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Unveiling the link between stress-related disorders and autonomic dysfunction in Parkinson's disease: a cross-sectional study

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Abstract

Objective: *Recent evidence has underscored the detrimental effects of chronic stress on health, particularly its impact on neurodegenerative disorders such as Parkinson's disease (PD). Our study seeks to investigate the complex relationship between autonomic dysfunction and stress-related disorders in PD, aiming to enhance our understanding of these conditions.* **Methods:** *We conducted an observational cross-sectional study of PD patients from a movement disorders clinic in Monterrey, Mexico. Sociodemographic and clinical data were collected. Autonomic symptoms were assessed using the Scale for Outcomes in PD-Autonomic (SCOPA-AUT), with patients stratified into two groups based on scores (≥ 10 or < 10). Post-traumatic stress disorder (PTSD) assessment included traumatic experiences and structured interviews using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), Checklist for DSM-5 PTSD (PCL-5), acute stress disorder scale, DSM-5 criteria for adaptive disorder, and the Adverse Childhood Experiences Questionnaire.* **Results:** *The study included 32 PD patients and revealed a significant association between post-traumatic stress symptoms and autonomic dysfunction. Those with higher post-traumatic stress symptoms, as measured by the PCL-5 scale, exhibited more pronounced autonomic dysfunction, as indicated by higher SCOPA-AUT scores. Traumatic events were also more prevalent in the group with severe autonomic dysfunction, suggesting a link between trauma and autonomic symptoms in PD patients.* **Conclusions:** *Our study suggests that post-traumatic stress symptoms may exacerbate autonomic dysfunction in PD patients. This underscores the need for further research to explore mechanisms and therapeutic implications and emphasizes the importance of considering stress-related disorders in the management of PD.*

Keywords: *Parkinson's disease. Post-traumatic stress disorder. Autonomic dysfunction. Chronic stress. Neurodegenerative disorders.*

Revelando la conexión entre los trastornos relacionados con el estrés y la disfunción autonómica en la enfermedad de Parkinson: un estudio transversal

Resumen

Objetivo: *Nuestro estudio busca investigar la compleja relación entre la disfunción autonómica y los trastornos relacionados con el estrés en la EP.* **Métodos:** *Realizamos un estudio observacional transversal en pacientes con EP de una clínica de trastornos del movimiento. Se recopilaron datos sociodemográficos y clínicos. Los síntomas autonómicos se evaluaron*

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utilizando la Escala de Resultados en la Enfermedad de Parkinson-Autonómica (SCOPA-AUT), con pacientes estratificados en dos grupos según sus puntajes (≥ 10 o < 10). La evaluación del trastorno de estrés postraumático (TEPT) incluyó experiencias traumáticas y entrevistas estructuradas utilizando la Escala de TEPT Administrada por el Clínico para DSM-5 (CAPS-5), Lista de Síntomas para TEPT DSM-5 (PCL-5), Escala de Trastorno de Estrés Agudo (ASDS), criterios DSM-5 para trastorno adaptativo y el Cuestionario de Experiencias Adversas en la Infancia (ACE). **Resultados:** *El estudio incluyó 32 pacientes con EP y reveló una asociación significativa entre los síntomas de estrés postraumático y la disfunción autonómica. Aquellos con síntomas de estrés postraumático más pronunciados, según la escala PCL-5, exhibieron una disfunción autonómica más marcada, indicada por puntajes más altos en SCOPA-AUT. Los eventos traumáticos también fueron más prevalentes en el grupo con disfunción autonómica severa, sugiriendo un vínculo entre el trauma y los síntomas autonómicos en pacientes con EP.* **Conclusiones:** *Nuestro estudio sugiere que los síntomas de estrés postraumático pueden exacerbar la disfunción autonómica en pacientes con EP. Esto subraya la necesidad de más investigación para explorar los mecanismos e implicaciones terapéuticas.*

Palabras clave: *Enfermedad de Parkinson. Trastorno de estrés postraumático. Disfunción autonómica. Estrés crónico. Trastornos neurodegenerativos.*

Introduction

In recent years, there has been growing evidence highlighting the detrimental impact of chronic stress on health[1]. Stress is defined as a state in which the brain perceives an excessive quantity of stimulation or regards its quality as threatening, leading to a generalized physiological response[2]. Moreover, stress has been shown to alter the immune system and oxidative stress defense mechanisms, ultimately leading to cellular apoptosis[3-5]. The hypothalamic-pituitary-adrenal (HPA) axis is a central component of the stress response within the central nervous system (CNS), influencing and sometimes disrupting various cerebral circuits. This intricate interplay involves the HPA axis, the autonomic nervous system (ANS), and the immune system, working together to coordinate hormonal and inflammatory stress responses[6]. Chronic stress, whether arising from major life events or persistent minor irritations and frustrations, induces prolonged activation of the HPA axis, paving the way for long-term pathological conditions[7]. The detrimental consequences on the CNS resulting from the complex interaction of inflammation and stress have been notably observed in the context of neurodegenerative disorders[8,9]. Therefore, stress is closely linked to neurodegenerative and mood disorders[10] and plays a pivotal role in the onset of neuropsychiatric conditions[11]. An expanding body of evidence underscores the central function of stress in priming midbrain microglia to enhance the inflammatory response, potentially serving as a contributing factor in the degenerative processes associated with Parkinson's disease (PD)[12].

Post-traumatic stress disorder (PTSD) emerges as a significant risk factor within the context of PD. A nationwide longitudinal study revealed that individuals diagnosed with PTSD face a 3.5-fold elevated risk of developing PD, often at an earlier age than those without a PTSD diagnosis[13]. A population-based matched case–control study among veterans demonstrated that individuals with a diagnosis of PTSD are at a 2.71-fold increased risk of developing PD[14]. Another population-based cohort study reported that PTSD patients had a 1.48-fold excess risk for PD compared with non-PTSD patients[15]. Most recently, a case–control study examining traumatic brain injury (TBI) and PTSD related to early trauma in military veterans reported that TBI and PTSD increased the odds from 1.5 to 2.1 of subsequent PD[16].

Given the information regarding the impact of stress on the HPA axis and its effect on the ANS and other circuits, we deem it crucial to investigate the relationship between stress-related disorders and the presence and severity of autonomic symptoms in PD. Leveraging the scientific background on stress-related disorders and their potential impact on PD, we aim to shed light on this connection to contribute valuable insights into the holistic understanding of PD pathology and offer potential avenues for therapeutic intervention.

Materials and methods

We conducted an observational, cross-sectional study previously approved by the Institutional Review Board: DEISC-19 01 22 030. The patient selection for this study was conducted using a non-probabilistic consecutive convenience sampling method, with participants recruited from a private practice clinic specializing in movement disorders in Monterrey, Mexico, during the period from July to December 2022. The inclusion criteria encompassed patients diagnosed with

PD by a specialist in movement disorders based on established clinical diagnostic criteria published previously[17]. Exclusion criteria comprised individuals under the age of 18, those diagnosed with atypical Parkinsonism, dementia, or psychotic symptoms related to the disorder. Furthermore, patients without accessible medical records, those unable to engage in a structured interview, or those with a history of TBI were excluded from the study. Patients with concurrent diagnoses or the presence of another neurological disorder were also excluded from the study.

Sociodemographic data were documented, including age, gender, marital status, employment status, years of education, history of COVID-19, exposure to pesticides, and family history of PD. Clinical data, including age of disease onset, disease duration, and motor subtype of PD, were also documented[18]. Assessments to determine our main dependent variable, presence, and severity of autonomic symptoms in PD were conducted using the Scale for Outcomes in PD-Autonomic (SCOPA-AUT)[19]. The SCOPA-AUT is an assessment tool used to measure the presence and severity of autonomic symptoms in PD. It evaluates nine different autonomic domains, with each domain consisting of specific questions or items. Responses to these items are scored on a Likert scale, where "Never" equals 0, "Sometimes" equals 1, "Regularly" equals 2, and "Often" equals 3. The scores for all items are then summed to calculate the total SCOPA-AUT score. A higher score indicates a greater severity of autonomic symptoms, providing a quantitative measure for assessing autonomic dysfunction in PD.

Previous studies have utilized SCOPA-AUT cutoff scores between 9 and 13 based on their own criteria[20,21]. We established a cut-off value of 10 based on our previous study[22], wherein the mean (standard deviation [SD]) total SCOPA-AUT score among control subjects was 5.8 (3.7), while in Parkinson's patients, the lower 95% confidence interval (CI) limit for the mean was 8.9 and the upper limit was 10.2. This meticulous approach facilitated the stratification of the PD cohort into two distinct groups: Individuals with SCOPA-AUT scores < 10 and those with scores ≥ 10. By employing this criterion, our objective was to delineate autonomic symptoms specific to the disease rather than those influenced by age-related factors.

For the initial assessment of PTSD, we collected information about the patient's life experiences before the diagnosis of PD. This information was obtained through a question from the life events scale, which inquiries about potential stressful events[23] and traumatic experiences listed in the Traumatic Experiences Questionnaire (PQ)[24]. A structured interview was then conducted to inquire about any event that the patient considered traumatic. If there was a positive response to any of the queried events, an evaluation for stress disorders was conducted using the following scales and clinical assessment. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)[25] and the Checklist for DSM-5 PTSD (PCL-5)[26] were administered for the diagnosis of PTSD. The CAPS-5 scale will be used for the assessment of PTSD through interviews, and to facilitate data collection and analysis, we will use the validated PCL-5 scale. The CAPS-5 scale is administered through a structured 30-min clinician interview, consisting of 47 items scored on a four-point Likert scale to measure the frequency and intensity of PTSD symptoms. To diagnose PTSD using the CAPS-5, specific criteria must be met. On the other hand, the PCL-5 scale is a self-administered or patient-read questionnaire comprising 20 items rated on a 5-point Likert scale, and it aligns with the DSM-5 criteria for PTSD. Scores from the PCL-5 scale will be utilized to assess PTSD symptoms. In addition, the acute stress disorder scale was used to identify acute stress disorder[27], for the diagnosis of adaptive disorder, we utilized the diagnostic criteria based on the structured interview according to the DSM-5[28], and the Adverse Childhood Experiences (ACEs) Questionnaire was used to identify childhood trauma[29].

Statistical analysis

We employed descriptive statistics to present means, SDs, and frequencies with corresponding percentages where applicable. The normality of continuous data were assessed using the Shapiro–Wilk test. Categorical variables underwent analysis through either the χ^2 test or Fisher's exact test, while continuous variables were examined to identify differences between SCOPA-AUT groups using either the Student's T test or Mann–Whitney U test, as appropriate. These continuous variables were further evaluated for correlations with SCOPA-AUT scores, utilizing either Pearson's or Spearman's correlation coefficients. Statistical significance was determined at $p < 0.05$. The analysis was conducted using IBM Statistical Package for the Social Sciences version 25 software.

Results

Thirty-two PD patients were included in the analysis, with 16 of them having a SCOPA-AUT total score of ≥ 10, while the remaining 16 had a SCOPA-AUT total

Table 1. Sociodemographic and clinical profile of the PD cohort (n = 32)

Variables	Total	SCOPA-AUT < 10 (n = 16)	SCOPA-AUT ≥ 10 (n = 16)	p-value
Male, n (%)	15 (46.9)	8 (53.3)	7 (46.7)	0.723
Age, years mean (standard deviation)	67.2 (10.5)	64.2 (9.2)	70.1 (11.1)	0.110
Living with partner, n (%)	27 (84.4)	12 (44.4)	15 (55.6)	0.333
Non-employed/retired, n (%)	16 (50)	5 (31.3)	11 (68.8)	0.034
Education, years mean (SD)	12.7 (3.5)	11.7 (3.5)	13.7 (3.3)	0.110*
COVID-19 infection, n (%)	13 (40.6)	7 (53.8)	6 (46.2)	0.719
Pesticides exposure, n (%)	7 (21.9)	4 (57.1)	3 (42.9)	1.000
FH of PD, n (%)	10 (31.3)	7 (70.0)	3 (30.0)	0.252
Age of onset, years mean (SD)	60.6 (10.3)	57.7 (10.7)	63.5 (9.3)	0.110
Disease duration, years (DE)	6.6 (3.8)	6.5 (2.9)	6.6 (4.6)	0.752*
PIGD Motor subtype, n (%)	14 (43.8)	8 (57.1)	6 (42.9)	0.771
SCOPA-AUT, total score (DE)	10.9 (8.9)	4 (2.4)	17.8 (7.5)	< 0.0001*

FH of PD: family history of Parkinson's disease; PIGD: postural instability with gait difficulty; SCOPA-AUT: scales for outcomes in Parkinson's disease–autonomic dysfunction; SD: standard deviation.
*Mann-Whitney U Test.

score of < 10. No significant differences were observed in sociodemographic and clinical variables related to the disease, except for individuals who were unemployed or retired, as they were 4.84 times more likely to score ≥ 10 on the SCOPA-AUT. Table 1 displays all the characteristics.

The analysis revealed significant differences in the PCL-5 scores between the SCOPA-AUT ≥ 10 group (23.1, SD = 6.1) and the SCOPA-AUT < 10 group (3.2, SD = 2.5), with a p = 0.013, as shown in Fig. 1. Furthermore, a positive and moderate correlation was observed between the PCL-5 score and the SCOPA-AUT total score for the entire cohort, with a correlation coefficient of ρ = 0.530 and a p = 0.002. The correlation remained significant even after controlling for age, employment status, years of education, and age of disease onset (ρ = 0.720, p < 0.0001). Our findings suggest that as post-traumatic stress symptoms increase, dysautonomic symptoms tend to become more pronounced in patients with PD.

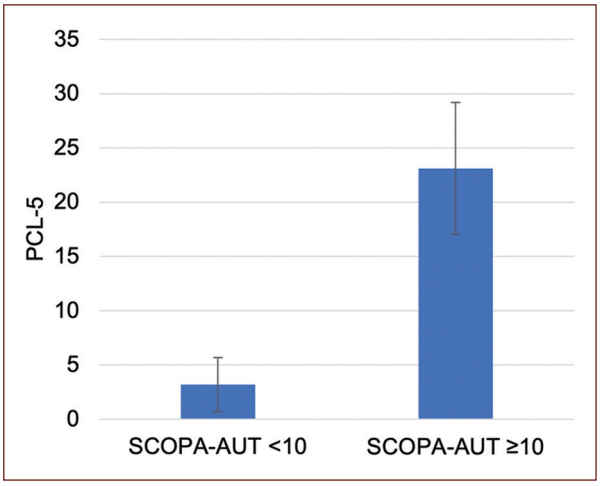

Figure 1. PCL-5 scores between SCOPA-AUT groups. The analysis revealed significant differences in the PCL-5 scores between the SCOPA-AUT ≥ 10 group (23.1, SD 6.1) and the SCOPA-AUT < 10 group (3.2, SD 2.5), with a p = 0.013. SCOPA-AUT: scale for outcomes in Parkinson's disease-autonomic; SD: standard deviation.

In our investigation of the presence of traumatic events among patients, 16 out of 32 individuals reported experiencing traumas of sufficient magnitude to induce significant distress before the onset of PD symptoms. Subsequent analysis unveiled differences in the occurrence of traumatic events between the study groups. The SCOPA-AUT ≥ 10 group exhibited a prevalence of 68.8%, whereas the SCOPA-AUT < 10 group had a lower frequency of 31.3% (p = 0.034, odds ratio [OR] = 4.84, 95% CI: 1.09-21.58). Similarly, when examining 13 out of 32 patients who presented with stress-related disorders, significant distinctions emerged between the study groups. The prevalence of these disorders was

Table 2. Relationship between stress disorders and SCOPA-AUT groups in our PD population

Variables	Total	SCOPA-AUT < 10 (n = 16)	SCOPA-AUT ≥ 10 (n = 16)	p-value
PCL-5, mean (SD)	13.1 (20.9)	3.2 (2.5)	23.1 (6.1)	0.013*
PTSD, n (%)	6 (18.8)	1 (16.7)	5 (83.3)	0.172**
Experience of the traumatic event, n (%)	16 (50)	5 (31.3)	11 (68.8)	0.034
Presence of stress-related disorders, n (%)	13 (40.6)	2 (15.4)	11 (84.6)	0.003**
Adjustment disorder, n (%)	8 (25)	1 (12.5)	7 (87.5)	0.037**

PCL-5: PTSD Checklist for DSM-5; SCOPA-AUT: scales for outcomes in Parkinson's disease–autonomic dysfunction; PTSD: post-traumatic stress disorder.
*Mann-Whitney U Test.
**Fisher's exact Test.

notably higher in the SCOPA-AUT ≥ 10 groups at 84.6%, as opposed to the SCOPA-AUT < 10 group, which had a prevalence of 15.4% (p = 0.003, OR = 15.4, 95% CI: 2.50-95.06). Furthermore, variations in the occurrence of adjustment disorders among 8 out of 32 patients were observed between the study groups. The SCOPA-AUT ≥ 10 group exhibited a prevalence of 87.5%, while the SCOPA-AUT < 10 group had a prevalence of 12.5% (p = 0.037, OR = 11.7, 95% CI: 1.23-110.96). Table 2 provides a detailed description of the association between stress-related disorders and the study groups. Regarding the ACEs questionnaire, 18 out of 32 (56.3%) PD patients reported having experienced at least one ACE. However, only 2 out of the 18 (11.1%) reported a score of 4 or more ACEs. No significant association was observed between the SCOPA-AUT study groups.

Discussion

Our observational cross-sectional study explored the complex relationship between stress-related disorders, particularly PTSD, and PD, with a particular focus on autonomic dysfunction. Our findings indicate that individuals with PD who also have higher post-traumatic stress symptoms tend to experience more pronounced autonomic dysfunction. We believe this observation is significant as autonomic dysfunction is a prevalent non-motor symptom in PD and can significantly impact patients' quality of life. While previous studies have established a link between PTSD and an increased risk of developing PD[13-16], our study is the first to add to the literature by highlighting the potential impact of stress on non-motor symptoms, specifically autonomic dysfunction, in patients already diagnosed with PD.

Our study also examined the presence of traumatic events in PD patients before the onset of PD symptoms. We found that a significant proportion of patients reported experiencing traumatic events significant enough to induce distress. Importantly, these traumatic events were more prevalent in the group with higher SCOPA-AUT scores, indicating a potential link between trauma and autonomic dysfunction. In addition, stress-related disorders were more common in the group with higher SCOPA-AUT scores, further emphasizing the possible connection between stress-related conditions and autonomic symptoms in PD. Chronic stress has increasingly been recognized as a significant factor impacting health, with its detrimental effects on various physiological and immune responses well-documented[30]. Stress, through its influence on the HPA axis, ANS, and the immune system, can contribute to the development of pathological conditions, including neurodegenerative disorders, such as PD[31]. The connection between stress and neurodegenerative conditions has garnered attention due to its potential impact on both motor and non-motor symptoms. Furthermore, individuals with PTSD exhibit irregular fluctuations in their autonomic states. This persistent defensive autonomic state can result in dysfunctional autonomic reactions. These phenomena might be influenced by right hemisphere systems, potentially playing a role in sympathetic activation and the adoption of defensive strategies in PTSD[32]. PTSD should be considered as a maladaptive disorder of the autonomic system that responds in an erroneous physiologic way to the environment's demands[33].

Our results should be interpreted with caution, as this is an observational, cross-sectional study with a limited sample size. Longitudinal studies with larger cohorts are needed to confirm these findings and establish

causality. Several confounding variables linked to dysautonomia, such as diabetes and medication use, including beta-blockers, levodopa, and pramipexole, were not directly assessed or recorded in our study. Nevertheless, our study contributes to the growing body of evidence highlighting the importance of considering stress-related disorders in the management of PD, particularly in addressing non-motor symptoms, such as autonomic dysfunction.

Conclusion

Our study suggests that post-traumatic stress symptoms may exacerbate autonomic dysfunction in PD patients. Further research is needed to explore the underlying mechanisms and potential therapeutic implications of these findings. Understanding the relationship between stress-related disorders and non-motor symptoms in PD can have important implications for the holistic management of this complex neurological condition.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have used generative artificial intelligence, specifically ChatGPT 3.5 in the writing of this manuscript. AI was not used in the creation of images, graphics, tables, or their corresponding captions.

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