

Serum Norepinephrine, Chromogranin A, and Orexin A in Parkinson Disease With Orthostatic Hypotension: A Cross-Sectional Study

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Abstract

Purpose

To compare serum chromogranin A, norepinephrine, and orexin A concentrations in patients with Parkinson disease with and without orthostatic hypotension and to examine their associations with autonomic and sleep-related measures.

Methods

This single-center cross-sectional study included 118 patients with Parkinson disease, of whom 63 had orthostatic hypotension and 55 did not. Blood pressure was measured after supine rest and at one and three minutes after standing. Motor severity, disease stage, non-motor symptoms, autonomic symptoms, nocturnal sleep problems, and daytime sleepiness were assessed using validated clinical scales. Serum biomarkers were measured by enzyme-linked immunosorbent assay. Group comparisons, correlation analyses, and exploratory receiver operating characteristic analyses were performed.

Results

Chromogranin A concentrations were lower in the orthostatic hypotension group than in the group without orthostatic hypotension (1436 ± 322 versus 1907 ± 971 nanograms per liter; $p = 0.034$), as were orexin A concentrations (402 ± 115 versus 544 ± 410 nanograms per liter; $p = 0.030$). Norepinephrine concentrations did not differ significantly. Motor examination, autonomic symptom, and Hoehn and Yahr stage scores were higher in the orthostatic hypotension group. Orexin A was not associated with subjective sleep measures but showed weak inverse associations with autonomic symptom and motor examination scores. All evaluated markers had limited discrimination for orthostatic hypotension.

Conclusion

Lower serum chromogranin A and orexin A were associated with orthostatic hypotension in Parkinson disease, whereas resting norepinephrine was not. These biomarkers remain investigational and should not replace standardized orthostatic blood pressure testing.

Introduction

Parkinson disease (PD) is characterized by both motor and non-motor manifestations. Autonomic dysfunction and sleep disturbances are common non-motor features and may have a substantial effect on quality of life [1]. Orthostatic hypotension (OH) affects approximately one-third of patients with PD in pooled analyses and is associated with syncope, falls, functional impairment, and increased clinical complexity [2, 3].

The pathophysiology of autonomic dysfunction in PD extends beyond nigrostriatal dopamine loss. Degeneration of non-dopaminergic systems, including central and peripheral noradrenergic pathways, may contribute to impaired cardiovascular regulation [3, 4]. The locus coeruleus is the major central noradrenergic nucleus and participates in arousal, attention, blood pressure regulation, and autonomic control; it is also affected during PD neurodegeneration [5].

Chromogranin A (CgA) is co-stored and co-released with catecholamines and has been investigated as a relatively stable marker of sympathoadrenal secretory activity. Lower cerebrospinal fluid CgA concentrations have been reported in early PD with OH, but evidence concerning circulating CgA remains limited [6]. Orexin A (ORX), a hypothalamic neuropeptide involved in wakefulness and autonomic regulation, has dense functional connections with the locus coeruleus and can enhance sympathetic cardiovascular activity [7, 8]. The relationship of circulating ORX with OH and sleep symptoms in PD is not established.

This study compared serum norepinephrine (NE), CgA, and ORX concentrations in patients with PD with and without OH and examined their associations with motor severity, autonomic dysfunction, and subjective sleep measures.

Materials and methods

Study design and participants

This single-center cross-sectional observational study was conducted at the Neurology Outpatient Clinic of Sultan II. Abdülhamid Han Training and Research Hospital between June 2023 and February 2024 and was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement [9]. Patients older than 45 years with an established clinical diagnosis of PD were enrolled after written informed consent. Patients were classified according to the presence or absence of OH at the study visit. The final sample comprised 118 participants: 63 with OH and 55 without OH. Exclusion criteria were parkinsonism due to causes other than PD, renal failure, heart failure, hepatic dysfunction, hyperthyroidism, complete bedridden status, and inability to provide informed consent.

The study was approved by the University of Health Sciences Hamidiye Clinical Research Ethics Committee (approval no. 35038; 21 May 2021) and was conducted in accordance with the Declaration of Helsinki.

Orthostatic blood pressure assessment

After approximately 10 minutes of supine rest, blood pressure and pulse were measured without changing position and then repeated at one and three minutes after standing. OH was defined as a fall in

systolic blood pressure of at least 20 mmHg and/or a fall in diastolic blood pressure of at least 10 mmHg within three minutes of standing [10].

Clinical assessments

Age, sex, PD duration, diabetes mellitus, hypertension, antihypertensive and dopaminergic medication use, and time since the last dopaminergic dose were recorded. Motor severity was assessed using the Unified Parkinson Disease Rating Scale Part III (UPDRS III), disease stage using the Hoehn and Yahr scale, non-motor symptoms using the Unified Parkinson Disease Rating Scale Part I (UPDRS I), autonomic symptoms using the Scales for Outcomes in Parkinson Disease-Autonomic Dysfunction questionnaire (SCOPA-AUT), nocturnal sleep problems using the Parkinson Disease Sleep Scale (PDSS), and daytime sleepiness using the Epworth Sleepiness Scale (ESS).

Blood sampling and biomarker assays

Venous access was established in the antecubital region between 09:30 and 11:30. To reduce acute sympathetic activation related to posture, stress, and venipuncture, participants rested supine in a quiet room for 30 minutes before sampling from the pre-established line. Blood was collected into serum separator tubes, centrifuged, and the separated serum was stored at -80°C until analysis. Serum human CgA, ORX, and NE concentrations were measured using commercial enzyme-linked immunosorbent assays and a BioTek Epoch 2 microplate spectrophotometer with an ELx50 microplate strip washer (BioTek, USA). Colorimetric absorbance was read at 450 nm and concentrations were calculated according to the manufacturers' instructions.

Statistical analysis

Analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Distributional assumptions were assessed with the Kolmogorov-Smirnov test and visual inspection. Continuous variables were compared using the independent-samples t test or Mann-Whitney U test, as appropriate, and categorical variables using the chi-square test. Associations were evaluated using Pearson or Spearman correlation coefficients according to variable distribution. Exploratory receiver operating characteristic analyses were performed for CgA, ORX, and UPDRS III. All tests were two-sided, and $p < 0.05$ was considered statistically significant. No adjustment was made for multiple comparisons; correlation and receiver operating characteristic analyses should therefore be considered exploratory.

Results

Participant characteristics

The study included 118 patients with PD: 63 with OH and 55 without OH. The groups did not differ significantly in age, sex, PD duration, hypertension, diabetes mellitus, dopaminergic medication use, or time since the last dopaminergic dose (Table 1).

Table 1
Demographic and clinical characteristics of the study groups

Characteristic	Orthostatic hypotension (n = 63)	No orthostatic hypotension (n = 55)	p value
n	63	55	-
Female sex, n (%)	23 (36.5)	23 (41.8)	0.615c
Age, years	70.0 ± 9.0 71 (46–86)	68.2 ± 8.2 70 (50–84)	0.145a
Parkinson disease duration, years	6.4 ± 3.8 6 (1–22)	6.1 ± 4.4 4 (1–17)	0.314a
Dopaminergic medication use, n (%)	62 (98.4)	54 (98.2)	0.923c
Hypertension, n (%)	15 (23.8)	7 (12.7)	0.123c
Diabetes mellitus, n (%)	8 (12.7)	7 (12.7)	0.996c
Time since last dopaminergic dose, hours	5.0 ± 4.8 3 (1–24)	4.6 ± 3.9 3 (1–16)	0.904a

Values are mean ± standard deviation and median (range), unless otherwise indicated. a Mann-Whitney U test; c chi-square test.

Clinical scale scores

PDSS, ESS, and UPDRS I scores did not differ significantly between groups. UPDRS III, SCOPA-AUT, and Hoehn and Yahr scores were higher in patients with OH (Table 2).

Table 2
Clinical scale scores according to orthostatic hypotension status

Measure	Orthostatic hypotension (n = 63)	No orthostatic hypotension (n = 55)	p value
UPDRS III	28.3 ± 14.7 25.5 (3–65)	21.3 ± 13.2 18 (1–55)	0.009b
UPDRS I	14.3 ± 7.3 14 (0–31)	11.9 ± 6.3 10.5 (2–29)	0.066b
PDSS	91.3 ± 30.2 92 (10–149)	90.5 ± 32.8 97 (0–140)	0.895b
ESS	9.2 ± 5.1 9 (1–21)	8.5 ± 7.2 7 (1–44)	0.491b
SCOPA-AUT	19.2 ± 9.0 18 (4–40)	15.3 ± 8.8 12.5 (4–39)	0.019b
Hoehn and Yahr stage	2.7 ± 1.0 3 (1–5)	2.2 ± 0.9 2 (1–4)	0.016a

Values are mean ± standard deviation and median (range). a Mann-Whitney U test; b independent-samples t test. ESS, Epworth Sleepiness Scale; PDSS, Parkinson Disease Sleep Scale; SCOPA-AUT, Scales for Outcomes in Parkinson Disease-Autonomic Dysfunction; UPDRS, Unified Parkinson Disease Rating Scale.

Serum biomarkers

Serum NE concentrations were similar between groups. Serum CgA and ORX concentrations were lower in patients with OH (Table 3).

Table 3
Serum biomarker concentrations according to orthostatic hypotension status

Biomarker	Orthostatic hypotension (n = 63)	No orthostatic hypotension (n = 55)	p value
Chromogranin A, ng/L	1436 ± 322 1380 (516–2116)	1907 ± 971 1529 (1119–4800)	0.034
Norepinephrine, ng/L	426 ± 118 438 (136–839)	460 ± 268 400 (118–1790)	0.637
Orexin A, ng/L	402 ± 115 392 (116–753)	544 ± 410 407 (116–2033)	0.030

Values are mean ± standard deviation and median (range). P values were calculated using the Mann-Whitney U test.

Correlation analyses

Serum ORX was not significantly associated with PDSS or ESS scores. Weak inverse correlations were observed with SCOPA-AUT and UPDRS III scores. ORX showed a very weak positive correlation with CgA and no significant correlation with NE (Table 4).

Table 4
Spearman correlations of serum orexin A with clinical measures and other biomarkers

Variable	Spearman r	p value
Epworth Sleepiness Scale	-0.094	0.313
Parkinson Disease Sleep Scale	0.117	0.207
SCOPA-AUT	-0.267	0.003
UPDRS III	-0.246	0.007
Chromogranin A	0.189	0.040
Norepinephrine	0.158	0.087

SCOPA-AUT, Scales for Outcomes in Parkinson Disease-Autonomic Dysfunction; UPDRS III, Unified Parkinson Disease Rating Scale Part III. P values are unadjusted and the analyses are exploratory.

Exploratory receiver operating characteristic analysis

None of the evaluated variables showed acceptable stand-alone discrimination for OH. The area under the curve was 0.618 for CgA, 0.620 for ORX, and 0.652 for UPDRS III (Table 5).

Table 5
Exploratory discrimination of orthostatic hypotension

Variable	Cutoff	Sensitivity, %	Specificity, %	Area under curve	95% confidence interval	p value
Chromogranin A	≤ 2000 ng/L	90.8	29.1	0.618	0.523–0.706	0.033
Orexin A	≤ 395 ng/L	54.0	79.9	0.620	0.525–0.708	0.026
UPDRS III	> 23	62.9	70.4	0.652	0.558–0.738	0.003

Cutoffs and performance estimates were derived in the same cohort and have not been externally validated. UPDRS III, Unified Parkinson Disease Rating Scale Part III.

Discussion

In this cross-sectional cohort, patients with PD and OH had lower serum CgA and ORX concentrations than patients without OH, whereas resting serum NE did not differ significantly. The OH group also had greater motor severity, disease stage, and autonomic symptom burden. ORX was not associated with subjective sleep measures, and all evaluated markers showed limited diagnostic discrimination. These findings support associations with autonomic involvement but do not establish causality or an anatomically specific mechanism.

The absence of a significant difference in resting NE is biologically plausible. Previous studies have shown lower supine NE in some patients with PD and OH, but circulating catechol concentrations may remain within the reference range or may be relatively preserved compared with pure autonomic failure [11, 12]. NE secretion is highly dynamic, and peripheral venous measurements are influenced by posture, stress, local reuptake, metabolism, and organ-specific sympathetic spillover [13–15]. Because all samples in the present study were obtained during supine rest, they may not capture the impaired sympathetic response to standing that is most relevant to OH.

CgA was examined as a potentially more stable correlate of sympathoadrenal secretory activity. It is co-stored with catecholamines and is less sensitive than NE to rapid short-term fluctuations, although concentrations are affected by preanalytical conditions, renal function, medications, and assay characteristics [16, 17]. Prior PD studies have reported both higher CgA concentrations with greater disease severity and lower concentrations in more advanced disease or autonomic involvement [6, 18–21]. In the present cohort, CgA was lower in the OH group, but its area under the curve was only 0.618. Lower CgA should therefore be interpreted as a preliminary biological association rather than a clinically useful diagnostic biomarker.

Patients with OH had higher UPDRS III and Hoehn and Yahr scores, consistent with studies linking OH to greater disease severity and symptom burden [22, 23]. Other work indicates that cardiovascular

autonomic dysfunction can also occur early and may progress partly independently of motor impairment [24, 25]. The cross-sectional design cannot determine whether greater motor severity contributes to OH, whether both reflect broader neurodegeneration, or whether they follow partially independent trajectories. The modest discrimination of UPDRS III confirms that motor severity cannot substitute for direct orthostatic blood pressure measurement.

The lower ORX concentration in the OH group is of particular interest. Orexinergic neurons in the lateral hypothalamus contribute to arousal, energy balance, and autonomic regulation and project densely to the locus coeruleus. Hypothalamic and orexinergic abnormalities have been described in PD [26, 27], and reduced ventricular cerebrospinal fluid ORX and loss of hypothalamic orexin neurons have been reported in advanced disease [28, 29]. However, serum ORX is an indirect peripheral measure and cannot establish the function of hypothalamic neurons or central receptor signaling. A study of plasma ORX reported higher concentrations in early and intermediate PD but lower concentrations in advanced PD, emphasizing the possible influence of disease stage and peripheral measurement characteristics [30]. The more severe motor phenotype in the OH group may therefore partly account for the observed difference.

ORX was not associated with PDSS or ESS scores. Sleep disturbance in PD is multifactorial and may reflect nocturnal motor symptoms, medication effects, mood symptoms, nocturia, circadian disruption, sleep-disordered breathing, periodic limb movements, or rapid eye movement sleep behavior disorder. PDSS and ESS are symptom-based instruments and do not characterize sleep architecture. The present findings do not exclude a role for orexin in sleep-wake regulation; rather, they indicate that a single serum ORX measurement was not a useful marker of subjective sleep disturbance in this cohort.

The combined pattern of lower CgA and ORX with preserved resting NE may indicate that relatively stable secretory or regulatory markers capture chronic autonomic involvement more consistently than a single labile catecholamine measurement. Nevertheless, circulating concentrations cannot localize dysfunction to central or peripheral pathways, and the exploratory correlations were weak. Standardized orthostatic blood pressure testing remains the appropriate clinical method for diagnosing OH in PD.

Strengths of the study include comparison of two clinically relevant PD groups, standardized supine sampling, simultaneous evaluation of three biologically related markers, and assessment of motor, autonomic, non-motor, and sleep-related features within the same cohort. Important limitations include the cross-sectional, single-center design; absence of a healthy control group; single-time-point peripheral measurements; lack of serial supine-to-standing biomarker sampling; reliance on questionnaires rather than polysomnography or actigraphy; possible residual confounding from medication, comorbidity, nutritional state, renal and endocrine function, stress, and preanalytical factors; and lack of correction for multiple testing. The receiver operating characteristic analyses were performed in the same cohort and require external validation. Future multicenter longitudinal studies should include detailed medication adjustment, standardized assay reporting, dynamic orthostatic sampling, comprehensive autonomic testing, and objective sleep assessment.

Conclusion

Patients with PD and OH had lower serum CgA and ORX concentrations, whereas resting NE concentrations were similar to those in patients without OH. ORX was not associated with subjective sleep disturbance. The findings are hypothesis-generating and suggest that CgA and ORX may be peripheral correlates of autonomic involvement, but neither should be used as a stand-alone diagnostic test. Prospective studies with dynamic biomarker sampling and external validation are required.

Declarations

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Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: The study was approved by the University of Health Sciences Hamidiye Clinical Research Ethics Committee (approval no. 35038; 21 May 2021) and was performed in accordance with the Declaration of Helsinki and its later amendments.

Consent to participate: Written informed consent was obtained from all participants.

Data availability: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions: Zeynep Meltem Arslan: conceptualization, methodology, investigation, project administration, resources, supervision, visualization, writing-original draft, and writing-review and editing. Mehmet Güney Şenol: data curation, investigation, validation, resources, supervision, and writing-review and editing. Fatih Özçelik: data curation, investigation, validation, resources, and writing-review and editing. Mustafa Karaoğlu: formal analysis, software, methodology, validation, visualization, and writing-review and editing. Mehmet Fatih Özdağ: supervision, validation, and writing-review and editing. All authors read and approved the final manuscript and agree to be accountable for the work.

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