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EDITORIAL

When our fate finds us: the growing impact of neurodegenerative disorders

Cuando el destino nos encuentre: el creciente impacto de las enfermedades neurodegenerativas

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"Let us search in spite of everything we face. Let us search, because it is the best way to find. And perhaps, thanks to our efforts, the verdict of tomorrow will not be the verdict of today'' – J. M. Charcot[1]

A global increase in neurodegenerative diseases is anticipated, primarily due to aging, the main risk factor. According to estimates from the *2019 Global Burden of Disease* study, approximately 600,000 cases of dementia were recorded in our country that year. By 2050, projections suggest that the number of cases will exceed one and a half million, representing an approximate increase of 209%[2].

This growth will pose a significant challenge to health systems worldwide. Although neurodegenerative diseases can be a major cause of mortality, the main problem lies in the loss of functionality, primarily manifesting in the years lost to disability that these diseases often cause.

For this reason, most research groups have focused on finding ways to prevent the onset of cognitive decline or, alternatively, to slow its progression. This year, the *Lancet* journal published the 2024 report on dementia prevention, highlighting new modifiable factors (such as blindness and high LDL cholesterol) that could impact up to 45% of all dementia cases. It concludes that almost half of all cases of neurodegenerative diseases are preventable[3].

Unfortunately, the lack of awareness campaigns on this topic causes many patients to be referred to consultation in moderate or advanced stages of the disease, which limits the therapeutic options and interventions that could improve their quality of life. In our country, the loss of memory and loss of independence in the elderly is often "normalized."

Therefore, it is essential to focus on interventions that address patient management beyond the preventive approach and in early stages. In this edition of the Mexican Journal of Neuroscience, an article prepared by a panel of Mexican experts lead by Peña de León is presented. Using a Delphi methodology, the group discusses pharmacological options such as cholinesterase inhibitors and memantine, as well as the potential combination with other agents used in daily practice, such as citicoline. The group concludes that combining rivastigmine with citicoline could be an effective therapeutic strategy. However, these findings should be taken with caution, as clinical trials with more convincing evidence are needed to support this conclusion. Nevertheless, this may represent a potential first step for development of more clinical trials and naturalistic studies exploring the efficacy and effectiveness of combined therapies for neurodegenerative diseases. The article demonstrates the growing need for

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research about effective interventions for the treatment of neurodegenerative diseases beyond prevention.

Another article included in this issue analyzes the risk factors associated with psychotic symptoms in Parkinson's disease. This cross-sectional study involved 306 patients and found associations between some non-motor symptoms and psychotic symptoms, including orthostatic hypotension, apathy, cognitive impairment, and the duration of the disease. The findings highlight how little we know about the development of psychosis in Parkinson's disease and other neurodegenerative diseases, and help identify patients at risk of developing neuropsychiatric complications early on[4].

The phrase "When our fate finds us" should not be an excuse for us to remain passive in the face of the growing need for prevention and effective treatments against neurodegenerative diseases. Instead, it should inspire us to be proactive and to lead initiatives that seek to alleviate the burden of these diseases on patients and their caregivers. It is crucial to act now, as we are all at risk, and to date, prevention measures do not guarantee complete protection.

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ORIGINAL ARTICLE

Factors associated with psychotic symptoms in Parkinson's disease: a cross-sectional study

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Abstract

Objective: *The study aimed to investigate the relationship between autonomic dysfunction, specifically orthostatic hypotension, and the presence of psychosis in Parkinson's disease (PD) patients. In addition, we aimed to identify other non-motor factors influencing the development of psychosis.* **Methods:** *We conducted a multicentric observational cross-sectional study to investigate the potential association between autonomic dysfunction and psychosis in PD patients. Approval was obtained from the institutional review board. Participants (n = 306) were recruited through non-probabilistic convenience sampling from the Mexican Parkinson Study Group cohort. Data collection occurred between July 2017 and June 2018. Demographic and clinical data were collected, including age, gender, disease duration, medication, and movement disorders society-unified Parkinson's disease rating scale (MDS-UPDRS) scores. Psychosis symptoms were assessed using MDS-UPDRS item 1.2, whereas autonomic dysfunction was assessed using items 1.10, 1.11, and 1.12. Descriptive statistics, Chi-square tests, Mann–Whitney U tests, and logistic regression were employed for analysis using IBM SPSS version 25.* **Results:** *In our multicenter cohort of 306 Mexican PD patients, 18% reported symptoms of psychosis. Among these patients, orthostatic hypotension on standing was significantly associated with symptoms of psychosis (p = 0.001, OR 2.82). Regression analysis identified apathy (p = 0.003), cognitive impairment (p = 0.012), and longer disease duration (p = 0.001) as predictors of symptoms of psychosis.* **Conclusions:** *While orthostatic hypotension is associated with symptoms of psychosis, cognitive impairment, apathy, and disease duration significantly contribute to its presence in our cohort. These findings underscore the complexity of factors contributing to psychosis in PD. Recognizing these non-motor factors is crucial for the comprehensive care and management of PD patients, especially those at risk of developing psychosis.*

Keywords: *Parkinson's disease. Psychosis. Apathy. Cognitive impairment. Autonomic dysfunction.*

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Factores asociados con síntomas psicóticos en la enfermedad de Parkinson: un estudio transversal

Resumen

Objetivo: *Investigar la relación entre la disfunción autonómica, específicamente la hipotensión ortostática, y la presencia de psicosis en pacientes con enfermedad de Parkinson (EP). Además, identificar otros factores no motores que influyen en el desarrollo de la psicosis.* **Métodos:** *Realizamos un estudio multicéntrico observacional de corte transversal. Se obtuvo la aprobación del comité de ética institucional. Los participantes (n = 306) fueron reclutados mediante muestreo de conveniencia no probabilístico de la cohorte del Grupo Mexicano de Estudio de Parkinson. La recolección de datos ocurrió entre julio de 2017 y junio de 2018. Se recopilaron datos demográficos y clínicos, incluyendo edad, género, duración de la enfermedad, medicación y puntajes MDS-UPDRS. Los síntomas psicóticos se evaluaron utilizando el ítem 1.2, mientras que la disfunción autonómica se evaluó utilizando los ítems 1.10, 1.11 y 1.12 del MDS-UPDRS. Se emplearon estadísticas descriptivas, pruebas de chi-cuadrado, pruebas U de Mann-Whitney y regresión logística para el análisis.* **Resultados:** *El 18% reportó síntomas de psicosis. Entre estos pacientes, la hipotensión ortostática se asoció significativamente con síntomas de psicosis (p = 0.001, RM 2.82). El análisis de regresión identificó la apatía (p = 0.003), el deterioro cognitivo (p = 0.012) y una duración más larga de la enfermedad (p = 0.001) como predictores de síntomas de psicosis.* **Conclusiones:** *Aunque la hipotensión ortostática se asocia con síntomas de psicosis, el deterioro cognitivo, la apatía y la duración de la enfermedad contribuyen significativamente a su presencia en nuestra cohorte. Estos hallazgos subrayan la complejidad de los factores que contribuyen a la psicosis en la EP.*

Palabras clave: *Enfermedad de Parkinson. Psicosis. Apatía. Deterioro cognitivo. Disfunción autonómica.*

Introduction

Parkinson's disease (PD) stands as the second most prevalent neurodegenerative disorder, affecting millions globally[1]. Characterized by distinct motor symptoms encompassing bradykinesia, rigidity, and/or resting tremor, PD is accompanied by a wide array of non-motor manifestations[2]. These encompass cognitive decline, psychiatric conditions, autonomic irregularities, and sleep disturbances, among others[3]. It is of notable significance that the appearance of psychosis and autonomic dysfunction represents a critical moment in the trajectory of PD, exerting a profound impact on the quality of life for patients and heightening the risks associated with hospitalization, morbidity, and mortality[4-6].

Psychosis in PD is reported in approximately 40-60% of patients and may manifest early in the disease course[7], with potential triggers including intrinsic disease pathophysiology, PD medications, or as part of non-motor fluctuations[8]. Various risk factors for psychosis in PD patients have been identified, encompassing prior medical history, both dopaminergic and non-dopaminergic medications, disease duration, genetic predispositions, prior psychiatric symptoms, vivid dreams, and cognitive decline[9]. Autonomic dysfunction occurs in the majority of PD patients at some stage, potentially compromising one or several organ systems including gastrointestinal, cardiovascular, urinary, sexual, thermoregulatory, and pupillomotor functions[10]. When present, such dysfunction is associated with a more aggressive disease course and an accelerated progression[4,11].

It is worth noting that only a limited number of studies have reported a potential association between autonomic disturbances and psychosis in PD[12]. Despite the lack of consensus regarding the direct correlation between psychosis and autonomic dysfunction in PD, there is an accumulating body of evidence that may inform clinical understanding of their relationship. This observational study investigates the association between autonomic dysfunction and psychosis within a PD patient cohort, aiming to enrich the growing body of evidence on the subject.

Material and methods

We conducted a multicentric observational cross-sectional study to investigate the potential association between autonomic dysfunction and psychosis in PD patients. The study received approval from the appropriate institutional review board. A total of 306 participants were recruited through non-probabilistic convenience sampling from the Mexican Parkinson Study Group cohort, a national database comprising demographic and clinical data of PD patients from various neurological clinics across Mexico. Data collection took place between July 2017 and June 2018. The sample size was determined using convenience sampling, based on patients' attendance at their

scheduled appointments during the designated sampling period. All 306 selected subjects were included in the final analysis. The documented demographic data were current age, age at diagnosis, gender, and years of education. The clinical characteristics documented were disease duration, side of initial symptoms, PD motor subtype (based on previously reported classification)[13], PD and non-PD medications, and the movement disorders society-unified Parkinson's disease rating scale (MDS-UPDRS)[14].

Outcome variables

To determine the presence of symptoms of psychosis as our dependent variable, we used item 1.2 from the MDS-UPDRS. Item 1.2 asks the patient if, over the past week, they have seen, heard, smelled, or felt things that were not really there. For this study, we registered the presence of symptoms if the score was from 1 (slight) to 4 (severe). If the score was 0 (normal), we registered symptoms as not present. To determine the presence of autonomic dysfunction as our independent variable, we used items 1.10 (urinary problems), 1.11 (constipation problems), and 1.12 (orthostatic hypotension) from the MDS-UPDRS. Item 1.10 asks the patient if, over the past week, they have had trouble with urine control; item 1.11 asks the patient if, over the past week, they have had constipation troubles that cause them difficulty moving their bowels; and item 1.12 asks the patient if, over the past week, they have felt faint, dizzy, or foggy when standing up after sitting or lying down. For this study, we registered the presence of symptoms if the score in either item was from 1 (slight) to 4 (severe). If the score was 0 (normal), we registered symptoms as not present.

Statistical analysis

Descriptive statistics were used to report central tendency measures, frequencies, and percentages as required. A Kolmogorov–Smirnov test was used to verify the assumptions of the distribution of continuous variables. A Chi-square test was used to determine associations between independent categorical variables and dependent categorical variables. We employed a Mann–Whitney U test to assess associations between independent continuous variables and dependent categorical variables. A multiple logistic regression model was constructed to identify variables that independently explained the presence of the items exploring psychosis in our cohort. The significantly associated variables ($p \leq 0.05$) from the univariate analysis were included in the model. The model with less deviance was selected. The IBM Statistical Package for the Social Sciences version 25 was used in the analysis.

Results

Table 1 provides an overview of the sociodemographic and clinical characteristics of our study cohort. In relation to symptoms of psychosis, among the 306 patients analyzed, 55 (18%) reported experiencing symptoms. Within this group, 32 (58.2%) reported slight symptoms, 13 (23.6%) reported mild symptoms, 8 (15.0%) reported moderate symptoms, and 2 (0.04%) reported severe symptoms. Concerning dysautonomic symptoms, a significant number of 229 (74.8%) patients reported experiencing one or a combination of these symptoms, which included orthostatic hypotension, urinary issues, and constipation problems.

The bivariate analysis revealed that the presence of urinary and constipation problems was not significantly associated with the presence of symptoms of psychosis ($p = 0.076$ and $p = 0.361$, respectively). The presence of orthostatic hypotension on standing was significantly associated with the presence of symptoms of psychosis ($p = 0.001$, OR 2.82, 95% CI 1.53-5.21). These results suggest that symptoms of orthostatic hypotension on standing but not urinary or constipation problems may affect the presence of symptoms of psychosis.

Other variables in the bivariate analysis found to be significantly associated with the presence of symptoms of psychosis were postural instability and gait difficulty motor subtype ($p = 0.048$, OR = 2.14, 95% CI 1.15-3.96), Hoehn and Yahr (HY) IV-V stage ($p < 0.001$, OR = 4.23, 95% CI 1.80-9.92), presence of symptoms of cognitive impairment ($p < 0.001$, OR 3.26, 95% CI 1.76-6.05), depression ($p = 0.030$, OR 1.99, 95% CI 1.06-3.76), anxiety ($p = 0.003$, OR 2.45, 95% CI 1.35-4.43), apathy ($p < 0.001$, OR 4.23, 95% CI 2.19-8.17), freezing of gait ($p = 0.006$, OR 2.51, 95% CI 1.29-4.89), disease duration ($p < 0.001$, $d = 0.67$), MDS-UPDRS part I ($p < 0.001$, $d = 0.99$), part II ($p = 0.037$, $d = 0.27$), part III ($p = 0.003$, $d = 0.40$), part IV ($p = 0.002$, $d = 0.43$), and the total score ($p < 0.001$, $d = 0.70$). These results suggest that other non-motor symptoms, such as cognitive impairment, depression, anxiety, and apathy, as well as PD motor subtype, HY stage, disease duration, and motor severity, may affect the presence of symptoms of psychosis.

Table 1. Sociodemographic and clinical characteristics of our PD cohort

Study variables	Total	Presence of symptoms of psychosis (n = 55)	Absence of symptoms of psychosis (n = 251)	p-value
Male, n (%)	171 (55.9)	29 (52.7)	142 (56.6)	0.603
Age, years. mean (SD)	65.29 (11.7)	67.73 (11.3)	64.76 (11.8)	0.110
Education, years. mean (SD)	10.55 (5.3)	10.31 (5.0)	10.61 (5.4)	0.719
Disease duration, years. mean (SD)	6.69 (4.8)	9.31 (5.0)	6.12 (4.6)	< 0.001
PIGD motor subtype, n (%)	160 (52.3)	37 (67.3)	123 (49.0)	0.048
Cognitive impairment, n (%)	134 (43.8)	37 (67.3)	97 (38.6)	< 0.001
Depression, n (%)	177 (57.8)	39 (70.9)	138 (55.0)	0.030
Anxiety, n (%)	123 (40.2)	32 (58.2)	91 (36.3)	0.003
Apathy, n (%)	53 (17.3)	21 (38.2)	32 (12.7)	< 0.001
Sleep problems, n (%)	166 (54.2)	33 (60.0)	133 (53.0)	0.344
Daytime sleepiness, n (%)	150 (49.0)	31 (56.4)	119 (47.4)	0.229
Pain, n (%)	151 (49.3)	30 (54.5)	121 (48.2)	0.394
Urinary problems, n (%)	173 (56.5)	37 (67.3)	136 (54.2)	0.076
Constipation, n (%)	161 (52.6)	32 (19.9)	129 (51.4)	0.361
Orthostatic symptoms, n (%)	78 (25.5)	24 (43.6)	54 (21.5)	0.001
Fatigue, n (%)	178 (58.2)	30 (54.5)	148 (59.0)	0.547
Freezing of gait, n (%)	55 (18.0)	17 (30.9)	38 (15.1)	0.006
MDS-UPDRS part I, mean (SD)	8.13 (6.2)	13.65 (8.3)	6.92 (4.9)	< 0.001
MDS-UPDRS part II, mean (SD)	5.32 (5.7)	6.78 (7.6)	5.0 (5.2)	0.037
MDS-UPDRS part III, mean (SD)	35.92 (15.7)	41.64 (19.8)	34.67 (14.4)	0.003
MDS-UPDRS part VI, mean (SD)	2.74 (4.0)	4.25 (4.7)	2.4 (3.8)	0.002
Hoehn and Yahr stage I-II, n (%)	281 (91.8)	44 (80.0)	237 (94.4)	< 0.001
LEED, mean (SD)	741.45 (479.9)	809.25 (484.8)	726.59 (478.6)	0.216

PIGD: postural instability with gait difficulty; MDS-UPDRS: movement disorders society-unified Parkinson's disease rating scale; LEED: levodopa equivalent daily dosage.

A regression model was constructed to identify variables that independently predict the presence of symptoms of psychosis. Those patients with the presence of apathy (p = 0.003, ß 2.99), cognitive impairment (p = 0.012, ß 2.33), and longer disease duration (p = 0.001, ß 1.10) were more likely to present symptoms of psychosis, as shown in table 2. The presence of orthostatic hypotension was not a significant independent predictor of symptoms of psychosis in our regression model (p = 0.052, ß 1.95). The results of the model suggest that non-motor symptoms of cognitive impairment and apathy, and disease duration best predicted the presence of symptoms of psychosis in our cohort.

Discussion

We conducted an observational cross-sectional study with the aim of investigating the association between autonomic dysfunction and the presence of symptoms of psychosis among a multicenter cohort of Mexican PD patients. The key findings of this study were as follows: (1) the reported frequency of dysautonomias (74.8%) was higher than that of symptoms of psychosis (18%); (2) patients who reported symptoms of orthostatic hypotension upon standing were 2.82 times more likely to exhibit symptoms of psychosis; and (3) patients presenting symptoms of apathy,

Table 2. Logistic regression model identifying predictors of symptoms of psychosis

Parameters	ß	SE	Wald	p	Exp (ß)	95% CI
Constant	–3.17	0.37	-	-	-	-
Presence of apathy	1.09	0.37	8.78	0.003	2.99	1.45-6.16
Presence of cognitive impairment	0.85	0.34	6.36	0.012	2.33	1.21-4.51
Disease duration	0.10	0.03	10.38	0.001	1.10	1.04-1.17
Presence of orthostatic hypotension	0.67	0.34	3.78	0.052	1.95	1.00-3.83

cognitive impairment, and longer disease duration were more likely to manifest symptoms of psychosis.

The reported frequency of symptoms of psychosis and dysautonomic symptoms in our study population is consistent with the literature, where the prevalence of psychosis varies from 16% to 75%[8], and that of dysautonomia varies from 27% to 87%[15], depending on the specific manifestations studied and the criteria or scales utilized. In our study, we employed Part I of the MDS-UPDRS scale, which assesses the presence of certain non-motor symptoms over the past week, potentially influencing the reported frequency.

We observed that PD patients reporting symptoms of orthostatic hypotension on standing were more likely to manifest symptoms of psychosis. This observation is consistent with findings from both a longitudinal study, which noted an increased risk of developing psychosis in the presence of orthostatic hypotension[16], and a cross-sectional study that reported a higher risk of psychosis associated with a greater burden of autonomic symptoms[17]. The association between dysautonomia and psychosis in PD may be explained by the higher density of Lewy bodies found in the brainstem nuclei, such as the dorsal vagal nucleus, of patients with PD who experience visual hallucinations[18]. Furthermore, the correlation between symptoms of psychosis and autonomic symptoms in PD may not merely be based on their presence but rather on the overall disease burden.

Our study population demonstrated that the symptoms most strongly associated with the presence of symptoms of psychosis were apathy, cognitive impairment, and a longer disease duration. These findings are consistent with prior literature reports. A cross-sectional study found that patients with lower scores on the Frontal Assessment Battery were more likely to develop psychosis at an earlier stage of the disease[19]. In addition, it has been documented that cognitive impairment or dementia are significant factors related to the presence of psychosis symptoms[20]. Apathetic symptoms, along with other affective neuropsychiatric disorders, are commonly reported in PD patients with psychosis[21]. Moreover, patients displaying symptoms of apathy have been linked to lower cognitive levels[22]. Apathy in PD is associated with not only executive dysfunction but also a decline in overall cognitive function, particularly in tasks related to the temporal lobes, which may contribute to its role as an early indicator of dementia in the disease[23]. It has also been previously reported that the duration of the disease is associated with the presence of visual hallucinations, typically occurring in the later stages of the disease[20]. These findings indicate that although there is an association between orthostatic hypotension and psychosis in PD, other non-motor symptoms such as cognitive impairment and apathy, along with disease duration, significantly contribute to the presence of symptoms of psychosis in the cohort. Furthermore, it is important to consider unexplored factors in our study, such as pharmacological treatments, disease severity, and genetics, among others.

Our study has several limitations that should be taken into consideration when interpreting our results. First, it was conducted within a specific cohort of Mexican PD patients, which prompts consideration of the generalizability of our findings to broader populations. Second, certain influential factors, such as pharmacological treatments, and lack of objective evaluation of other non-motor aspects such as sleep, disease severity, and genetic influences, were not included in our study, limiting the comprehensiveness of our results. We should also take into account that some patients may have an alternative cause of synucleinopathy. In addition, our reliance on Part I of the MDS-UPDRS scale, which assesses symptoms over the past week, might have influenced the reported frequency of certain symptoms and could be a limitation. We would like to emphasize the constraints posed by available resources and study design in utilizing more objective measures to assess dysautonomic symptoms, while also highlighting the potential for future investigations to

explore the incorporation of specific scales for psychotic symptoms to further enhance the comprehensiveness of our findings. The cross-sectional design of our study restricts our ability to establish causal relationships between variables. There may also be unmeasured confounding factors not accounted for in our analysis. Finally, the use of a specific language and cultural context in our study may introduce biases or limitations related to linguistic and cultural variations in symptom reporting.

Conclusion

Our findings suggest that while orthostatic hypotension is associated with symptoms of psychosis, other non-motor symptoms such as cognitive impairment and apathy, along with disease duration, significantly contribute to the presence of symptoms of psychosis in the cohort. These findings contribute to the body of literature on the complex interplay between non-motor symptoms and psychosis in PD.

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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 Chat GPT-3.5 in the writing of this manuscript. The authors declare that generative artificial intelligence was not used in the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

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.

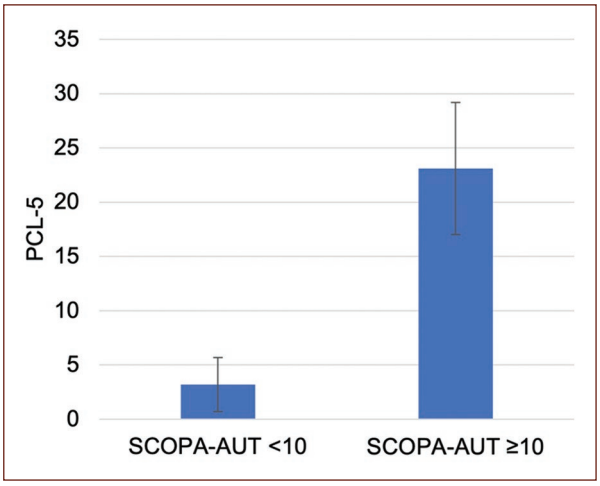

Figure 1. PCL-5 scores between SCOPA-AUT groups. The analysis revealed significant differences in the PCL-5 scores between the SCOPA-AUT ≥ 10 group (23.1, SD 6.1) and the SCOPA-AUT < 10 group (3.2, SD 2.5), with a p = 0.013. SCOPA-AUT: scale for outcomes in Parkinson's disease-autonomic; SD: standard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

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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ORIGINAL ARTICLE

Multidisciplinary consensus on the combined management of Alzheimer's disease by Mexican experts: recommendations and guidelines

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Abstract

Objective: *Alzheimer's disease (AD), affecting over 55 million people globally, poses a substantial public health challenge. Early diagnosis and appropriate treatment are vital to slowing its progression and enhancing patient quality of life. The fixed-dose combination of citicoline with rivastigmine emerges as a promising strategy AD treatment.* **Methods:** *A real-time Delphi consensus was reached with the participation of 11 Mexican experts.* **Results:** *The combination offers neuroprotective benefits, enhancing neuronal regeneration and reducing glutamate levels linked to neuronal damage in AD. These effects translate into improved cognitive function and delayed cognitive decline in AD.* **Conclusions:** *The Mexican Consensus for the Combined Management of AD endorses this fixed-dose combination of rivastigmine with citicoline as a new therapeutic perspective. Its efficacy and safety make it a valuable option for the treatment of this neurodegenerative disease.*

Keywords: *Alzheimer's disease. Citicoline. Rivastigmine. Cholinesterase inhibitors. Fixed dose combination.*

Consenso multidisciplinario sobre el manejo combinado de la enfermedad de Alzheimer por expertos mexicanos: recomendaciones y lineamientos

Resumen

Objetivo: *La enfermedad de Alzheimer, que afecta a más de 55 millones de personas en todo el mundo, representa un desafío creciente para la salud pública. El diagnóstico temprano y el tratamiento adecuado son fundamentales para ralentizar su progresión y mejorar la calidad de vida de los pacientes. En este contexto, la combinación de dosis fija de citicolina con rivastigmina emerge como una estrategia prometedora en el tratamiento de la EA.* **Métodos:** *Se llevó a cabo un consenso mediante la metodología Delphi en tiempo real con la participación de 11 expertos mexicanos.* **Resultados:** *La combinación de dosis fija de citicolina con rivastigmina ofrece beneficios de neuroprotección al tiempo que aumenta la regeneración*

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neuronal y reduce los niveles de glutamato, asociado con el daño neuronal en la EA. Estos efectos se traducen en mejoras en la función cognitiva a partir de los 3 meses de iniciado el tratamiento, así como en el retraso del deterioro cognitivo en la EA. **Conclusiones:** *El Consenso Mexicano para el Manejo Combinado de la Enfermedad de Alzheimer respalda esta combinación de dosis fija de rivastigmina con citicolina como una nueva perspectiva terapéutica para la enfermedad de Alzheimer. Su eficacia y seguridad la convierten en una opción valiosa para el tratamiento de esta enfermedad neurodegenerativa.*

Palabras clave: *Enfermedad de Alzheimer. Citicolina. Rivastigmina. Inhibidores de la colinesterasa. Combinación a dosis fija.*

Introduction

According to the World Health Organization, dementia affects over 55 million people worldwide, with more than 60% residing in low- and middle-income countries; and nearly 10 million new cases reported annually. Dementia is the result of various diseases and injuries affecting the brain; Alzheimer's disease (AD) accounts for 60 to 70% of dementia cases and poses a significant economic burden, costing the global economy approximately US$ 1.3 trillion in 2019[1].

Two drug classes are approved for dementia treatment: acetylcholinesterase inhibitors for mild-to-moderate stages, and N-methyl-D-aspartate receptor antagonists which modify the function of this receptor in the brain and decrease the negative effect of overexposure to glutamate. The latter are used in moderate to severe dementia, apparently with fewer side effects[2].

Despite efforts to develop new treatments, such as biologic drugs targeting amyloid and tau proteins, there is a trend toward reevaluating existing drugs' mechanisms of action, which could be effective in various AD pathophysiological pathways[3].

Reusing pharmacological agents is as a promising strategy in AD treatment, leveraging prior knowledge about safety profiles, pharmacokinetics, dosing, and manufacturing processes. This approach, accounting for 39% of all clinical trials, is crucial for advancing AD treatment[4].

In this context, the fixed-dose combination of rivastigmine, an acetylcholinesterase inhibitor, with citicoline, an integral neuroprotectant, is proposed. This combination aims to enhance selectivity for the hippocampus and cerebral cortex by increasing acetylcholine availability in the synaptic cleft, promoting neuronal regeneration, and raising neurotransmitters levels such as serotonin-1, acetylcholine, dopamine, and norepinephrine. The combination is expected to improve memory, learning, and cognitive functions by enhancing neurotransmission and neuroprotection.

Previous studies, including CITIRIVAD by Castagna et al. in 2016, demonstrated that adding citicoline is a safe and effective option to prolong and potentiate the benefits of cholinergic therapies such as rivastigmine in patients over 65 years with mild-to-moderate AD or mixed dementia[5]. Similarly, in 2017, Gareri et al. showed in the CITICHOLINAGE study that adding citicoline acetylcholinesterase inhibitor therapy, such as rivastigmine, prolongs and enhances the beneficial effect in mild to moderate AD[6].

A multidisciplinary consensus of Mexican experts was convened to evaluate the fixed-dose combination of rivastigmine with citicoline in AD treatment. After thorough review and extensive discussion of available scientific and the benefits and possible limitations of this combination therapy, the consensus resulted in a clinical guideline providing essential recommendations for managing the disease, aiming to enhance patient and family quality of life.

Methods

Consensus was reached through a Delphi system using a real-time ad hoc platform. Eleven panelists were selected based on their expertise, using criteria adapted from those used by the California Courts to determine the expertise of a medicolegal witness[7,8].

Each expert anonymously rated 31 statements, using a five-point Likert scale (1-strongly agree, 2-agree, 3-neutral, 4- disagree, or 5-strongly disagree). *A priori* consensus was defined as agreement by 80% of the panelists on the Likert scale. Subsequently, experts could provide comments and suggestions through text boxes, which were reviewed and used to modify the statements in subsequent survey rounds. The study facilitator did not participate in the voting or comment review process.

Ethical approval was not required, as the study did not involve patient data or biological material.

The authors conducted an independent systematic review of current literature following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[9]. Articles published between 2010 and 2023 were reviewed in PubMed, Scopus, and Web of

Science databases, using keywords such as "Alzheimer disease" and supplemented with "diagnosis," "evaluation," "treatment," "therapeutic goals," "citicoline," "rivastigmine," and "cholinesterase inhibitors." Two reviewers independently selected the articles, from which the 31 questions or statements were derived.

Cronbach's alpha coefficient was used to determine the internal consistency of the assessment tool after each round[8]. This coefficient, ranging from 0 to 1, demonstrated the relationship among a set of test items as a group. The final round of consensus was defined by achieving a Cronbach's alpha > 0.80[10]. Data analysis was performed between rounds to identify statements with 80% consensus and 100% participation; those statements that did not reach these criteria were included in the next round of voting. Categorical variables were expressed as proportions (%).

Results

AD is traditionally defined as a neurodegenerative disorder characterized by a progressive decline of cognition or neurobehavioral symptoms, severe enough to impact daily activities. However, there is a shifting paradigm toward a more biological definition, utilizing precise markers to enhance diagnostic accuracy.

Loss of functionality is a key factor in distinguishing dementia from mild cognitive impairment. AD is associated with characteristic neuropathological features, including extracellular deposits of β-amyloid plaques and phosphorylated tau protein, which lead to progressive impairment of memory, learning, and executive function[11].

AD has two primary etiological types: familial and sporadic. The latter being the most common. Mutations in the amyloid precursor protein genes, presenilin-1 and presenilin-2, can cause familial AD[12].

Clinical phenotypes of AD encompass various presentations, including amnestic AD, posterior cortical atrophy, logopenic variant of primary progressive aphasia, behavioral or frontal dysexecutive variant, corticobasal degeneration, and semantic variant of primary progressive aphasia[13].

Evaluation of AD

Accurate and timely diagnosis is essential for effective management. Current diagnostic approaches for AD include clinical history, cognitive testing, imaging studies, and laboratory tests[11]. A comprehensive neuropsychological evaluation complemented by screening tests such as the mini-mental state examination or the Montreal cognitive assessment is recommended for patients with cognitive disorders.

Magnetic resonance imaging (MRI) is preferred for imaging studies in suspected AD cases, as it offers greater sensitivity in detecting characteristic cortical atrophy patterns and ruling out other causes of dementia. Medial temporal lobe atrophy on MRI is considered a biomarker for AD. Neuroinflammation is also recognized as a significant pathophysiological component in AD progression.

In Mexico, biomarkers in cerebrospinal fluid (total tau, phosphorylated tau, and amyloid b-42) can aid in confirming AD diagnosis, although their availability is limited and they are not deemed essential in routine clinical practice.

Table 1. Mechanisms of action of citicoline in AD

Enhances phospholipids synthesis in cell membrane.
Increases synthesis of acetylcholine, dopamine, and noradrenaline.
Prevents free radical generation in ischemic tissue.
Reduces apoptosis and exerts a neuroprotective effect.

AD: Alzheimer's disease.

Treatment of AD

The goal of modifying treatment in AD is to slow progression, delay cognitive and functional decline, and enhance quality of life, independence, and reduce the need for institutionalization and long-term care.

Acetylcholinesterase inhibitors such as rivastigmine, donepezil, or galantamine have demonstrated beneficial effects on cognitive function, daily activities, and global assessment in mild-to-moderate AD. Conversely, oral memantine has shown benefits in global assessment, cognitive function, daily activities, and behavior in moderate-to-severe AD.

Citicoline with its diverse mechanisms of action holds promise in AD treatment (Table 1).

The effective clinical dose of citicoline ranges from 500 to 2000 mg daily. There is evidence showing the benefit of the combination of an acetylcholinesterase inhibitor (rivastigmine, donepezil, or galantamine), together with a therapeutic potentiating agent such as citicoline in AD patients AD.

A "fixed-dose" combination refers to a blend of more than one drug in a constant ratio and a single dosage form, for the treatment of a specific condition[14]. In AD patients, the fixed-dose combination of rivastigmine and citicoline may be more effective than the use of both drugs administered in monotherapy. Citicoline has been shown to potentiate and prolong the beneficial effects of rivastigmine in AD; also, in combination with rivastigmine, it could delay cognitive decline in the disease. It has been observed that this combination may also be useful in the management of vascular dementia and mixed dementia. The benefits of this combination on cognitive function may be evident after 3 months of treatment. In addition, it may improve the administration and adherence to treatment in dementia patients.

Dosing of the fixed-dose combination is based on rivastigmine, with titration starting at 1.5 mg every 12 h, increasing to 3 mg every 12 h if the initial dose is well tolerated. Subsequent increases (4.5 and 6 mg every 12 h) are based on tolerability of the dose and are indicated after 2 weeks of treatment. The maintenance dose of the combination rivastigmine with citicoline in AD is 3 to 6 mg rivastigmine every 12 h (500-1000 mg citicoline).

Adverse events associated with the rivastigmine-citicoline combination are generally mild and predominantly related to the acetylcholinesterase inhibitor. The most frequent events include nausea, vomiting, diarrhea, anorexia, and abdominal pain.

Conclusion

AD is a highly prevalent progressive neurodegenerative disease and the most common form of dementia, impacting over than 55 million individuals globally. The diagnosis of AD is in constant evolution, with a current focus on utilizing neuroimaging techniques such as MRI and the increasing use of biomarkers to detect the disease in its early stages.

In terms of treatment, acetylcholinesterase inhibitors have been a primarily option in mild-to-moderate stages of the disease. However, the fixed-dose combination of rivastigmine with citicoline has been explored as a promising therapeutic strategy. This combination offers neuroprotection, while stimulating neuronal regeneration and reducing glutamate levels, resulting in significant improvement in cognitive function and delaying cognitive decline in AD. Future advancements in identifying accurate biomarkers are expected to enable earlier and more precise diagnosis of AD.

The fixed-dose combination of rivastigmine and citicoline could represent a valuable therapeutic choice with substantial benefits in AD patients, enhancing their quality of life and delaying disease progression. AD continues to pose a significant public health challenge, but the development of innovative treatments offers hope for a more effective management of the disease in the future.

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REVIEW ARTICLE

Cisternal puncture and cervical puncture: current uses and historical review

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Abstract

A 61-year-old female diagnosed with neurocysticercosis was evaluated in the interventional neuroradiology department. Cerebrospinal fluid by cervical puncture was requested by the attending physician, and informed consent was obtained. The process was completed satisfactorily; fluid samples were obtained on the first attempt, and no complications were noted. Despite their drawbacks, both cisternal and cervical punctures continue to be techniques of great value and scope for various types of patients, whose descriptions and procedures must be remembered. This article describes a case report and a bibliographic review of the procedures, history and progress, indications and contraindications, as well as their probable complications.

Keywords: *Cisternal puncture. Cervical puncture. Diagnostic test. Intrathecal administration.*

Punción cisternal y punción cervical: usos actuales y revisión histórica

Resumen

Una mujer de 61 años diagnosticada con neurocisticercosis fue evaluada en el departamento de neurorradiología intervencionista. El médico tratante solicitó una punción cervical para obtener líquido cefalorraquídeo y se obtuvo el consentimiento informado. El proceso se completó satisfactoriamente; se obtuvieron muestras de líquido cefalorraquídeo en el primer intento y no se observaron complicaciones. A pesar de sus inconvenientes, tanto la punción cisternal como la cervical siguen siendo técnicas de gran valor y alcance para diversos tipos de pacientes, cuyas descripciones y procedimientos deben ser recordados. En este artículo se describe un caso clínico y una revisión bibliográfica de los procedimientos, antecedentes y evolución, indicaciones y contraindicaciones, así como sus probables complicaciones.

Palabras clave: *Punción cisternal. Punción cervical. Prueba diagnóstica. Administración intratecal.*

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Introduction

Cisternal puncture (CP), also known as suboccipital puncture, is a medical technique initially used to obtain a sample of cerebrospinal fluid (CSF) from the subarachnoid space[1]. Cervical puncture (CerP), which is also a way to access the CSF in the lateral upper cervical spinal region, is an alternative to this technique, which has also been described similarly[2]. While not as commonly performed as lumbar puncture (LP), CP and CerP play a crucial role in diagnosing and managing various neurological conditions[2].

CSF surrounds the brain and spinal cord, and its analysis provides valuable information about infections, hemorrhages, tumors, and other pathologies. Unlike LP, which is performed at the lower lumbar level, CP occurs just below the skull in the cisternal space[3], while CerP performs a lateral puncture for accessing the upper spinal canal[2].

Some of the current applications of these techniques include:

- Diagnostic sampling: They allow the collection of CSF for biochemical, microbiological, and cytological analysis[4]. This can aid in diagnosing infections, tumors, and other neurological conditions.
- Intrathecal medication: These procedures enable the direct introduction of medications into the meningeal space. For instance, they can be used to administer contrast agents for myelography or to deliver therapeutic drugs[5].
- Increased intracranial pressure: In cases of elevated intracranial pressure or hydrocephalus, they may be used as a therapeutic measure to drain excess CSF and relieve symptoms[6].

Despite their historical significance, CP and CerP are now less commonly performed due to advances in other diagnostic techniques. However, they remain relevant in specific clinical scenarios: their diagnostic accuracy and ability to detect early neurological diseases make them a valuable tool in medical practice.

In this article, we will explore the indications, techniques, and clinical considerations associated with CP and CerP.

Clinical case

A 61-year-old female patient with a medical record of neurocysticercosis was scheduled for CSF sampling by LP. During the procedure, LP was performed, but CSF could not be obtained. Later, consultation was carried out with the Interventional Neuroradiology to perform sampling through CerP.

The patient was scheduled for CerP, achieving adequate sample collection without major peri- and post-procedure complications. The patient was discharged from a short stay on the same day.

Once the CerP was performed, the samples were sent for their analysis. The patient did not report any symptoms or adverse events related to the CerP.

Procedure description

Under conscious sedation, the patient was placed in a prone position, and an aseptic maneuver was carried out in the posterior cervical area. With fluoroscopy, the C1 and C2 cervical segments of the spine, the space between them, and the spinolaminar line were located.

Once the anatomical structures were identified, a simulation of the needle orientation through the overlay was performed using lateral and anteroposterior radiographic projections. The puncture site was anesthetized with lidocaine.

A 22 g needle was inserted medially using fluoroscopy guidance and continued to be advanced horizontally through planes of skin, connective tissue, trapezius, and occipital muscles; finally, resistance was encountered when reaching the dura mater. After penetrating the dura, it was advanced by 2 more millimeters, and the flow of CSF was verified. When no sample was obtained, the needle was repositioned caudally, making an angulation of approximately 30° (Fig. 1). It was verified again, and on verifying the successful exit of CSF, obtaining samples began (Fig. 2). A total of 25 mL of CSF was drained. Samples were sent for cytological and cytochemical studies and cultures, as well as a vial for storage in case, new tests were requested.

At the end of sampling, the needle was removed, and momentary compression was performed. The patient remained under surveillance for a few hours and did not report symptoms.

Early indications and techniques

The CP was first performed on living human patients by Dr. Alexandru Obregia in 1908[1] using a suboccipital approach where a needle was advanced along the inferior midline to the occipital protuberance[7].

In 1919, Dr. Ayer described his technique of cisterna magna puncture, introducing a needle a thumb's length cranial to the spinal process of C1 in the cervical spine, directing the needle in the same orientation[8]. By 1920, the same author had published his experience with 43 patients, all of whom were successful[9].

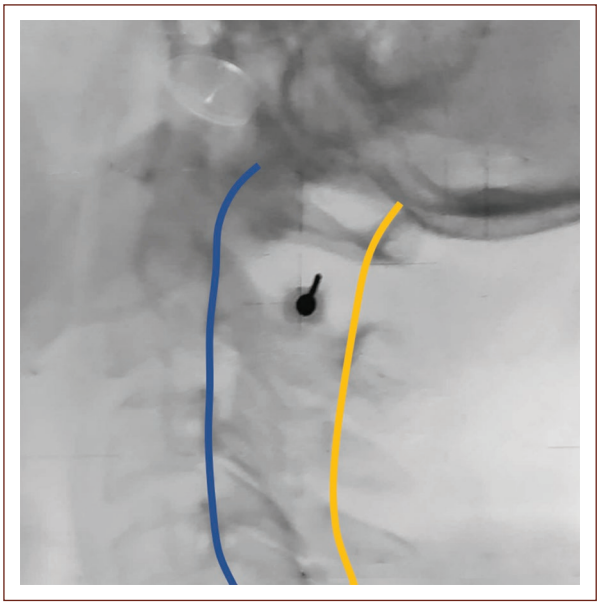

Figure 1. X-ray of the cervical spine showing the spinolaminar line in yellow and the posterior vertebral line in blue. Cervical puncture was performed near to the spinolaminar line, the needle is shown between them.

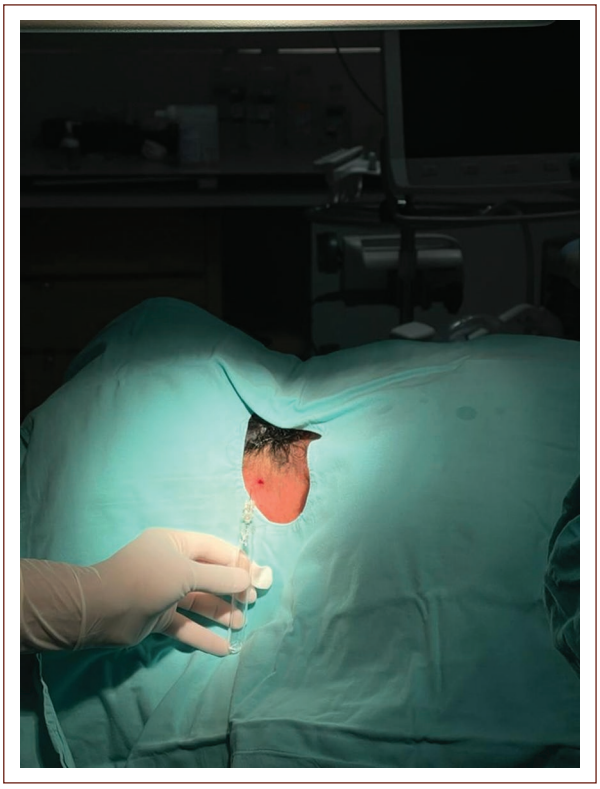

Figure 2. After the subarachnoid space was accessed, cerebrospinal fluid was collected and sent to analysis.

Initially, suboccipital punctures were performed for the sole purpose of obtaining CSF samples; however, with the advent of myelography, complication rates increased for this procedure, which led to the development of safer and more cost-effective techniques[10].

By the 1960s, various specialists in neurosurgery and radiology began to perform procedures using the C1-C2 space as access[11]. The CerP previously described is an example of this technique[2]. The advantage of this modified technique was the possibility of performing myelography with fewer complications and more direct access to the subarachnoid space[7,11].

Current use

With the advent of new non-invasive imaging techniques of the skull, brain, and central nervous system, mainly computed tomography and magnetic resonance imaging, the number of suboccipital puncture procedures decreased considerably, being relegated to patients with specific indications[7]. Likewise, lumbar access for contrast injection in myelograms gradually supplanted suboccipital or cervical access for myelograms, eventually falling into disuse.

Some of the current indications for CP or CerP include[7,8,12]:

- Failed or difficult LP
- Patients are not suitable for a radiographic investigation of the lumbar region
- Arachnoiditis, or infection of the site of the puncture
- Ankylosis or lumbar stenosis
- Spinal cord obstruction
- Intrathecal administration of drugs in patients who are not candidates for LP or radiographic investigation
- Stem cell transplantation
- Certain congenital spinal malformations.

Furthermore, some of the contraindications for these procedures include[7,8]:

- Lack of cooperation from the patient
- Local infection of the site of the puncture
- Coagulation disorders.

Regarding vertebral levels, CerP from C1-C2 is preferred over suboccipital access through the midline because a thickening forms in the subarachnoid space at the level of C2, allowing safer access for procedures to be performed[6]. In a lateral CerP, the remoteness of the vertebral artery from the puncture site provides a considerable safety margin for interventional manipulation

with a lower risk of bleeding[13]. This may vary depending on the disease and anatomical configuration of the vertebral artery and posterior cerebral circulation of each patient.

As mentioned, the lateral CerP at C1-C2 has several indications for this procedure. The vast majority of cases in which this intervention is performed are those with neurological pathology who have been candidates for LP but in which samples or successful access could not be obtained in the procedure. Some of the common causes of failed LP, include[6,12]:

- Ankylosis
- Lumbar stenosis
- Spinal cord malformations.

As previously discussed, these situations may encourage the physician to perform CerP or CP instead of LP.

For a lateral CerP, patients can be placed in a prone, lateral, or supine position with the head rotated, always keeping the possible access site visible[6,14]. The patient must be immobilized to prevent movement during the procedure. The puncture should be performed with a 20- to 23 g epidural needle and its stylet placed perpendicular to the patient (as close as possible to 90°) without changing its angulation until reaching the subarachnoid space[6].

Unlike a LP, the needle does not have the same support due to loose connective tissue, so the interventional doctor or an assistant must maintain the position and angle of the needle at all times while the procedure is completed[6,14].

For each vial or bottle of CSF, 1-2 mL must be collected, and samples can be obtained for storage in pathology, microbiology, and biochemistry laboratories[4]. If necessary, a larger sample can be collected as long as the patient is stable and viable for an extension in the duration of the procedure[4,6].

As happened in the clinical case, if CSF does not come out when the needle is in the correct position, the needle can be redirected 30° caudally to have better access to the subarachnoid space. If bleeding occurs during the procedure, it should be suspended and the needle removed as soon as possible to avoid injury to the subarachnoid space that could lead to neurological disability.

Limitations and complications

The complication rate from a CerP is around 0.05%, according to studies[15]. The most common side effect recorded was headache, mostly mild to moderate in intensity and self-limiting. The second is nausea and vomiting.

One of the most feared complications of CerP is bleeding due to a puncture or dissection of the arteries of the posterior circulation. The anatomical variants and pain of the vertebral artery, especially in its V3 segment, increase the possibility of complications due to bleeding[7]. However, if there is suspicion of normal variations, the patient can be turned slightly to anteriorize the vertebral arteries and reduce the risk of injury.

This technique, despite its adverse effects and the emergence of safer procedures, continues to be used in selected patients with contraindications to LP[15]. Eighty-five percentages of neuroradiology departments in the United States perform this procedure at least once a year, and most interventional radiology and interventional neuroradiology programs consider CerP within their curricula[16].

Certain authors have questioned the usefulness of CerP today, given access to imaging studies and diagnoses with a lower probability of complications. However, consensus among interventional radiologists and neuroradiologists has confirmed the usefulness of this study, as well as its value in the diagnosis and treatment of difficult patients[15,16]. Some studies have even hypothesized that CerP is an underused technique that could have a higher frequency in complicated cases[2].

Another point to highlight is the low complication rate of this procedure when performed by trained physicians with a high number of cases of CerP[2]. This supports the proposal to reintroduce or reinforce the teaching of the puncture technique, as well as the dissemination of its diagnostic advantages.

Ongoing research

Despite their infrequent usage, CP and CerP continue to be the subject of scientific studies and reviews. In 2017, the use of a lateral atlanto-occipital puncture was proposed instead of the standard C1-C2 technique for CSF sampling. The results of their study demonstrated similar efficacy to traditional punctures with a lower complication rate. Among the most common adverse events were headaches and transient elevations of blood pressure[17]. This technique has also been tested experimentally in animals using ultrasound as imaging support for the procedure instead of radiographic projections[3].

Likewise, CerP has regained utility for access to the epidural space[18] and drug administration[5] in patients with pathologies that limit the therapeutic approach through LP.

Conclusion

CP and CerP are safe and effective alternatives to performing procedures that involve access to the subarachnoid space whenever the LP is unsuccessful or is not significant.

Although rarely performed, they offer an alternative to LP. Despite their infrequent use, CP and CerP remain valuable techniques in specific clinical scenarios.

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study. The authors declare that the procedures followed were in accordance with the regulations of the relevant Clinical Research Ethics Committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data. The anonymity of the participants was preserved, and the data were used solely for scientific purposes.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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