones), but studies on this topic are lacking. Only one study on a large sample evaluated dysautonomia, without specifying data on OH, among carriers of distinct *GBA* classes of variants (complex vs. severe vs. mild vs. risk) showing no differences among groups (64.3 vs. 44.1 vs. 60.0 vs. 66.7%, respectively) [3]. In our study, the small sample size of each *GBA*-variant subgroups has prevented stratification analysis and limited the genotype-phenotype correlations so far.

To note, the analysis of clinical and instrumental features in these well-characterized cohorts of patients suggests that levodopa-induced somnolence is a hallmark feature of *GBA*-mutated patients (39.1% vs. 0%). This clinical feature is not related to differences in prevalence of sleep disorders (RBD, OSAS and snoring), disease severity or LEDD between groups, and could impact the clinical practice and therapeutic strategies in *GBA*-PD patients. Moreover, *GBA*-mutated patients presented an earlier disease onset and more frequently showed akinetic-rigid phenotype, FOG, postural instability in OFF medications, urinary urgency/frequency, nocturia and PD-MCI than non-mutated PD. Despite these clinical features did not reach statistical significance, these results, in line with previous studies [5, 29, 42], describe a more severe disease in these patients, characterized by worse axial, cognitive and urinary features.

The strengths of our study are the recruitment of two well-characterized prospective cohorts with a systematic and extensive clinical and instrumental evaluation including CRTs, which represent the gold standard for the characterization of cardiovascular autonomic profile, along with questionnaires, brain MRI, neuropsychological evaluation, psychiatric evaluation, VPSG, levodopa response test and genetic analysis. Moreover, all patients were diagnosed and followed in a single center, ensuring uniformity of data, RBD and OSAS were diagnosed by VPSG, cardiovascular autonomic pattern was documented by history taking, questionnaires and CRTs.

The study's main limitation is the small sample size, which has prevented stratification for disease duration or *GBA* variants. However, the rate of *GBA* patients reflects the prevalence expected in the sample size of the two cohorts recruited for this study (23 *GBA*-mutated patients in 213 PD patients, 10.8%).

Further analyses including instrumental evaluation, on larger samples, and probably with a multicenter nature, are required to confirm our results, and to evaluate the role of disease duration and *GBA* variants in the cardiovascular pattern of this subgroup of patients. Moreover, advanced neuroimaging and postmortem neuropathological studies should also be carried out to confirm the presence and determine the burden of synucleinopathy (Lewy Bodies pathology) in *GBA* carriers.

In conclusion, *GBA*-PD patients did not show different cardiovascular autonomic pattern than non-mutated PD. Therefore, considering that OH in PD strongly correlated with reduced survival and with increased risk of dementia, falls and postural instability [7], our results suggest that *GBA*-PD patients,

from a cardiovascular point of view, did not show autonomic instrumental markers suggestive of an aggressive phenotype.

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## CONFLICT OF INTEREST

Outside the present work, GC-B has received honoraria for speaking engagements or consulting activities from Abbvie and Zambon. The remaining authors have no conflict of interest to report.

## DATA AVAILABILITY

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JPD-230334.

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