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## Editorial



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EDITORIAL

# Revista Mexicana de Neurociencia: achievements, responsibility, and a shared vision for the future

## *Revista Mexicana de Neurociencia: logros, responsabilidad y una visión compartida para el futuro*

*Antonio Arauz*

*Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City, Mexico*

As Editor-in-Chief of the *Revista Mexicana de Neurociencia (RMN)*, it is both a privilege and a responsibility to reflect on the progress the journal has achieved and to outline the direction in which we aspire to move forward. In an era of rapid scientific transformation and increasing demands for rigor, transparency, and relevance, the journal has strengthened its role as a key platform for neurological scholarship in Mexico and Latin America.

One of the most important accomplishments of the *RMN* has been the consolidation of its editorial processes. Over recent years, we have worked to reinforce peer-review standards, promote methodological quality, and ensure ethical integrity across all published content. These efforts have resulted in a more robust and diverse portfolio of manuscripts, spanning clinical neurology, basic and translational neuroscience, neuroimaging, neurorehabilitation, neuroepidemiology, and public health – oriented research. Upholding scientific credibility remains the cornerstone of our editorial mission.

Equally central to our identity is the journal's commitment to serving as a voice for regional neuroscience. Neurological diseases represent a growing burden across Latin America, often within health systems characterized by limited resources, social inequities, and heterogeneous access to specialized care. By publishing research that reflects these realities, the *RMN* contributes evidence that is not only scientifically sound but also contextually meaningful. This perspective is essential for informing clinical practice, guiding health policy, and fostering solutions tailored to regional needs.

At the same time, the journal continues to evolve alongside the broader advances shaping modern neuroscience. The field is increasingly defined by precision medicine, multimodal neuroimaging, molecular and genetic insights, and data-driven methodologies. Traditional clinical paradigms are being complemented – and at times challenged – by network-based models of brain function, biomarker-guided diagnosis, and integrative approaches to neurological disease. As Editor-in-Chief, I view it as our responsibility to ensure that the journal remains receptive to innovation while maintaining critical appraisal and clinical relevance.

Therapeutic advances across neurology further underscore the importance of a balanced editorial vision. From acute stroke care and neuroimmunology to neurodegenerative diseases and neuromodulation, new treatments are reshaping patient outcomes. The *RMN* aims to serve as a conduit between discovery and practice by prioritizing articles that translate scientific progress into actionable knowledge for clinicians, educators, and researchers.

**Correspondence:**
Antonio Arauz
E-mail: antonio.arauz@prodigy.net.mx

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Looking ahead, several strategic priorities will guide the journal's development. First, the integration of digital health technologies, artificial intelligence, and machine learning into neuroscience research presents both opportunities and challenges. These tools hold promise for improving diagnosis, prognostication, and personalized treatment, yet they also require careful validation and ethical oversight. The journal is committed to promoting rigorous evaluation of these technologies and fostering informed discussion on their appropriate implementation.

Second, our understanding of neurological outcomes must continue to expand beyond traditional endpoints. Functional independence alone does not fully capture the long-term impact of neurological disease. Cognitive impairment, fatigue, mood disorders, social participation, and return to work are increasingly recognized as critical dimensions of recovery. Encouraging research that incorporates patient-centered outcomes and long-term follow-up will be essential to aligning neuroscience with the real-world experiences of those we serve.

Third, nurturing the next generation of neuroscientists and clinicians is a central component of our mission. The journal provides an academic space where early-career researchers can develop their scholarly voice, engage with the peer-review process, and contribute to the advancement of neurological knowledge. Strengthening mentorship, offering constructive editorial guidance, and maintaining high standards will ensure that this educational role continues to flourish.

Finally, collaboration remains fundamental to progress. Neurological diseases are complex and multifactorial, requiring multidisciplinary and multicenter approaches. By fostering national and international collaborations, the *RMN* can continue to act as a bridge between local expertise and the global neuroscience community, enhancing both visibility and impact.

In closing, the *RMN* stands on a solid foundation built through the collective efforts of its authors, reviewers, editorial board members, and readers. As Editor-in-Chief, I remain committed to guiding the journal with integrity, inclusiveness, and a forward-looking vision. Looking ahead to 2026, I extend my sincere best wishes to the neuroscience community for a year of continued scientific rigor, collaboration, and innovation. By embracing progress while remaining grounded in clinical reality and regional relevance, the journal will continue to serve as a trusted forum for advancing neurological knowledge, improving patient care, and strengthening the academic values that sustain our discipline in Mexico, Latin America, and beyond.

I look forward to a productive and impactful 2026 for our neuroscience community.

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ORIGINAL ARTICLE

# Prospective memory assessment in a Mexican sample with depression

*Derian Mandujano-Torres[1]*, Georgina Cardenas-López[1], Azzizudin Khan[2], and Raúl Durón-Figueroa[1]*

*[1]Universidad Nacional Autónoma de México, México City, Mexico; [2]Indian Institute of Technology Bombay, Bombay, India*

## Abstract

**Objective:** *To evaluate deficits in time-based and event-based prospective memory (PM) in Mexican individuals diagnosed with moderate to severe depression.* **Methods:** *Two PM paradigms and a high cognitive load task were administered to 22 participants (with and without depression). Performance in time-based and event-based tasks was compared using screen click frequency as an indicator of errors and overall performance.* **Results:** *Differences were found in event-based task performance compared to time-based tasks across both groups. Participants achieved an overall average score of 64.67 (SD = 15.45). No significant differences were found between conditions, except for a marginal effect observed in Task 6 ($p = 0.049$).* **Conclusions:** *These findings suggest variations in PM execution under cognitive load. However, the marginal statistical significance highlights the need for further studies with larger samples to obtain more robust data on cognitive impairment in this population.*

***Keywords:*** *Depression. Prospective memory. Cognition. Time.*

## *Evaluación de la memoria prospectiva en una muestra mexicana con depresión*

## Resumen

**Objetivo:** *Evaluar los déficits en la memoria prospectiva (MP) basada en tiempo y eventos en individuos mexicanos con diagnóstico de depresión moderada a severa.* **Métodos:** *Se administraron dos paradigmas de MP y una tarea de alta carga cognitiva a 22 participantes (con y sin depresión). Se comparó el desempeño en tareas basadas en tiempo y en eventos utilizando la frecuencia de clics en pantalla como indicador de error y rendimiento.* **Resultados:** *Se identificaron diferencias en el desempeño de las tareas basadas en eventos en comparación con las de tiempo en ambos grupos. Los participantes obtuvieron una puntuación promedio general de 64.67 (DE = 15.45). No se hallaron diferencias significativas entre condiciones, a excepción de un efecto marginal observado en la Tarea 6 ($p = 0.049$).* **Conclusiones:** *Los hallazgos sugieren variaciones en la ejecución de la MP bajo condiciones de carga cognitiva, aunque la sutil diferencia estadística subraya la necesidad de estudios con muestras más amplias para obtener datos más robustos sobre el deterioro cognitivo en la población afectada.*

***Palabras clave:*** *Depresión. Memoria prospectiva. Cognición. Temporalidad.*

***Correspondence:**
Derian Mandujano-Torres
E-mail: deriantorres@outlook.es

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## Introduction

Depression is the most prevalent mood disorder worldwide and one of the most common mental health conditions. It affects over 350 million people globally, with higher prevalence among women and individuals from lower socioeconomic backgrounds[1]. According to the Diagnostic and Statistical Manual of Mental Disorders[2], depression is characterized by persistent sadness, anhedonia, hopelessness, low self-esteem, and suicidal ideation, which must persist for at least 2 weeks for a clinical diagnosis[3,4]. These symptoms often coincide with cognitive impairments, including reduced flexibility and diminished executive functioning.

The etiology of depression involves genetic, epigenetic, and environmental factors that impact brain biochemistry and neural functioning. These changes can affect cognition, appetite, libido, and sleep, ultimately reducing individuals' quality of life and daily functioning[5]. Cognitive deficits in depression include impairments in psychomotor speed, attention, memory, and executive functions such as inhibition, motivation, and working memory. Neuroimaging studies report alterations in fronto-thalamic and limbic-frontal circuits[6], which tend to worsen with recurrent episodes, although partial cognitive recovery is observed during remission.

A key cognitive function affected by depression is prospective memory (PM) – the ability to remember and execute intended actions in the future. PM failures negatively impact daily functioning and emotional well-being. PM is typically divided into two subtypes: event-based PM (EBPM), where intentions are triggered by external cues, and time-based PM (TBPM), which relies on self-initiated processes to act at a specific time[7-12]. TBPM is considered more cognitively demanding, especially under high cognitive load, and particularly sensitive to impairments in attention and executive control[13-17]. Studies have shown that individuals with depression exhibit deficits in both types of PM, with TBPM being more affected[18-25].

Recent findings suggest that increased cognitive load further impairs PM performance, especially in TBPM tasks that require sustained monitoring and self-regulation[26]. However, little research has explored these effects in clinical populations within Latin America.

Given previous findings and the relevance of PM in everyday functioning, the present study aimed to compare time-based and EBPM performance between individuals with depression and non-clinical controls. We hypothesized that the depression group (DG) would show significantly poorer performance in both PM types, with greater impairment in TBPM tasks due to their higher cognitive demands.

### *Objective*

The objective of the study is to compare PM performance in Mexican patients with depression and a control group (CG) of non-clinical individuals.

## Methods

### *Participants*

The final sample included 22 participants aged 18-29 years (M = 22.96, standard deviation [SD] = 4.95), divided into a DG (DG; n = 13) and a CG (CG; n = 9). All participants had at least 8 years of education. The DG consisted of individuals with beck depression inventory (BDI) scores above 24, while the CG included participants with BDI scores below 24 and no history of depressive episodes, either current or remitted. Individuals undergoing pharmacological treatment or with a history of psychiatric or neurological conditions were excluded from both groups.

Although the inclusion criteria for the DG allowed for participants up to 65 years of age, the oldest participant included was 47, whereas in the CG, the maximum age was 26. This discrepancy in age ranges was not intentional but rather a consequence of the recruitment process. Nevertheless, all participants fell within the young adult range, minimizing the likelihood of age-related cognitive variability.

The severity of depression in the clinical group was classified as either mild or moderate. None of the participants in the DG were undergoing pharmacological treatment, psychotherapy, or any other form of intervention that could potentially influence memory performance.

Both groups were randomly assigned to two experimental conditions using the Pinetools software (Table 1).

### *Instruments and experimental paradigms*

#### *BDI*[27,28]

This inventory assesses depressive symptoms through 21 items, divided into two factors: affective-cognitive and vegetative-somatic. It uses a Likert-type scale ranging from 0 to 3, where 0 indicates no symptoms and 3 indicates severe symptoms. The version

**Table 1.** Number of participants by group and condition

| DG | | CG | |
|---|---|---|---|
| EEPM | TBPM | EEPM | TBPM |
| 6 | 6 | 7 | 6 |

EBPM: event-based prospective memory condition; TBPM: time-based prospective memory; DG: depression group; CG: control group.

adapted for the Mexican population (Jurado et al., 1998) has a Cronbach's Alpha of 0.94, ensuring high reliability.

### TBPM and EBPM experimental paradigm[26]

This 30-min paradigm consists of 120 multiple-choice general knowledge questions, with 15 s to respond to each. If a response is not provided within the allotted time, the question automatically advances. Simultaneously, the PM task is carried out under two conditions:

- EBPM: when the words "coin," "planet," or "state" appeared, participants had to click on the right side of the screen.
- TBPM: participants had to click on the right side of the screen every 5 min, with a clock placed nearby to assist them.

### High cognitive load task (QUEST1; Khan, 2007)

This task consists of 120 multiple-choice general knowledge questions, with a response time of 10 s per question. Unanswered questions were recorded as omissions. This task served as a distractor to assess PM under high cognitive load.

### Procedure

Participants were voluntarily recruited through social media. After explaining the study's objective, they received an informed consent form, followed by an interview and BDI administration. Based on the BDI results and the interview, participants were assigned to one of two groups: the DG or the CG. Random assignment to experimental conditions was conducted using Pinetools.

Experimental sessions lasted between 45 min and 1 h, conducted in a closed, well-lit, and ventilated room. Participants used an HP laptop with the necessary software installed, while the evaluator positioned themselves at a 135° angle from the participant.

### Description of each paradigm

#### Time-based task

In this paradigm, participants had to respond to six temporal stimuli by pressing the screen exactly every 5 min. A clock was placed near the participants, but they were explicitly instructed to avoid looking at it. Simultaneously, 120 general knowledge questions were presented to distract the participant and make it harder to accurately perceive the passage of time.

The QUEST1 task was administered simultaneously with the PM tasks. It was an independent task that participants performed in parallel to the main PM activities.

#### Event-based task

This task followed a similar structure, with 120 general knowledge questions presented. However, in this case, participants had to click on the right side of the screen whenever the words "coin," "planet," or "country" appeared in either the question or response options. It is important to note that only these specific words were relevant, and their occurrence was programmed to appear approximately every 5 min, similar to the time-based task.

### Statistical analysis

SPSS V.27 was used to calculate response frequencies by condition and to analyze sociodemographic data. Due to the non-parametric nature of the data, two statistical tests were applied: the Kruskal-Wallis test and the Mann-Whitney U test, to examine differences between conditions.

## Results

The descriptive and inferential results are summarized in tables 1-5. Table 1 outlines the distribution of participants across experimental groups and task conditions, showing a relatively balanced allocation. Tables 2 and 3 provide sociodemographic data, confirming that the overall sample consisted primarily of young adults, with no extreme demographic disparities between groups. In table 4, the Kruskal-Wallis test revealed no statistically significant differences across

**Table 2.** General sample sociodemographic data

| Data | Age | Sex | Occupation | Marital status | Total score |
|---|---|---|---|---|---|
| Total | M = 22.96<br>SD = 4.95 | F = 18<br>M = 7 | Student = 11<br>Graduate = 8<br>Employee = 6 | Single = 19<br>In a relationship = 6 | M = 64.67<br>SD = 15.45 |

M: mean; SD: standard deviation.

**Table 3.** Sociodemographic data by group

| Data | No depression (n = 13) | | | | With depression (n = 12) | | | |
|---|---|---|---|---|---|---|---|---|
| | Minimum | Maximum | Mean | Standard deviation | Minimum | Maximum | Mean | Standard deviation |
| Age | 18 | 47 | 23.15 | 7.4 | 18 | 26 | 22.75 | 2.09 |
| BDI | 2 | 13 | 7.76 | 3.63 | 16 | 50 | 27.16 | 9.33 |

BDI: beck depression inventory score.

**Table 4.** Kruskal-Wallis test for independent samples by condition

| Items | Significance |
|---|---|
| Correct click 1 | 0.252 |
| Correct click 2 | 0.488 |
| Correct click 3 | 0.126 |
| Correct click 4 | 0.126 |
| Correct click 5 | 0.583 |
| Correct click 6 | 0.049 |

**Table 5.** Mann-Whitney U test for independent samples by population

| Items | Significance |
|---|---|
| Correct click 1 | 0.728 |
| Correct click 2 | 0.689 |
| Correct click 3 | 0.810 |
| Correct click 4 | 0.810 |
| Correct click 5 | 0.980 |
| Correct click 6 | 0.936 |

conditions for most items, except for Task 6, which yielded a marginally significant result (p = 0.049). Table 5 presents the Mann-Whitney U test results comparing the depressed and non-depressed groups directly, where no significant differences were found for any task item. Together, these results suggest a general consistency in performance across groups and conditions, with only a slight deviation observed in one task that may warrant further exploration.

The sample primarily consisted of females aged 18-27, with a mean age of 22.96 years (SD = 4.95). Most participants were students and single. As shown in table 1, the total sample included 22 participants with a mean age of 22.96 years (SD = 4.95). Of these, 18 were women and 7 were men. Regarding occupation, 11 were students, 8 were recent graduates, and 6 were employed. In terms of marital status, 19 were single, and 6 were in a relationship. The average total score was 64.67 (SD = 15.45). Tables 2 and 3 present the sociodemographic data based on the experimental groups.

The difference in age ranges between groups was not intentional. While our inclusion criteria allowed for participants up to 64 years of age, the oldest participant in the DG was 47 years old, compared to a maximum age of 26 in the CG. This discrepancy was not pre-planned but rather a result of recruitment outcomes.

Subsequently, two non-parametric statistical analyses were conducted to compare performance in PM tasks based on the Population variable (participants with and without depression) and the Condition variable (Depression + Event, Depression + Time, No Depression + Event, No Depression + Time).

The Kruskal-Wallis test (Table 3) was used to evaluate differences in performance across experimental conditions. No statistically significant differences were found in most items, except for Task 6 ($p = 0.049$), where a marginal difference was observed. Meanwhile, the Mann-Whitney U test (Table 4) compared groups at the population level, with no significant differences detected in any of the evaluated tasks. Overall, the results suggest that neither the experimental condition nor the presence of depressive symptoms significantly influenced global performance in PM tasks.

## Discussion

The objective of this study was to compare the performance of individuals with and without depression in two PM conditions: time-based and event-based. The results indicate that there were no statistically significant differences in PM task performance between the experimental conditions, as all four groups exhibited similar and positive performance. Likewise, no significant differences were found between depression severity and performance in both PM conditions.

These findings are consistent with previous studies suggesting that PM impairment is not related to the severity of depressive symptoms[29-31]. However, they contrast with research on the persistence of cognitive deficits in patients with depression in remission.

Although our results suggest a trend toward lower performance in EBPM compared to TBPM, this difference was not statistically significant and should therefore be interpreted with caution. Furthermore, the presence of a visible clock during the tasks may have influenced participants' performance in the TBPM condition, potentially reducing the self-initiated monitoring demands typically associated with this paradigm. This factor represents a limitation, as it may have diminished the sensitivity of the TBPM measure.

Our comparison with Khan et al.[26] highlights important divergences that warrant further exploration. Differences in cultural context, participant characteristics, or methodological aspects – such as task design, cognitive load manipulations, or the nature of cues – could underlie the contrasting findings. For instance, the strategies employed by participants to estimate time or the presence of external timekeeping aids might vary across studies, affecting performance outcomes. Future research should consider these factors to better understand the conditions under which TBPM and EBPM differ, especially within diverse populations.

Moreover, Khan et al.[26], also reported that cognitive load (measured through the general knowledge questionnaire) had a greater impact on TBPM than on event-based memory. In contrast, in our study, questionnaire scores exceeded 65 points in the time conditions, whereas in the event conditions, most participants scored below 60. This suggests that the questionnaire did not interfere with TBPM performance, as most participants in this condition responded adequately to the tasks, particularly those with depression.

One of the main limitations of this study is the small sample size, which limits the generalizability of the results. Low participation, possibly related to the stigma associated with depression, hindered broader representation of the general population. Future research should aim to increase the number of participants and control for variables such as age and sex. Given this, replicating this study with a larger sample and in different population contexts would be highly recommended to evaluate the impact of various factors on PM.

One noteworthy finding is the marginally significant difference observed in Task 6 ($p = 0.049$). Although this result does not meet the conventional threshold for statistical significance, it may reflect an emerging pattern related to cognitive load or the structure of the task. Given the limited sample size, this result should be interpreted with caution. Nevertheless, it highlights the need for further studies with greater statistical power to determine whether this trend represents a true effect.

It should be noted that no corrections for multiple comparisons were applied in this study. This decision was made due to the exploratory nature of the research and the relatively small number of comparisons. However, this may increase the risk of Type I errors. Future studies should consider implementing correction procedures, such as Bonferroni or False Discovery Rate adjustments, to address this limitation.

Another limitation of this study lies in the lack of control over individual factors that may influence cognitive performance, such as anxiety, fatigue, or variations in circadian rhythms. Although these elements were not directly assessed, they could have had an impact on participants' execution of PM tasks. In addition, the absence of complementary assessments that could provide a broader understanding of the cognitive profile – such as measures of working memory, sustained attention, or processing speed – limits the interpretation of the specific processes involved. Including such evaluations in future research

would allow for a more nuanced analysis of the relationship between depressive symptoms and PM, as well as the executive components that underlie this function.

## Conclusion

The results of this study suggest that, within the studied population, there are no significant differences in PM performance between individuals with and without depressive symptoms, nor between time-based and event-based conditions. These findings indicate that, under the current experimental conditions, the presence of depression does not appear to affect PM performance. However, given the limitations related to sample size and demographic variability, these results should be interpreted with caution. Further research with larger, more diverse samples and additional controlled variables is necessary to clarify the relationship between depression and PM functioning. Considering the impact of PM deficits on daily life and their link to executive dysfunction, incorporating PM tasks into clinical cognitive assessments may contribute to the early detection of subtle cognitive impairments and inform more targeted, functionally relevant interventions for individuals with depression.

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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 considerations

**Protection of human subjects and animals.** The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

**Confidentiality, informed consent, and ethical approval.** The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

**Declaration on the use of artificial intelligence (AI).** The authors declare that an artificial intelligence tool was used to support the preparation of the manuscript (artificial intelligence tools, such as ChatGPT, were used solely for translation and stylistic editing purposes. The content of the manuscript is entirely original and was written by the authors).

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ORIGINAL ARTICLE

# Risk factors associated with phrenic nerve damage in patients post-COVID-19

*Amabeli Y. Longoria-Castro[1], Hermelinda Hernández-Amaro[1], Erika A. Torres-Carranza[1], Susana Reyes-Bravo[1], Heber J. Pech-Ortega[2], Rosario Gonzales-Vallejo[3], and Gerardo Marín-Márquez[4]**

*[1]Traumatology and Orthopedics Hospital, Mexican Social Security Institute "Dr. Victorio de la Fuente Narváez", Mexico City, Mexico; [2]Universidad Autónoma de Nuevo Leon, Facultad de Medicina, Monterrey, Mexico; [3]Education Research Institute, Universidad Veracruzana, Xalapa, Veracruz, Mexico; [4]Neural Dynamics and Modulation Lab, Cleveland Clinic, Cleveland,United States*

## Abstract

**Objective:** *To identify risk factors for phrenic nerve injury, a condition impacting respiratory function, in post-COVID-19 patients, and to understand its role in neurological complications to inform clinical strategies.* **Methods:** *A cross-sectional study with retrospective data collection analyzed medical records and electrophysiological studies of 228 post-COVID-19 patients (114 with phrenic nerve damage confirmed by nerve conduction studies and 114 controls without it) from a public rehabilitation unit (Mexican Social Security Institute, Jan-Jul 2021). Analyzed variables included demographics, pre-existing comorbidities (e.g., obesity, asthma, and type 2 diabetes), COVID-19 clinical details, and electrophysiological parameters confirming phrenic nerve status.* **Results:** *Multivariable logistic regression identified obesity (odds ratio [OR] 10.36, $p < 0.001$), asthma (OR 7.93, $p = 0.02$), male sex (OR 2.2, $p = 0.01$), and advanced age (OR 1.07/year, $p < 0.001$) as significant independent risk factors for phrenic nerve damage. Type 2 diabetes mellitus approached statistical significance ($p = 0.05$) but was not an independent predictor in the final model. Descriptively, in patients with phrenic nerve damage, 49.12% received corticosteroids and 68.42% had other peripheral nerve involvement; however, these were not identified as significant independent risk factors in the adjusted analysis.* **Conclusions:** *Phrenic nerve injury is an important post-COVID-19 complication. The conditions of obesity, asthma, being of male sex, and presenting an advanced age emerged as significant independent risk factors, identified through multivariable analysis, adjusting for potential confounders. These findings highlight the need for vigilant monitoring and tailored management strategies in post-COVID-19 patients with these characteristics.*

***Keywords:*** *Phrenic nerve damage. COVID-19. Risk factors. Long-term effects. Electrophysiological study.*

## *Factores de riesgo asociados con el daño al nervio frénico en pacientes Post-COVID-19*

## Resumen

**Objetivo:** *Identificar factores de riesgo para el daño al nervio frénico, una condición que afecta la función respiratoria, en pacientes post-COVID-19 y comprender su papel en complicaciones neurológicas para orientar estrategias clínicas.* **Métodos:** *Estudio transversal con recolección retrospectiva que analizó expedientes médicos y estudios electrofisiológicos de 228 pacientes post-COVID-19 (114 con daño confirmado al nervio frénico mediante estudios de conducción nerviosa y 114 controles sin daño) en una unidad pública de rehabilitación (IMSS, enero-julio 2021). Se evaluaron variables demográ-*

***Correspondence:**
Gerardo Marín-Márquez
E-mail: drmarin.neuroscience@gmail.com

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*ficas, comorbilidades preexistentes (obesidad, asma, diabetes tipo 2), detalles clínicos de COVID-19 y parámetros electrofisiológicos.* **Resultados:** *La regresión logística multivariada identificó como factores de riesgo independientes significativos la obesidad (OR 10.36, p < 0.001), el asma (OR 7.93, p = 0.02), el sexo masculino (OR 2.2, p = 0.01) y la edad avanzada (OR 1.07 por año, p < 0.001). La diabetes tipo 2 estuvo cerca de la significancia estadística (p = 0.05) pero no fue predictor independiente en el modelo final. Descriptivamente, el 49.12% de pacientes con daño al nervio frénico recibió corticosteroides y el 68.42% presentó afectación de otros nervios periféricos; sin embargo, estos no fueron factores de riesgo independientes tras el análisis ajustado.* **Conclusiones:** *El daño al nervio frénico es una complicación relevante post-COVID-19. Obesidad, asma, sexo masculino y edad avanzada son factores de riesgo independientes. Estos resultados destacan la importancia de monitorear y manejar de forma personalizada a pacientes post-COVID-19 con estas características.*

***Palabras clave:*** *Daño al nervio frénico. COVID-19. Factores de riesgo. Efectos a largo plazo. Estudio electrofisiológico.*

## Introduction

COVID-19 was declared a global pandemic by the World Health Organization on March 11, 2020, a significant milestone in global health[1,2]. In addition to respiratory symptoms, individuals affected by COVID-19 have been reported to encounter a range of neurological consequences, including cognitive changes, headaches, and more severe illnesses, such as encephalitis and stroke[3]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) capacity to traverse the blood-brain barrier indicates a direct route for causing neurological harm[4]. Around 82% of COVID-19 patients who are admitted to the hospital show signs of neurological problems[5]. This highlights the urgent requirement for a thorough understanding of how the virus affects the nervous system, given the wide range of symptoms observed[6,7].

Moreover, the extended COVID syndrome encompasses neurological dysfunctions as a prevalent consequence of the disease, exhibiting symptoms that vary from weariness and difficulty breathing to severe neurological disorders[8,9]. Furthermore, neurological complications, specifically the impact on the phrenic nerve, are crucial for respiratory function and the possible vulnerability to COVID-19 infections. This is of utmost importance in this situation, as evidenced by its contribution to restoring respiratory function in patients recovering from COVID-19[10,11]. COVID-19 has been found to be associated with neuropathies, such as mononeuritis of the phrenic nerve[12]. This highlights the importance of further investigating these neurological symptoms.

This study specifically examines the occurrence of phrenic nerve injury in post-COVID-19 patients who received treatment at the North Physical Medicine and Rehabilitation Unit of the Mexican Social Security Institute (IMSS). It aims to explore risk variables associated with this condition, with an emphasis on demographic and clinical factors commonly observed in post-COVID-19 patients. By analyzing medical data and conducting electrophysiological investigations, our objective is to provide valuable insights into this problem that occurs after COVID-19. This will contribute to further clarifying an area that, despite emerging interest, still requires more targeted research regarding its pathophysiology and clinical implications.

## Materials and methods

### Study design

This study utilized a cross-sectional design with retrospective data collection. All information was obtained from existing medical records and previously conducted electrophysiological studies performed between January and July 2021. No prospective or contemporaneous data were collected during the study period.

### Participants and sampling

This study included patients from the North Physical Medicine and Rehabilitation Unit of Traumatology, Orthopedics, and Rehabilitation, "Dr. Victorio de la Fuente Narváez" of the IMSS. A consecutive sampling method was used.

Inclusion criteria were: age 18 years or older, confirmed positive polymerase chain reaction (PCR) test for COVID-19, completion of an electrophysiological study for phrenic nerve conduction, and provision of informed consent. Exclusion criteria included: negative PCR result, history of cardiothoracic surgery, prior phrenic nerve damage, incomplete records, or absence of an electrophysiological study.

A total of 114 patients with phrenic nerve damage and 114 control individuals (without such damage), as confirmed through electrophysiological studies, were

included in the analysis. Their medical records were reviewed to identify potential associated risk factors.

A non-probabilistic cluster sampling approach was employed, with the sample including all eligible patients who met the inclusion criteria during the predefined period (January-July 2021) at the study site.

All patients with confirmed post-COVID-19 status who were referred for electrophysiological evaluation at the unit during the study period were considered for inclusion, regardless of the presence or absence of respiratory symptoms. However, referral patterns might have favored patients with clinical suspicion of neuromuscular or respiratory complications, which may introduce a degree of selection bias.

The timing between the onset of COVID-19 symptoms and the phrenic nerve conduction study did not exceed 3 months, as the retrospective analysis included data up to 6 months before the study period.

The following clinical and demographic variables were analyzed as covariates to assess their potential association with phrenic nerve damage in post-COVID-19 patients: corticosteroid administration, mechanical ventilation (MV), cerebrovascular accident (CVA), Guillain-Barré syndrome, type 2 diabetes mellitus (T2DM), systemic arterial hypertension (SAH), post-COVID-19 peripheral nerve injury, obesity, hypothyroidism, asthma, chronic obstructive pulmonary disease (COPD), prone positioning, age, sex, and weight. These variables were selected based on their known or suspected involvement in the pathophysiology of COVID-19-related neurological or respiratory complications.

## Enhancing diagnostic precision in phrenic nerve analysis

Nerve conduction studies were performed using a Nicolet VikingQuest electromyography system. All studies were conducted by attending physicians and residents specialized in Physical Medicine and Rehabilitation.

Phrenic nerve conduction studies were performed using a bipolar surface electrode setup. The active electrode was placed on the eighth intercostal space along the midclavicular line, adjacent to the costochondral junction, on the same side as the electrical stimulus. The reference electrode was positioned 2 cm lateral to the active electrode, near the anterior axillary line, and the ground electrode was placed at the midsternal line. Electrical stimulation was delivered at Herb's point using intensities ranging from 70 to 100 mA, employing the method described by Flores et al.[13].

### *Criteria for electrophysiological abnormalities*

Defining prolonged motor responses in the electrophysiological studies was anchored in scientifically established criteria. Latencies classified as prolonged were set between 6 and 8 ms, and reduced amplitudes were defined within a range of 500-800 mV. These criteria, reflecting the parameters found in Ricoy et al.'s research on diaphragmatic dysfunction, facilitated a consistent and accurate identification of electrophysiological abnormalities across the patient cohort[14].

### *Data analysis*

Descriptive statistics were used to summarize patient characteristics. Continuous variables were reported as mean ± standard deviation or median and interquartile range, depending on their distribution. Categorical variables were summarized as frequencies and percentages.

Phrenic nerve injury was analyzed as a binary dependent variable (present = 1, absent = 0). A multivariable binary logistic regression model was used to assess associations between phrenic nerve injury and selected covariates. Each covariate was coded as binary (1 = present, 0 = absent). Results are reported as odds ratios with 95% confidence intervals and corresponding p-values.

The $\chi^2$ test was used separately to compare baseline characteristics between patients with and without phrenic nerve damage. This was not part of the regression model but served to identify initial group differences.

$p < 0.05$ was considered statistically significant. All statistical analyses were performed using R Statistical Software (version 4.2.0).

## Results

### *Baseline characteristics*

A total of 114 post-COVID-19 patients with phrenic nerve damage were included. The mean age was 49 ± 10.7 years, with a range of 27-71 years, and 74.5% (n = 85) were male.

The most frequent comorbidities observed were obesity (37.71%), T2DM (32.45%), and SAH (28.94%). Other less prevalent conditions included asthma (5.26%), hypothyroidism (5.26%), CVA (4.38%), Guillain-Barré syndrome (1.75%), and COPD (0.78%).

Regarding treatment modalities, 56 patients (49.12%) received corticosteroids during hospitalization, and 20 patients (17.54%) required MV. This aligns with the

**Table 1.** This table provides a detailed breakdown of the most frequent neuropathic conditions identified in patients post-COVID-19. Each condition represents a specific type of peripheral nerve involvement, with frequencies and percentages reflecting their incidence within the patient cohort. The category "other types of neuropathies" includes less common neuropathies

| Condition | Frequency | % |
|---|---|---|
| Right phrenic nerve neuropathy | 36 | 11.84 |
| Bilateral phrenic nerve neuropathy | 35 | 11.51 |
| Bilateral tibial nerve neuropathy | 31 | 10.20 |
| Left peroneal nerve neuropathy | 24 | 7.89 |
| Left phrenic nerve neuropathy | 21 | 6.91 |
| Right peroneal nerve neuropathy | 20 | 6.58 |
| Right median nerve neuropathy | 19 | 6.25 |
| Bilateral peroneal nerve neuropathy | 17 | 5.59 |
| Left median nerve neuropathy | 15 | 4.93 |
| Right tibial nerve neuropathy | 14 | 4.61 |
| Left tibial nerve neuropathy | 11 | 3.62 |
| Left superficial peroneal nerve neuropathy | 10 | 3.29 |
| Right sensory median nerve neuropathy | 6 | 1.97 |
| Bilateral superficial peroneal nerve neuropathy | 6 | 1.97 |
| Other types of neuropathies | 39 | 12.83 |

recommendations from the treatment guidelines for COVID-19 in Mexico, which advise the use of corticosteroids in patients with severe disease to improve clinical outcomes, particularly among those requiring supplemental oxygen[15].

While the primary focus of this study was phrenic nerve damage, other peripheral nerve involvements were identified and are detailed in table 1.

Phrenic nerve conduction studies measured latency and amplitude of compound muscle action potentials (CMAP). Normal latency ranges from 6 to 8 m in healthy adults, with typical CMAP amplitudes between 500 and 800 μV. Prolonged latency or reduced amplitude indicates phrenic nerve dysfunction, consistent with demyelination or axonal injury.

The logistic regression model's fit was assessed using the Hosmer-Lemeshow goodness-of-fit test, which yielded a borderline p-value ($p \approx 0.05$). This result suggests a marginally acceptable fit but also indicates that the model may not perfectly capture the data structure.

**Table 2.** Comorbidities in patients with phrenic nerve damage. Detailed breakdown of the percentage of patients with each comorbidity. Include the prevalence of obesity, type 2 diabetes mellitus, and systemic arterial hypertension, and consider adding other relevant comorbidities

| Comorbidity | % |
|---|---|
| Obesity | 37.71 |
| Type 2 diabetes mellitus | 32.45 |
| Systemic arterial hypertension | 28.94 |
| Cerebral vascular accident | 4.38 |
| Asthma | 5.26 |
| Hypothyroidism | 5.26 |
| Guillain-Barré syndrome | 1.75 |
| COPD | 0.78 |

COPD: chronic obstructive pulmonary disease.

### *Risk factors*

Table 2 provides a detailed analysis of potential risk factors for phrenic nerve damage. It compares the prevalence of specific variables in patients with and without phrenic nerve damage and includes results from the binary logistic regression analysis.

The risk factor analysis in table 3 suggests that obesity, asthma, male sex, and increasing age are significant risk factors for phrenic nerve damage. Type 2 diabetes approaches significance, but the possibility of a type 1 error cannot be ruled out. The Hosmer-Lemeshow test yielded a $p = 0.05$, indicating that the model fits well and can predict data within the observed range.

## Discussion

Our study identified age as a primary risk factor for phrenic nerve damage in post-COVID-19 patients. This aligns with findings by Wu et al., who suggest an increased likelihood of neurological complications with advancing age[16]. Pietrobon et al. define immunosenescence as a decline in innate and adaptive immunity leading to increased pro-inflammatory cytokines,

**Table 3.** Risk factors associated with phrenic nerve damage

| Risk factor | W/L phrenic nerve | WO/L phrenic nerve | B | $\chi^2$ | p | OR | IC 95% | |
|---|---|---|---|---|---|---|---|---|
| Age | $\bar{x}$ = 49 ± 10.7 | $\bar{x}$ = 44 ± 9.7 | 0.07 | 14.66 | < 0.001 | 1.07 | 1.03 | 1.1 |
| Sex | M (85) F (29) | M (63) F (51) | 1.08 | 2.46 | 0.01 | 2.2 | 1.19 | 4.4 |
| Asthma | 6 | 2 | 2.07 | 2.195 | 0.02 | 7.93 | 1.39 | 65.12 |
| Obesity | 43 | 7 | 2.33 | 16.28 | < 0.001 | 10.36 | 4.49 | 27.34 |
| T2DM | 37 | 19 | 1.15 | 4.24 | 0.05 | - | - | - |
| PN injury | 78 | 50 | –0.83 | 2.2 | 0.14 | - | - | - |
| CVA | 5 | 5 | –1.54 | 1.31 | 0.25 | - | - | - |
| SAH | 33 | 18 | –0.08 | 0.02 | 0.88 | - | - | - |
| GBS | 2 | 0 | 20.41 | 0 | 1 | - | - | - |
| MV | 20 | 0 | 30.08 | 0 | 1 | - | - | - |
| Prone | 5 | 0 | 16.49 | 0 | 1 | - | - | - |
| COPD | 1 | 0 | –9.35 | 0 | 1 | - | - | - |
| Hypothyroidism | 6 | 1 | –12.26 | 0 | 1 | - | - | - |
| Corticosteroids | 56 | 0 | 29.85 | 0 | 1 | - | - | - |

W/L: with lesion (non-control group); WO/L: without lesion (control group); PN injury: periferic nerves injury; CVA: cerebrovascular event; SAH: systemic arterial hypertension; GBS: Guillian-Barre syndrome; T2DM: type 2 diabetes mellitus; MV: mechanical ventilation; Prone: prone position; COPD: chronic obstructive pulmonary disease; OR: odds ratio.
By analyzing only the statistically significant variables, age, sex, asthma, and obesity, the regression model achieves a similar result compared to a model that includes all variables (in R Studio).

which could contribute to this damage, as observed in SARS-CoV-2 patients[17].

Previous research has identified an association between COVID-19 and cerebrovascular disease, including ischemic and hemorrhagic strokes, attributed to hyperinflammatory and hypercoagulable states induced by the infection[18]. These align with our observations, suggesting that similar inflammatory mechanisms may contribute to peripheral nerve damage, such as the phrenic nerve.

In addition, a systematic review with meta-analysis showed a significant relationship between age and the development of neurological complications in COVID-19 patients, including cerebrovascular diseases, peripheral neuropathies, and encephalopathies[19]. This suggests that observing aging-associated chronic inflammatory processes may predispose older individuals to a higher risk of neurological damage.

A retrospective study highlights a relationship between COVID-19 and abnormalities in electroneuromyographic studies, such as an increase in non-evoked motor and sensory nerves, as well as impairments in motor nerve latency, amplitude, and conduction velocity[20]. This suggests that the interaction between comorbidities and the severity of the disease may exacerbate neuromuscular damage, highlighting the need for detailed neurophysiological evaluations in this population.

Advanced age, alongside diabetes mellitus and other factors, significantly increases the risk of developing severe neurological complications in COVID-19 patients, which in turn raises the risk of death by 7.6 times, highlighting the importance of considering age in the management of post-COVID-19 patients[21].

In addition, risk factors for severe COVID-19 in hospitalized adults of different ages can influence the severity and outcomes of COVID-19[22]. This is relevant for a better understanding of how age influences the risk and severity of phrenic nerve damage in post-COVID-19 patients. Collectively, these findings highlight the importance of a detailed neurological assessment in elderly post-COVID-19 patients, especially those with comorbidities that may exacerbate neurological damage.

The mean age in our study was 49 years, consistent with data from the Secretary of Prevention and Promotion of Health[23]. Likewise, to relate male gender as a significant risk factor for phrenic nerve damage in post-COVID-19 patients, one can include a study by Jin et al., where it was found that there were more severe

COVID-19 cases in men than in women, according to the clinical classification of severity. This study suggests that there are differences in morbidity and mortality between men and women with COVID-19[24]. These findings highlight the need to consider gender in the evaluation and treatment of patients with COVID-19, especially in those who present neurological manifestations such as phrenic nerve damage.

Most patients with post-COVID-19 phrenic nerve damage in our study were male, a trend also noted by Vahidy et al., and others about severe COVID-19 outcomes[25].

In our post-COVID-19 study, obesity, SAH, and T2DM emerged as predominant comorbidities associated with phrenic nerve damage. Nalbandian et al. have reported a range of post-COVID-19 clinical manifestations, including persistent dyspnea and exercise intolerance, which are not always explainable through conventional clinical assessments[26].

In addition, the predominant presence of obesity, SAH, and T2DM in our study reflects findings reported in the literature, where these comorbidities are associated with an increase in the severity of COVID-19[27].

An extensive analysis indicates that these patients have a higher risk of severe clinical outcomes, including intensive care unit (ICU) admission and higher mortality rates. This pattern of comorbidities could influence the development of neurological complications, such as damage to the phrenic nerve. The relationship between these chronic conditions and post-COVID-19 phrenic nerve dysfunction underscores the importance of a comprehensive assessment that includes metabolic and vascular risk factors in the recovery of post-COVID-19 patients[28].

Clinical manifestations such as persistent dyspnea and exercise intolerance, reported by Nalbandian et al.[26], may be more frequent in patients with these comorbidities, as these symptoms, often not fully explainable through conventional clinical assessments, could be related to phrenic nerve dysfunction. This reinforces the need to improve systematic evaluations of phrenic nerve function in post-COVID-19 patients, especially in those with obesity, hypertension, and diabetes. Implementing detailed evaluation protocols for phrenic nerve function could help better identify and manage these neurological complications, contributing to a more effective and personalized recovery[29].

Our study addressed this gap by implementing an electrophysiological survey on phrenic nerve conduction. This survey revealed a significant association between these comorbidities and phrenic nerve damage, which has important implications for treating and predicting outcomes in post-COVID-19 patients.

We also identified asthma as a risk factor, though its relationship with COVID-19 severity remains a subject of ongoing debate[30].

Diaphragmatic dysfunction can occur in COVID-19 patients, potentially exacerbated using thoracic support devices, as suggested by Ramani et al. Our study found a lower proportion of patients requiring MV, yet we consider direct neuromuscular involvement by SARS-CoV-2 a plausible contributor to diaphragmatic dysfunction. Autopsy studies have revealed ACE2 expression in the human diaphragm and SARS-CoV-2 ribonucleic acid in some COVID-19 patients[31].

The relationship between asthma and phrenic nerve damage in COVID-19 patients could be mediated through various pathways. Studies have suggested that alterations in lung function and inflammatory responses in asthmatic patients may influence the severity of respiratory infections, including COVID-19[32]. On the other hand, an analysis by Sunjaya et al. indicates that asthmatic patients did not show a significant increase in the severity of COVID-19, suggesting a complex interaction between asthma, an anti-inflammatory medication used, and the body's response to the virus[33].

Therefore, our findings suggest that asthma in post-COVID-19 patients warrants particular attention in neurological evaluation, particularly those showing phrenic nerve damage. Given that respiratory function can be compromised in asthmatic patients, it is crucial to consider how asthma might affect the recovery from phrenic nerve damage. Understanding the interplay between asthma, COVID-19, and phrenic nerve damage can offer valuable insights for improving neurological and respiratory outcomes in this population[34].

Notably, in our study, obesity was the most significant comorbidity. Obese patients faced a higher risk of hospitalization and severe disease, including an increased likelihood of ICU admission. Men with obesity, type 2 diabetes, or SAH were particularly susceptible to complications[35].

In this context, obesity emerges as a critical risk factor in the exacerbation of phrenic nerve damage. Obesity, characterized by a chronic inflammatory state, has been shown to increase the severity of COVID-19, leading to a greater need for hospitalization and MV, as evidenced in studies reporting a higher prevalence of obesity in critical COVID-19 patients[36]. Given that the majority of our post-COVID-19 phrenic nerve damage patients were male, it is crucial to consider how the

intersection of gender and obesity may influence the severity of neurological damage.

Moreover, obesity not only increases the risk of severe COVID-19 complications but also complicates its management and diagnosis. The accumulation of visceral fat, particularly in young patients with obesity, can be a predictor of COVID-19 severity, contributing to respiratory failure and, potentially, phrenic nerve damage, as obesity has been shown to negatively impact the efficacy of MV, which is particularly relevant for our study, where most patients with phrenic nerve damage required ventilatory support[37].

Collectively, these findings highlight the importance of a detailed neurological evaluation of post-COVID-19 patients, especially those with comorbidities such as obesity, which can exacerbate neurological damage.

Corticosteroid treatment in the ICU has been linked to muscle weakness, as noted by McClafferty et al., but was less common in our study[38].

In contrast to our findings of a significant prevalence of demyelinating neuropathies in post-COVID-19 patients, the study by Law et al.[39] reports a lower rate of phrenic nerve neuropathy in a similar cohort. In addition, this higher prevalence counters studies such as that of Lotan et al. and others, which suggest that although demyelinating events of the central nervous system associated with SARS-CoV-2 infection have been reported, the rate of these events is relatively low compared to the prevalence of SARS-CoV-2 infection[40]. This indicates that, although there is a relationship between COVID-19 and demyelinating diseases, their incidence may be lower than what our results suggest.

The variability in the presentation of these neurological symptoms reflects the complexity of COVID-19's impact on the nervous system and could contribute to the differences observed in studies on demyelinating neuropathies[41].

Critical illness polyneuropathy (CIP), described by Ramani et al.[31] and others, is a concern in patients with extended hospital stays. Interestingly, in our post-COVID-19 patients with phrenic nerve damage, we found that demyelinating pathology was more prevalent. Therefore, the prevalence of demyelinating pathology in our study highlights the need for a personalized diagnostic and therapeutic approach for post-COVID-19 patients with phrenic nerve damage. The findings suggest that CIP and other demyelinating neuropathies may be a significant concern in these patients, especially those with prolonged hospital stays. Thus, continued research is crucial to understanding these pathological mechanisms better and developing more effective treatment strategies[42].

Finally, it is crucial to recognize the importance of assessment tools in COVID-19. A study conducted by Alvarado-Martínez et al. evaluated the accuracy of prognostic scales for predicting mortality in COVID-19 patients. They found that certain scales, such as the COVID-GRAM critical illness risk score, were particularly effective. This underscores the need for precise and reliable evaluation methods in the clinical management of COVID-19. The underlying risk factors and complications associated with COVID-19, such as phrenic nerve damage, require meticulous attention and detailed evaluations to improve patient outcomes and quality of life[43].

### *Limitations of the study*

This study has limitations that should be acknowledged. First, the sample was derived from a single rehabilitation center using non-probabilistic cluster sampling, which may introduce selection bias, particularly as patients referred for electrophysiological studies likely had neuromuscular or respiratory symptoms. In addition, data on some potentially relevant clinical variables, such as the severity of COVID-19 infection or duration of MV, were limited or unavailable, which may confound the associations observed. Finally, electrophysiological measurements were based on specific latency and amplitude thresholds that, while grounded in literature, may not capture the full spectrum of phrenic nerve dysfunction.

### *Implications for future research*

Future studies should aim to address the limitations identified in this research by adopting prospective longitudinal designs that allow for causal inference and temporal assessment of phrenic nerve injury progression in post-COVID-19 patients.

## Conclusion

Obesity, SAH, asthma, advanced age, and male gender are identified as significant risk factors for phrenic nerve damage in post-COVID-19 patients. Despite tending significance, type 2 diabetes failed to establish itself as an unequivocal risk factor. These observations underscore the importance of conducting thorough demographic analysis and assessing comorbidities when attempting to comprehend the neurological consequences of COVID-19. They also emphasize the need

for diligent clinical monitoring and care among a wide range of patients. Identifying these particular risk factors enhances our understanding of the neurological consequences of COVID-19 and facilitates the development of more customized and effective treatment strategies. Acquiring such knowledge is crucial for the clinical management of those affected, supporting an integrated approach that combines risk factor investigation with clinical evaluation to improve recovery and quality of life for individuals who have recovered from COVID-19.

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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 considerations

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

**Confidentiality, informed consent, and ethical approval.** The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

**Declaration on the use of artificial intelligence (AI).** The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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ORIGINAL ARTICLE

# Grades 3 and 4 adult-type diffuse gliomas: epidemiology and radiomics in Guanajuato, Mexico

*Luis E. Ayala-Hernández[1], Raúl Gómez-Gómez[2], Armando Gallegos[1]*, and Raúl A. Hernández-Estrada[2]*

[1]*Departamento de Ciencias Exactas y Tecnología, Centro Universitario de los Lagos, Universidad de Guadalajara, Lagos de Moreno, Jalisco;* [2]*Servicio de Neurocirugía, Unidad Médica de Alta Especialidad, Hospital de Especialidades 1 Centro Médico Nacional del Bajío, León, Guanajuato. Mexico*

## Abstract

**Objective:** *The objective of the study is to report epidemiological characteristics and prognostic factors of patients with adult-type gliomas treated in the neurosurgery department of the National Medical Center of Bajío, as well as to evaluate, for the 1st time in Mexican patients, surface regularity (SR).* **Methods:** *Epidemiological and clinical features were statistically compared with international references. Survival was estimated using the Kaplan-Meier method. Kaplan-Meier curves were compared with the log-rank test. SR was obtained by segmenting magnetic resonance imaging.* **Results:** *Median age of patients with glioblastomas was less than that of patients in the United States (p = 0.021). The administration of radiotherapy (RT) and temozolomide (TMZ) prolonged survival (median gain of 35 months). Median SR was 0.6006 and was close to being statistically lower than the value reported in a large cohort (p = 0.09).* **Conclusions:** *Glioblastomas were diagnosed at younger ages and appeared to be more aggressive. The administration of RT and TMZ prolonged substantially survival.*

***Keywords:*** *Central nervous system neoplasms. Glioblastoma. Radiomics. Survival analysis. Age of onset.*

## *Gliomas difusos de tipo adulto grado 3 y 4: epidemiología y radiómica en Guanajuato, México*

## Resumen

**Objetivo:** *Reportar las características epidemiológicas y los factores pronósticos de los pacientes con gliomas de tipo adulto tratados en el servicio de neurocirugía del Centro Médico Nacional del Bajío, así como evaluar, por primera vez en pacientes mexicanos, la regularidad de la superficie.* **Métodos:** *Se compararon estadísticamente las características epidemiológicas y clínicas con referencias internacionales. La supervivencia se estimó mediante el método de Kaplan-Meier. Las curvas de Kaplan-Meier se compararon con la prueba de log-rank. La regularidad de la superficie se obtuvo mediante la segmentación de la resonancia magnética.* **Resultados:** *La mediana de edad de los pacientes con glioblastomas fue menor que la de los pacientes en Estados Unidos (p = 0.021). La administración de radioterapia y temozolomida prolongó la supervivencia (ganancia mediana de 35 meses). La regularidad de la superficie mediana fue de 0.6006 y estuvo cerca de ser estadísticamente menor que el valor reportado en una cohorte grande (p = 0.09).* **Conclusiones:** *Los glioblastomas se diagnosticaron a edades más jóvenes y parecieron ser más agresivos. La administración de radioterapia y temozolomida prolongó sustancialmente la supervivencia.*

***Palabras clave:*** *Neoplasias del sistema nervioso central. Glioblastoma. Radiómica. Análisis de supervivencia. Edad de inicio.*

***Correspondence:***
Armando Gallegos
E-mail: gallegos@culagos.udg.mx.

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## Introduction

Adult-type diffuse gliomas represent the bulk of adult neuro-oncology practice[1]. Treatment mainly consists of surgical resection, radiotherapy (RT), and chemotherapy. However, findings in recent years indicate that enrolling patients in clinical trials is now the preferred option[2]. Prognosis varies depending on type of tumor. Glioblastoma IDH-wildtype has the worst prognosis, and oligodendroglioma IDH-mutant and 1p/19q-codeleted have the best prognostic[1,3]. Annual age-adjusted incidence rates for glioblastoma have increased in recent years in the United States and Canada[4,5]. The World Health Organization (WHO) suggests that environmental factors might be responsible for this increase[1]. Recent studies have revealed ethnic variations in incidence, epidemiology, and survival in patients with adult-type diffuse gliomas[6]. In Mexico, there is a lack of studies reporting information on this subject and the few addressing consider mainly patients treated in care centers located in Mexico City[7-10]. Thus, there are regions that have never been explored, such as the State of Guanajuato. This lack of information hinders the practice of neuro-oncology in accordance with the Mexican context.

On the other hand, radiomics is defined as the conversion of medical images to higher-dimensional data and the subsequent mining of these data for improved decision support[11]. Given the central role of medical imaging in diagnosing and managing various diseases, cancer care centers in developing countries are typically equipped with medical imaging equipment. In contrast, other technologies, such as those required to assess molecular profiles, are rarely available in such centers. Hence, there is a growing interest in incorporating radiomics into the clinical management of adult-type diffuse gliomas in developing countries. The glioblastoma surface regularity (SR), a measure describing how much the tumor resembles a sphere, obtained from contrast-enhanced pre-treatment T1-weighted magnetic resonance imaging (MRI), was found to be a predictor of overall survival (OS)[12].

The aims of this study, focusing on grade 3 or 4 adult-type diffuse gliomas, are (1) to report epidemiological and clinical aspects, OS, and prognostic factors of patients treated at the National Medical Center of Bajío (CMNB by its Spanish acronym) and (2) to evaluate SR of the patients with glioblastoma.

## Materials and methods

### Study design and participating patients

With code R-2023-1001-038, the study was approved by the research ethics committee of the CMNB. No informed consent was necessary. We conducted a retrospective cohort investigation, reviewing the medical records of patients treated in the neurosurgery department between January 2019 and December 2023. 65 glioma diagnoses were identified. To include patients in the study, inclusion criteria were (i) age ≥ 18 years at surgery, (ii) grade of tumor 3 or 4 at diagnosis, (iii) availability of diagnostic histopathological results, (iv) availability of information on treatments received, and (v) availability of information on OS or last follow-up, as applicable. A total of 35 patients satisfied the inclusion criteria.

### Histopathological classification

With the histopathological results, tumors were classified, when possible, according to the current WHO classification of central nervous system (CNS) tumors published in 2021 (2021 WHO classification). This classification requires the assessments of the status of *IDH1* and *IDH2* genes and 1p/19q codeletion to assign the type of adult-type diffuse gliomas[13]. When it was not possible to classify tumors according to the 2021 WHO classification due to the lack of molecular information, in most cases, the mutations in *IDH1* and *IDH2* genes other than IDH1-R132H, the term “by pathologist experience” was added to the diagnosis stated in the histopathological reports. Because 4-7% of patients > 55 years only rarely develop a glioma that is IDH-mutant[14,15], and the IDH1-R132H mutation accounts for 89-93% of all IDH1 and IDH2 mutations[14-17], the WHO recommends not testing for non–IDH1-R132H mutations in patients >55 years whose tumors are negative for IDH1-R132H by immunohistochemistry. Thus, patients with a diagnosis of glioblastoma in the histopathological results with a negative test for IDH1-R132H mutation by immunohistochemistry and >55 years at surgery were classified as IDH-wildtype glioblastoma.

### Images and SR

From this 35 patient population, the glioblastoma patients with availability of a pre-treatment contrast-enhanced T1-weighted MRI with section thickness ≤ 2.0 mm, spacing between sections ≤ 1.0 mm, gap ≤ 0 mm, and pixel spacing ≤ 1.0 mm, were selected for

a radiomics study. Image inclusion criteria were taken from the work by Pérez-Beteta et al.[12] Figure SM1 in supplementary material (SM) shows a flow chart of the patients included in the study.

T1-weighted MRIs were loaded into 3D Slicer software[18] version 5.6.1 and were manually segmented in the axial plane to identify the tumor region. Once MRIs were segmented, 3D Slicer computed the volume and surface of the tumors. 3D slicer uses two methods to calculate geometric measurements: the "Label Map" method and the "Closed Surface" method. We chose the latter because it is appropriate for calculating surfaces. Following Pérez-Beteta et al.[12] methodology, the surface regularity was then calculated using the mathematical formula

$$S_R = 6\sqrt{\pi}\frac{T_V}{\sqrt{T_S^3}}$$

where $T_V$ corresponds to the total tumor volume and $T_S$ is the total tumor surface. Given the limited number of patients who met image inclusion criteria, an exhaustive radiomic analysis was not feasible. Therefore, we opted not to perform a segmentation reproducibility analysis. Figure 1 shows an example of a segmented tumor with its three-dimensional reconstruction.

### Statistical analysis

The statistical analysis was performed in R software version 4.3.2[19]. Using the EnvStats package[20], one-sample sign test was applied to statistically compare a median with a reference value. Once the mathematical assumptions were verified, i.e., expected successes and failures > 5, one-proportion Z test was used to compare a proportion with a reference value. Proportion comparison between two groups was done using the Fisher test. The association between two variables was evaluated with the Spearman correlation coefficient. OS probabilities from the date of surgery were calculated using the Kaplan-Meier method. Patients who were alive until April 24, 2024 (last database revision) were treated as censored events. The function survfit defined in the survival package[21] and the function ggsurvplot in the survminer package[22] were used to calculate OS and plot Kaplan-Meier curves, respectively. Differences between Kaplan-Meier curves were evaluated with the log-rank test. Cox proportional hazards model was used to calculate the hazard ratio (HR) of a variable in the OS analysis. Confidence intervals (CI) for HRs were calculated with the Wald statistic. $p < 0.05$ was considered statistically significant.

## Results

### Study population and clinical findings

Patient characteristics are detailed in table 1. Astrocytomas were diagnosed at a younger age (median age at surgery 32 years) than glioblastomas (median age at surgery 58 years), the group formed by glioblastoma by pathologist experience and IDH-wildtype glioblastoma (n = 30), and oligodendrogliomas (median age at surgery 47 years). The median age at surgery for patients with glioblastomas was statistically less than that of patients in the United States (p = 0.02), 66 years reported by the Central Brain Tumor Registry of the United States (CBTRUS) in 2023[23]. Due to the few patients with astrocytomas (n = 3) and oligodendrogliomas (n = 2), median ages at surgery for these groups were not statistically compared with those reported by CBTRUS 2023.

Regarding biological sex, most patients with astrocytic tumors (glioblastomas and astrocytomas) were males (67%) and oligodendroglial tumors were diagnosed only in women. The proportion of males with glioblastomas (67%) was not statistically greater (p = 0.18) than that reported by CBTRUS 2023 (58.5%)[23]. The most common initial symptoms for glioblastoma patients were classified, following WHO standards[1], as focal neurological deficits (73%, 22/30), followed by symptoms of elevated intracranial pressure (70%, 21/30). Both seizures and symptoms of elevated intracranial pressure were the most common initial symptoms for astrocytoma patients (67%), and for oligodendroglioma patients, the most common initial symptoms were the same as for glioblastoma patients (Table 1). The median time from symptom onset to surgery was 46 days (range 12-410 days) for glioblastoma patients. For 77% of them, the time from initial symptoms to surgery was < 3 months. No statistical differences were observed when compared to 68% reported by the WHO[1] (p = 0.15). The median time from symptom onset to surgery for astrocytoma and oligodendroglioma patients can be consulted in table 1.

### OS and its prognostic factors

At the time of the final analysis, 18 (75%) glioblastoma patients by pathologist experience, 5 (83%) IDH-wildtype glioblastoma patients, 1 (33%) astrocytoma by pathologist experience patient, and 1 (50%) oligodendroglioma by pathologist experience patient had died after a median follow-up of 5.1 (range 0.16-50.2 months),

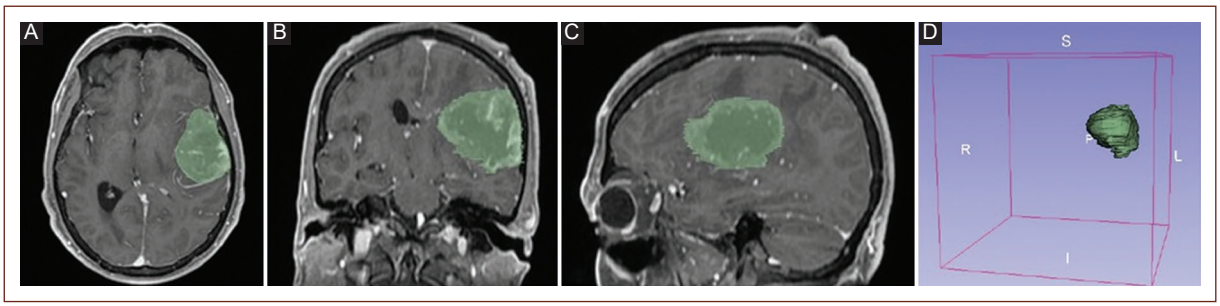


**Figure 1.** Images showing a segmented glioblastoma included in the study. **A:** axial, **B:** coronal, and **C:** sagittal views of a segmented glioblastoma included in the study. **D:** three-dimensional reconstruction of tumor shape performed by segmenting all the slices with high signal intensity.

3.5 (range 1-10.3 months), 58.7 (range 23.3-59.8 months), and 17.3 (range 0.9-33.8 months) months, respectively.

Due to the few patients in the astrocytoma by pathologist experience and oligodendroglioma by pathologist experience groups, Kaplan-Meier survival curves were only constructed for glioblastoma patients and can be consulted in figure 2. Kaplan-Meier survival curves for glioblastoma patients separated into glioblastoma patients by pathologist experience and IDH-wildtype glioblastoma patients are found in figure SM2 and figure SM3 in SM.

We looked for the age cut-off that best selects patients with a better survival prognosis. Several age cut-offs were tested, 65 years was the cut-off with the less p-value when comparing the Kaplan-Meier survival curves. The obtained p = 0.1 and the HR were 2 with a 95% CI equal to 0.83-4.9 (Fig. 3). This result shows that age at surgery was not a prognostic factor for survival in our cohort. On the contrary, the administration of RT and temozolomide (TMZ) showed substantial survival benefits ($p < 0.001$, HR = 0.1 [0.03-0.33], Fig. 4). To ensure that the improved survival times in the group of patients receiving RT and TMZ were not because this group had, proportionally, more patients with totally resected tumors, the proportions of type of surgery in each group were statistically compared. The proportion differences were not significant (p = 0.78, see Fig. SM4 in SM).

### *SR*

Pérez-Beteta et al.[12] found that glioblastoma SR obtained from high-resolution contrast-enhanced pre-treatment T1 MRI is a predictor of OS. MRIs were available for 23 of the 30 patients with glioblastomas, but only 9 met the imaging inclusion criteria. Imaging characteristics for the 9 patients are summarized in table 2.

With a p = 0.09, median SR (0.6006) was less than that obtained by Pérez-Beteta et al.[12] (0.635), a possible trend suggesting greater tumor aggressiveness in our patients. In addition, Pérez-Beteta et al.[12] found 0.629 as the value of SR that best selects the patients with a better survival prognostic. As shown in table 2, six of the nine patients were in the group with a poor survival prognosis ($S_R < 0.629$). A quantitative summary of the tumor volumes and surface areas obtained for the nine patients is also shown in table 2. On the other hand, age at surgery and SR were not correlated (Fig. SM5 in SM).

## Discussion

Due to the lack of a CNS tumor national registry, there is limited epidemiological information regarding gliomas in the Mexican population. Some monocentric studies have reported epidemiological characteristics of patients with gliomas treated in Mexico[7-10,24-31] and most of them were carried out in hospitals located in Mexico City. Only four studies, references[10,25-27], considered patients from regions different to those covered by Mexico City care centers, but none included patients from the State of Guanajuato. This is the first study reporting clinical features and epidemiological information of patients with gliomas treated in a hospital from Guanajuato. CMNB is one of the few institutions in Guanajuato treating glioma patients, thus the Guanajuato population is well represented in our study.

In our cohort, 86% of the patients were diagnosed with glioblastoma, which is consistent with the fact that glioblastoma is the most frequent primary malignant tumor of the CNS[1]. Without leaving aside that for some patients, the mutational status of *IDH1* and *IDH2* genes

**Table 1.** Summary of characteristics of the patients included in the study by type of tumor

| Characteristic | Glioblastoma by pathologist experience (n = 24) | Glioblastoma, IDH-wildtype (n = 6) | Astrocytoma by pathologist experience (n = 3) | Oligodendroglioma by pathologist experience (n = 2) |
|---|---|---|---|---|
| Patient characteristic | | | | |
| Age at surgery (years) | | | | |
| Median | 56 | 66 | 32 | 47 |
| Range | (28-75) | (56-75) | (24-46) | (44-50) |
| Sex, n (%) | | | | |
| Female | 8 (33) | 2 (33) | 1 (33) | 2 (100) |
| Male | 16 (67) | 4 (67) | 2 (67) | 0 (0) |
| Treatment | | | | |
| Type of resection, n (%) | | | | |
| Total | 17 (71) | 6 (100) | 0 (0) | 2 (100) |
| Subtotal | 6 (25) | 0 (0 | 3 (100) | 0 (0) |
| Biopsy | 1 (4) | 0 (0) | 0 (0) | 0 (0) |
| Radiotherapy administration, n (%) | | | | |
| Yes | 10 (42) | 1 (17) | 3 (100) | 1 (50) |
| No | 14 (58) | 5 (83) | 0 (0) | 1 (50) |
| Chemotherapy administration, n (%) | | | | |
| Yes | 10 (42) | 1 (17) | 3 (100) | 1 (50) |
| No | 14 (58) | 5 (83) | 0 (0) | 1 (50) |
| Symptoms | | | | |
| Time from onset of symptoms to surgery (days) | | | | |
| Median | 50.5 | 39 | 739 | 34.5 |
| Range | (13-410) | (12-79) | (27-1217) | (20-49) |
| Initial symptoms, n (%) | | | | |
| Focal neurological deficits | 16 (67) | 6 (100) | 1 (33) | 2 (100) |
| Seizures | 2 (8) | 0 (0) | 2 (67) | 1 (50) |
| Symptoms of elevated intracranial pressure | 18 (75) | 3 (50) | 2 (67) | 2 (100) |
| Behavioral and neurocognitive changes | 7 (29) | 2 (33) | 0 (0) | 0 (0) |

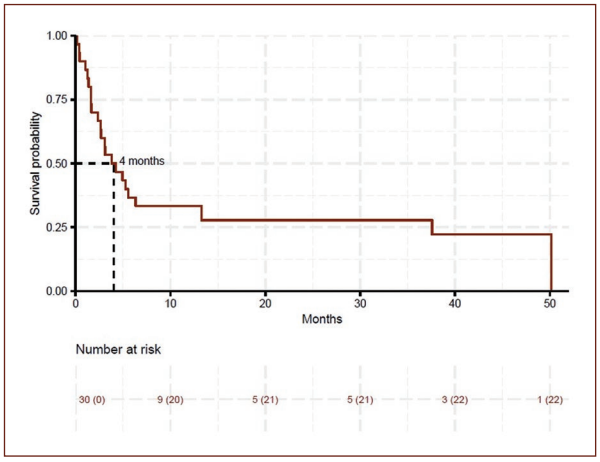


**Figure 2.** Kaplan-Meier overall survival curve for glioblastoma patients. Survival probability for 1.6, 4, 37.6, and 50.2 months after surgery were, respectively, 73, 50, 22, and 0%.

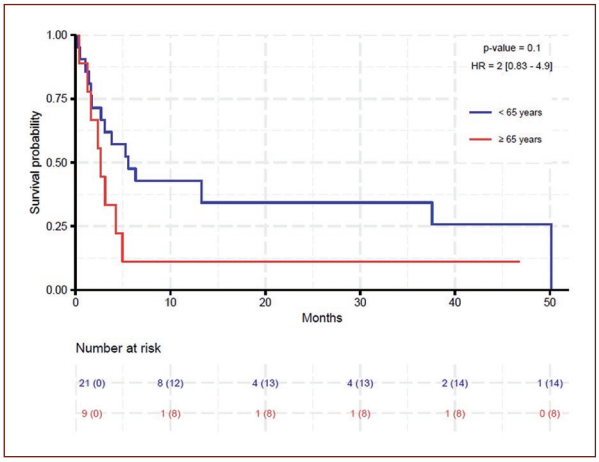


**Figure 3.** Kaplan-Meier overall survival curves for glioblastoma patients by age at surgery (≥ 65 vs. < 65 years at surgery). No statistical differences were observed. In brackets, the 95% confidence interval for the Hazard ratio.

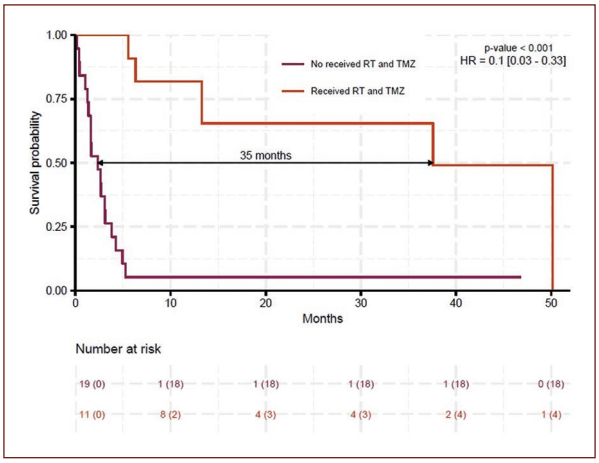


**Figure 4.** Kaplan-Meier overall survival curves for glioblastoma patients by administration of radiotherapy and temozolomide. Large statistical differences were obtained. In brackets, the 95% confidence interval for Hazard ratio.

**Table 2.** Summary of contrast-enhanced T1-weighted magnetic resonance imaging parameters and geometric measurements for the nine glioblastoma patients who met imaging inclusion criteria

| Parameter | p |
|---|---|
| MR imaging parameter | |
| Pixel spacing (mm) | 0.44 (0.43-0.49) |
| Section thickness (mm) | 1.11 (1-2) |
| Spacing between sections (mm) | 1 (1-1) |
| Gap (mm) | −0.11 ( −1-0) |
| Geometric measurement | |
| Tumor volume ($cm^3$) | 61 (31-106) |
| Surface area ($cm^2$) | 150 (65-367) |
| Tumor regularity* | 0.6006 (0.1027-0.6874) |
| Number of patients below the best regularity threshold reported by Pérez-Beteta et al. [12], 0.629 | 6 (67%) |
| Number of patients above the best regularity threshold reported by Pérez-Beteta et al. [12], 0.629 | 3 (33%) |

Unless otherwise specified, values are means with ranges in parentheses.
*Median.

was unknown, and the few patients with grade 3 tumors, astrocytomas, and oligodendrogliomas were diagnosed mostly in young adults and glioblastomas at older ages. Several studies mention that glioblastomas affect the Mexican population at significantly younger ages, i.e., the ages of Mexicans at glioblastoma diagnosis are significantly less compared to other ethnicities[6,7,9,30,32]. Our results are in complete agreement with these findings (median age 58 years and significant p-value when compared to patients in the United States). Similar to other studies[6,8,10,23,31,33], gender distribution in astrocytomas and glioblastomas showed a male preponderance in our cohort (68%). Clinical features and time from symptom onset to diagnosis were presented similarly to the WHO report[1].

Median OS after surgery for glioblastoma patients was 4 months (Fig. 1). Survival information of each patient is required to statistically compare survival times of our cohort of glioblastoma with those obtained in other studies. Unfortunately, that information is not usually available and patient survival is strongly influenced by the presence of IDH1 or IDH2 mutations[16], thereby precluding a rigorous comparative analysis of survival times of our glioblastoma patients. To obtain a general, although imprecise, indication of how long or short the survivals of our patients is, median survival can be compared. McCormack et al.[32] in patients with glioblastomas from the Mexican Institute of Neurology and Neurosurgery obtained a median survival of approximately 15 months and a median survival of approximately 16 months in patients from the United States. On the other hand, Beltrán et al.[8] in patients from the General Hospital of Mexico obtained a median survival of 24 months. However, this study contains a few glioblastoma patients; therefore, this value is a rough estimate. Comparing our median of 4 months with the medians in these studies, it seems that the survivals of our patients are lower.

Several studies in different countries, including one in Mexico[9], have found that younger patients have longer survival times. Our survival analysis for age (Fig. 3) reflects this result, with a p-value close to statistical significance. We believe that significance for age would be achieved with a larger cohort. On the other hand, as observed in seminal clinical trials[34], the administration of RT and TMZ significantly prolonged OS for glioblastoma patients in our cohort (Fig. 4). However, in our study, the survival gain (difference in medians equal to 35 months) was substantially greater. A similar result was found by Wegman et al. in patients from the Mexican Institute of Neurology and Neurosurgery[9]. Although more studies are needed to determine the exact survival benefits provided by RT and TMZ in Mexican patients, huge efforts should be made to ensure all Mexican patients with good performance status receive RT and TMZ.

Inspired by a mathematical model[35], the shape of the tumor in the pretreatment contrast-enhanced T1 MRI has been studied as a survival prognostic factor in glioblastoma patients[12,36]. SR was found to positively correlate with OS[12]. Consequently, the more irregular

the tumor, the more aggressive it is. We found that glioblastomas were, in general, more irregular than the patients of the study where SR was found to predict OS[12] (0.6006 vs. 0.635 in median SR) and a statistical trend was observed (p = 0.09). This means that our results of SR suggest an even more aggressive tumor behavior in glioblastoma patients treated at CMNB, indicating potential clinical relevance. This should be interpreted with caution because of the small sample size in the radiomic subanalysis. A larger cohort of patients treated at CMNB with pre-treatment MRIs meeting imaging inclusion criteria is needed to obtain conclusive results. Due to this is the first study evaluating SR in Mexican patients with glioblastoma, it was not possible to compare our results with patients from other medical institutions in Mexico.

This study shows the current clinical management of patients with adult-type diffuse gliomas at a reference care center in Mexico. Although our results cannot be generalized to the Mexican population because of the small number of patients, this study provides valuable information that can help guide future research involving larger cohorts of Mexican patients and reveals the limitations that must be addressed to improve the clinical management of these patients.

## Future perspectives

A natural extension of this work would be to include additional patients treated at CMNB from 2024 and repeat the analysis performed here.

Multicenter studies in Mexico with rigorous inclusion criteria that control clinical variables affecting patient survival, i.e., tumor diagnosis according to 2021 WHO classification, administration of RT and chemotherapy, type of surgical procedure, and extent of the resection evaluated with a post-operative MRI, among others, are needed to confirm whether glioblastomas exhibit increased aggressiveness in the Mexican population.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical considerations

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

**Confidentiality, informed consent, and ethical approval.** The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed.

**Declaration on the use of artificial intelligence (AI).** The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

## Supplementary data

Supplementary data are available at DOI: 10.24875/RMN.25000005. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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ORIGINAL ARTICLE

# Relationship between executive function alterations and academic performance in university students at risk of ADHD

*Dafne Romero-Zavala*[1], *Yesica Sánchez-Cervantes*[1], *Ricardo Pedraza-Medina*[1,2], *and Minerva Ortiz-Valladares*[1,3]*

[1]*Laboratory of Neuroscience, School of Psychology, University of Colima;* [2]*Medical Science Postgraduate Program, School of Medicine, University of Colima;* [3]*Sinergia Clínica de Atención Neuropsicológica. Colima, Mexico*

## Abstract

**Objective:** *This study aims to identify executive function (EF) deficits associated with attention deficit hyperactivity disorder (ADHD) risk and their impact on academic performance (AP) among Mexican university students.* **Methods:** *The adult ADHD self-report scale v1.1 was administered to 200 university students. A total of 103 students scored within the high-risk range for ADHD. In the second phase of the study, students at high risk for ADHD were invited to undergo a neuropsychological evaluation. Forty-four students (18 men and 26 women) completed the Neuropsychological Battery of Frontal and EF to assess EF. AP was determined based on the average high school and university scores, verified through official school records. Statistical analyses included analysis of variance and correlation tests to explore relationships among the variables.* **Results:** *Over 50% of the evaluated participants met the criteria for high ADHD risk, highlighting a high prevalence of undiagnosed symptoms. EF impairments were observed, particularly in the dorsolateral prefrontal cortex. Despite achieving higher AP, women scored significantly lower on EF tasks compared to men. A positive correlation was found between orbitofrontal cortex functioning and AP. In men, higher ADHD risk was negatively associated with EF efficiency.* **Conclusions:** *These findings underscore the importance of implementing systematic ADHD screening strategies in university settings. They also suggest the potential presence of compensatory mechanisms in women at high risk for ADHD. Further research is needed to develop targeted interventions aimed at enhancing EFs and supporting academic success in this population.*

***Keywords:*** *Executive functions. Attention deficit hyperactivity disorder. University students. Sex differences. Academic performance.*

## *Relación entre alteraciones en la función ejecutiva y el rendimiento académico en universitarios con riesgo de TDAH*

## Resumen

**Objetivo:** *Este estudio tiene como propósito identificar los déficits en funciones ejecutivas asociados al riesgo de TDAH y su impacto en el desempeño académico de jóvenes universitarios mexicanos.* **Métodos:** *Se aplicó la Escala de Autoinforme para el TDAH en Adultos (ASRS v1.1) a 200 estudiantes universitarios. Un total de 103 estudiantes obtuvieron un puntaje indicativo de alto riesgo para TDAH. En la segunda fase del estudio, los estudiantes con alto riego para TDAH fueron invitados a*

***Correspondence:**
Minerva Ortiz-Valladares
E-mail: movalladares@ucol.mx

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*una evaluación neuropsicológica, 44 estudiantes (18 hombres y 26 mujeres) completaron la Batería Neuropsicológica de Funciones Frontales y Ejecutivas (BANFE-3), con el objetivo de evaluar su desempeño en funciones ejecutivas. Asimismo, el rendimiento académico se determinó a partir del promedio de calificaciones en educación media superior y universitaria, verificado mediante documentos escolares oficiales. Se realizaron análisis estadísticos mediante ANOVA y pruebas de correlación para explorar las relaciones entre las variables.* **Resultados:** *Más del 50% de los participantes evaluados cumplieron con los criterios de alto riesgo para TDAH, lo que evidencia una alta prevalencia de síntomas no diagnosticados. Se observaron alteraciones en funciones ejecutivas, particularmente en la corteza prefrontal dorsolateral (CPFDL). A pesar de registrar un mejor rendimiento académico, las mujeres obtuvieron puntajes significativamente más bajos en funciones ejecutivas en comparación con los hombres. Además, se identificó una correlación positiva entre el funcionamiento de la corteza orbitofrontal y el rendimiento académico. En los hombres, un mayor riesgo de TDAH se asoció negativamente con la eficiencia en funciones ejecutivas.* **Conclusiones:** *Los hallazgos subrayan la relevancia de implementar estrategias de detección sistemática del TDAH en el ámbito universitario. Asimismo, sugieren la posible existencia de mecanismos compensatorios en mujeres con alto riesgo de TDAH. Se requiere investigación adicional para diseñar intervenciones dirigidas a fortalecer las funciones ejecutivas y favorecer el desempeño académico en esta población.*

***Palabras clave:*** *Funciones ejecutivas. Trastorno por déficit de atención e hiperactividad. Estudiantes universitarios. Diferencias por sexo. Rendimiento académico.*

## Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that significantly interferes with daily functioning. Inattention symptoms typically include difficulty concentrating, disorganization, and forgetfulness, whereas hyperactivity-impulsivity is marked by excessive fidgeting, constant talking, and frequent interruptions of others[1]. According to diagnostic criteria, these symptoms must appear before age 12, occur in at least two distinct settings, and result in substantial impairment in social, academic, or occupational domains. ADHD is classified into three presentations: predominantly inattentive, predominantly hyperactive-impulsive, and combined. Globally, prevalence estimates range from 5% to 7.2% in youth and from 2.5% to 6.7% in adults[2].

Beyond attentional deficits, individuals with ADHD commonly exhibit impairments in executive functions (EFs). EFs are cognitive processes essential for planning, organizing, controlling impulses, sustaining attention, and working memory (WM), collectively responsible for regulating behavior and guiding goal-directed actions. Deficits in these areas may manifest as difficulties maintaining attention over extended periods, managing time effectively, controlling impulses, and adapting flexibly to new demands[3,4]. As a result, executive dysfunction can significantly impact academic achievement, as affected individuals often struggle to follow instructions, organize tasks, and handle complex academic situations. These difficulties become particularly evident in educational contexts as academic demands increase.

Adult ADHD frequently remains underdiagnosed due to misconceptions that ADHD exclusively affects children or misinterpretations of symptoms such as personality traits or stress responses. Furthermore, symptoms often overlap with other disorders such as anxiety or depression, complicating accurate diagnosis[5]. Consequently, many adults with ADHD remain untreated, facing considerable challenges, especially within university settings that require heightened academic and social functioning.

As students transition to higher education, the demands for planning, organization, and self-regulation increase significantly. These heightened requirements often expose EF deficits that students may have previously compensated for or masked. Consequently, such deficits frequently lead to difficulties in task completion, adherence to deadlines, and adaptation to increased academic responsibilities, ultimately negatively impacting overall academic performance (AP)[6].

Effective screening tools, such as the adult ADHD self-report scale (ASRS), facilitate the identification of students at risk for ADHD, enabling timely symptom detection and prompt diagnostic intervention[7]. In addition, standardized instruments such as the Neuropsychological Battery of Frontal and EFs (BANFE-3) offer objective evaluation of specific EF deficits, supporting the development of targeted interventions to improve academic outcomes and student well-being.

This study aims to investigate the relationship among ADHD risk, EF impairments, and AP deficits within a university population. Understanding the specific executive challenges associated with ADHD symptoms is key for early identification, the implementation of effective

interventions, and raising awareness about the importance of timely diagnosis and support. Ultimately, this approach seeks to enhance educational outcomes and improve the quality of life among university students facing ADHD-related challenges.

## Methods

### Participants

The initial sample consisted of undergraduate students aged 18-27 from health-related fields (Nutrition, Medicine, and Psychology). The ASRS was administered as a preliminary screening tool to identify students meeting the criteria for "high risk of ADHD." Participants included those who provided informed consent, had no previous diagnosis of ADHD or other psychopathologies (e.g., anxiety, depression, and bipolar disorder), and were not receiving psychopharmacological treatment. In the first phase, 200 responses were collected (153 women and 47 men). Of these, 143 students obtained a high-risk score for ADHD. However, 40 students were excluded due to previously reported psychopathological diagnoses, resulting in a final sample of 103 students who met the criteria for high ADHD risk. In the second phase, 31 students declined to participate, citing a lack of interest in the outcome of the neuropsychological evaluation as their primary reason for withdrawal. The remaining 72 students (men and women) were invited to undergo an EF assessment using the Spanish version of the Neuropsychological BANFE-3. Of these, 28 did not attend their scheduled appointment, reporting the length of the evaluation (approximately 60 min) as their main reason for non-participation. Ultimately, 44 students (18 men and 26 women) completed the neuropsychological assessment. AP was assessed through the review of official academic records from their institution.

### Procedure

#### ADHD RISK EVALUATION

The ASRS v1.1, developed collaboratively by the World Health Organization and the Adult ADHD Task Force, was employed in this study. This instrument is a validated and widely recognized screening tool for identifying adults at risk for ADHD. Developed by prominent experts in the field, including Dr. Lenard Adler (New York University Medical School), Dr. Ronald Kessler, and Dr. Thomas Spencer (both from Harvard Medical School), the ASRS v1.1 evaluates core ADHD symptoms and has demonstrated strong reliability aligned with DSM criteria. In this study, the ASRS v1.1 was administered online via Google Forms, and all participants provided informed consent before beginning the questionnaire. All procedures adhered to the ethical standards established by the Ethics Committee of the Faculty of Psychology at the University of Colima. Results from this scale indicate whether individuals exhibit symptoms that warrant further evaluation through a comprehensive clinical interview, serving as a basis for guiding subsequent diagnostic assessments and targeted therapeutic interventions.

#### EF EVALUATION

The third edition of the Neuropsychological BANFE-3, a comprehensive instrument with high reliability and validity, was employed in this study. This battery evaluates cognitive processes, specifically EFs, primarily mediated by the prefrontal cortex. It is used with Spanish-speaking individuals aged 6-90 years, and the assessment typically takes approximately 50 min to administer. The BANFE-3 battery includes various tests, such as the Stroop test, which measures the inhibition of automatic responses and response selection, and the Iowa Gambling Task, which evaluates decision-making under conditions of uncertainty. The Mazes test assesses impulsivity control and planning, whereas tasks such as visuospatial WM, and self-directed pointing focus on cognitive strategies. In addition, the Tower of Hanoi is used to examine sequential planning abilities. The battery also incorporates verbal fluency, proverb interpretation, semantic classification, and the metamemory curve tests, which assess cognitive flexibility, abstract reasoning, and memory self-assessment.

The BANFE-3 selected the test based on anatomical and functional criteria, focusing on three main regions: the orbitofrontal cortex (OFC), anterior prefrontal cortex (APC), and dorsolateral prefrontal cortex (DLPFC) (Table 1). These tests help identify impairments in EF by offering a global performance index and specific scores for each targeted area. The battery is proven effective in detecting dysfunctions related to frontal lobe damage, such as those arising from traumatic brain injuries. Its specificity has been validated through research with individual brain injuries and supported by findings from functional neuroimaging studies, reinforcing its value as a reliable neuropsychological tool for evaluating EF in affected populations.

**Table 1.** Neuropsychological assessment by the BANFE-3: targeted brain structures and corresponding tests

| Function and structures involved | Test for evaluation |
|---|---|
| Metafunctions (APC) | Metamemory<br>Understanding figurative meaning<br>Abstract attitude |
| Executive functions (DLPFC) | Verbal fluency<br>Productivity<br>Mental flexibility<br>Visuospatial planning<br>Sequential planning<br>Reverse sequence<br>Encoding control |
| Working memory (DLPFC) | Self-directed visual working memory<br>Verbal working memory-ordering<br>Visuospatial working memory-sequential |
| Functions basic (OFC) | Inhibitory control<br>Rule following<br>Risk-benefit processing |

APC: anterior prefrontal cortex; DLPFC: dorsolateral prefrontal cortex; OFC: orbitofrontal cortex.

### *AP register*

AP is commonly evaluated through grade point average, standardized test scores, educational aspirations, and educational attainment metrics. These indicators reflect an individual's academic abilities, providing measurable estimates of knowledge acquired through formal instruction or training. Furthermore, they represent the proficiency level achieved in specific academic subjects, as demonstrated by quantitative assessments. The students' AP was assessed based on the average of their high school and university scores. These grades were verified through official academic records, ensuring the accuracy of the reported data. Collectively, these measures provide a reliable representation of the participants' current academic achievement and capabilities.

### *Data analysis*

Data were presented as means ± standard deviation or frequencies, depending on the nature of the variables. Statistical analyses were performed using the Statistical Package for the Social Sciences 26, and data visualization was conducted with GraphPad Prism 8. Quantitative variables were tested for normality before analysis. A one-way analysis of variance (ANOVA) was used to compare differences between men and women. For all statistically significant ANOVA results, effect sizes were calculated using eta squared ($\eta^2$) to assess the magnitude of group differences. In addition, Spearman's correlation analyses were conducted to examine the relationships between AP, EFs, and ADHD risk. A significance level of 95% ($p \leq 0.05$) was applied to all statistical tests.

## Results

### *EF deficits associated with ADHD risk*

In the initial phase, 200 students participated (153 women and 47 men), with women representing a significantly higher proportion of the sample. Of these, 143 students obtained a high-risk score for ADHD. However, 40 students were excluded due to previous psychopathological diagnoses, and 103 students (51.5% of the total sample) met the criteria for high ADHD risk, indicating that more than half of the eligible participants exhibited symptoms warranting further evaluation. Of these, 31 declined further participation citing a lack of interest in the outcome of the neuropsychological evaluation as their primary reason for withdrawal, leaving 72 students who were invited to undergo an EF assessment, 28 participants did not attend their scheduled appointment, reporting the length of the evaluation (approximately 60 min) as their main reason for non-participation. Ultimately, 44 students (26 women and 18 men) (Table 2) completed the neuropsychological evaluation, during which AP data were also collected.

Among the evaluated students, the results of neuropsychological evaluation indicated an average total score of 82.18 on the complete battery assessment, corresponding to a diagnosis of mild functional impairment. When analyzing the results by structure, the DLPFC associated with EF showed an average score of 81.36, indicating mild impairment. However, the DLPFC-associated WM function was preserved, with an average score of 105, corresponding to normal functioning. Nevertheless, overall functionality (WM + EF) demonstrated mild impairment, with an average score of 83.90. Regarding the APC, the data also indicated mild impairment (82.18), while the OFC functions were preserved, with an average score of 93.88 (Table 2).

### *Sex differences in EF among students at risk for ADHD*

Comparisons between sexes indicated no significant differences in the average risk of ADHD between men

**Table 2.** Neuropsychological performance and ADHD risk in university students

| Variable | Total (n = 44) | | | |
|---|---|---|---|---|
| | Mean (SD) | | | |
| Age | 21.15 (2.31) | | | |
| ADHD risk | 42.63 (12) | | | |
| BANFE | | | | |
| Orbitofrontal | 93.88 (16.50) | | | |
| Anterior prefrontal | 82.18 (16.47) | | | |
| Dorsolateral (memory) | 105.09 (10.65) | | | |
| Dorsolateral (EF) | 81.36 (18.35) | | | |
| Total dorsolateral | 83.90 (12.66) | | | |
| Total score | 80.95 (13.60) | | | |
| **BANFE diagnostic** | **High normal** | **Normal** | **Mild impairment** | **Severe impairment** |
| | % (n) | | | |
| Orbitofrontal | 2.3 (1) | 77.3 (34) | 6.8 (3) | 13.6 (6) |
| Anterior prefrontal | 2.3 (1) | 43.2 (19) | 25 (11) | 29.5 (13) |
| Dorsolateral | - | 45.5 (20) | 43.2 (19) | 11.4 (5) |
| Total | - | 50 (22) | 45.5 (20) | 13.6 (6) |

ADHD: attention deficit hyperactivity disorder; SD: standard deviation; BANFE: Batería Neuropsicológica de Funciones Ejecutivas y Lóbulos Frontales; EF: executive function.

and women. However, in the analysis of EF efficiency, women demonstrated lower performance in tasks associated with the DLPFC (WM + EF), F (1, 42) = 16.43, $p < 0.0001$. The effect size was large ($\eta^2 = 0.281$), suggesting that sex accounted for 28.1% of the variance in total dorsolateral performance.

When analyzed separately, men exhibited scores corresponding to a normal diagnosis, whereas women showed mild impairment. Similarly, for EF related to the DLPFC, women displayed significantly lower scores, indicating mild impairment, F (1, 42) = 7.34, p = 0.01, whereas men remained within the normal range. A moderate-to-large effect size was observed ($\eta^2 = 0.149$), indicating meaningful sex-related differences in EF tasks.

Finally, although WM functions related to the dorsolateral cortex were preserved in both men and women, the latter obtained significantly lower scores, F (1, 42) = 13.8, p = 0.00 (Table 3). The effect size was large ($\eta^2 = 0.247$), meaning that almost a quarter of the variance in WM performance could be explained by sex.

Similarly, although women obtained lower scores in the APC, the difference was not statistically significant, F (1, 42) = 3.73, p = 0.06. Finally, in terms of overall test efficiency, women exhibited significantly lower performance compared to men, F (1, 42) = 11.93, p = 0.001 (Table 3). This difference was accompanied by a large effect size ($\eta^2 = 0.221$), indicating robust sex-related differences in overall EF.

## *EF and ADHD risk: a predictor of AP*

Regarding AP averages, the evaluated students had a general mean score of 9.12 on a 1-10 scale, which falls within the parameters of good performance. However, data analysis revealed that women exhibited significantly better AP compared to men, F (1, 42) = 4.74, p = 0.03, despite their lower efficiency in EFs. The effect size was moderate ($\eta^2 = 0.101$), indicating that sex accounted for approximately 10% of the variance in AP.

A Pearson correlation analysis was conducted to examine the relationship between AP and EF efficiency. A positive correlation was found between OFC functions and AP, indicating that better OFC function was associated with higher AP, r (44) = 0.481, $p < 0.001$ (Fig. 1A). When the data were analyzed by sex, a positive correlation was observed between OFC functions and AP in men (Fig. 1B), r (18) = 0.649, p = 0.004, as well as with overall performance on the BANFE (Fig. 1C), r (18) = 0.490, p = 0.03.

Furthermore, in men, a negative correlation was identified between EF efficiency and ADHD risk level, as measured by the ASRS. Higher ASRS scores were associated with lower EF efficiency (Fig. 1D), r (18) = –0.469, p = 0.04. Similarly, a negative correlation was found between dorsolateral cortex efficiency and higher ASRS scores (Fig. 1E), r (18) = –0.468, p = 0.05, indicating that greater ADHD risk was related to poorer performance in tasks associated with dorsolateral cortex functions.

**Table 3.** Comparison of executive function performance and ADHD risk by sex

| Variable | Male (n = 18) | Female (n = 26) | p |
|---|---|---|---|
| | Mean (SD) | Mean (SD) | |
| Age | 21.72 (2.80) | 20.76 (1.86) | 0.182 |
| Academic performance | 8.97 (0.43) | 9.22 (0.32) | 0.036 |
| ADHD risk | 44.66 (11.67) | 41.23 (12.24) | 0.357 |
| BANFE | | | |
| Orbitofrontal | 93.72 (17.53) | 94 (16.10) | 0.957 |
| Anterior prefrontal | 87.77 (16.81) | 78.30 (15.37) | 0.060 |
| Dorsolateral (memory) | 111.38 (4.67) | 100.73 (11.49) | **0.001** |
| Dorsolateral (EF) | 89.77 (12.61) | 75.53 (19.62) | **0.010** |
| Total dorsolateral | 91.88 (9.38) | 78.38 (11.76) | **< 0.001** |
| Total score | 88.55 (12.01) | 75.69 (12.23) | **0.001** |

| BANFE diagnosis | High normal | | Normal | | Mild impairment | | Severe impairment | |
|---|---|---|---|---|---|---|---|---|
| | % (n) | | | | | | | |
| | M | F | M | F | M | F | M | F |
| Orbitofrontal | 5.6 (1) | - | 66.7 (12) | 84.6 (22) | 5.6 (1) | 7.7 (2) | 22.2 (4) | 7.7 (2) |
| Anterior prefrontal | 5.6 (1) | - | 55.6 (10) | 34.6 (9) | 27.8 (5) | 23.1 (6) | 11.1 (2) | 42.3 (11) |
| Dorsolateral | - | - | 77.8 (14) | 23.1 (6) | 22.2 (4) | 57.7 (15) | - | 19.2 (5) |
| Total | - | - | 55.6 (10) | 23.1 (6) | 44.4 (8) | 53.8 (14) | - | 23.1 (6) |

F: female; M: male; ADHD: attention deficit hyperactivity disorder; SD: standard deviation; BANFE: *Batería Neuropsicológica de Funciones Ejecutivas y Lóbulos Frontales*; EF: executive function.
Bold data represents statistically significant difference.

## Discussion

This study identified a high prevalence of ADHD risk among university students, accompanied by EF impairments, especially in domains linked to the DLPFC. In addition, relevant differences between sexes and associations between OFC functioning and AP were observed. These results provide a comprehensive view of the cognitive challenges faced by students at risk of ADHD and highlight the importance of tailored academic support.

More than half of the participants met the criteria for high ADHD risk, highlighting the prevalence of undiagnosed symptoms in university students. ADHD often goes unnoticed in young adults due to reliance on self-reports, lack of childhood records, and symptom overlap with other conditions[8]. Many students only seek evaluation when faced with increased academic demands, which can exacerbate EF deficits[9]. Accurate diagnosis in university populations is challenging, with cases frequently missed or misattributed to other conditions[8]. These challenges, combined with the limitations of subjective screening tools, underscore the need for objective neuropsychological assessments and systematic screening in universities to enable early detection and intervention.

Our neuropsychological findings, based on BANFE-3 performance, indicate that students at risk for ADHD show reduced performance in tasks typically associated with DLPFC functions, such as WM, cognitive flexibility, and planning. While our study did not directly assess brain function, previous neuroimaging studies have reported reduced functional connectivity and hypoactivation in the DLPFC among individuals with ADHD[10,11]. Similarly, transcranial magnetic stimulation research has shown that enhancing DLPFC activation can improve EF[12]. These external findings provide a plausible neurobiological context for interpreting the behavioral patterns observed in our sample. The impairments identified, particularly in cognitive flexibility, verbal fluency, and planning, may hinder students' ability to manage academic responsibilities. Therefore, although our data are limited to cognitive performance, these results support the potential benefit of targeted cognitive interventions or neuromodulation strategies for students at risk of ADHD.

Building on these findings, sex differences in EF performance further highlight the complexity of ADHD-related cognitive impairments. In our sample, women showed significantly lower scores in DLPFC-related tasks compared to men, despite exhibiting similar levels of ADHD risk. These behavioral findings are

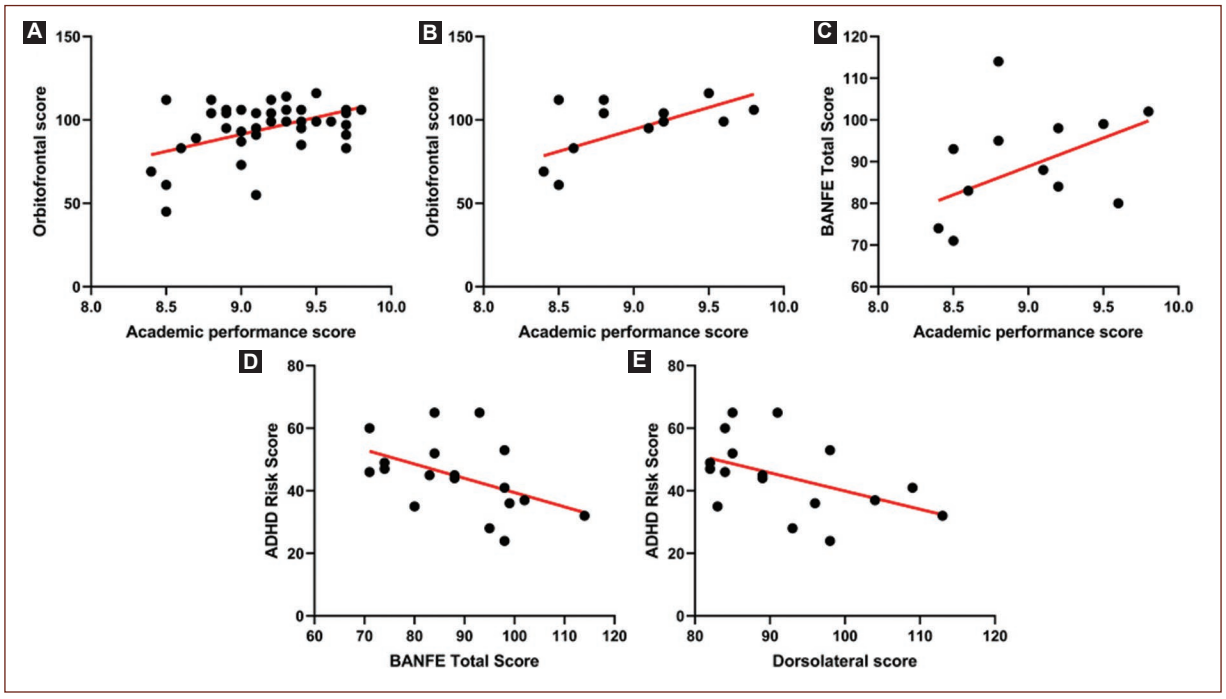


**Figure 1.** Correlations between academic performance, executive function efficiency, and attention deficit hyperactivity disorder (ADHD) risk. **A:** a positive correlation was found between the function of the orbitofrontal cortex and academic performance ($p < 0.001$). **B:** when analyzed by sex, a positive correlation was observed between orbitofrontal cortex function and academic performance in men ($p = 0.004$). **C:** in addition, overall BANFE-3 performance was positively correlated with academic performance in men ($p = 0.03$). **D:** a negative correlation was found between executive function efficiency and ADHD risk level, with higher adult ADHD self-report scale scores associated with lower executive function performance ($p = 0.04$). Similarly, **E:** a negative correlation was identified between dorsolateral cortex efficiency and ADHD risk, where greater ADHD risk was linked to poorer dorsolateral prefrontal cortex function ($p = 0.05$).

consistent with previous neuroimaging research suggesting that women with ADHD may show greater deficits in cognitive flexibility and WM, potentially due to differences in functional connectivity and compensatory mechanisms[13,14]. The observed differences were not only statistically significant but also moderate in effect size, reinforcing their relevance for both research and clinical practice. These neural models provide a useful framework for contextualizing the sex-related performance differences we observed.

Despite these EF challenges, women in this study demonstrated higher AP than men, suggesting alternative compensatory strategies that allow them to mitigate cognitive deficits through structured study habits and increased effort[15]. This paradox highlights a disconnect between executive performance and academic outcomes, raising questions about how effectively traditional assessments capture cognitive functioning[16]. These findings emphasize the need for individualized intervention strategies, considering both cognitive impairments and behavioral adaptations. Future research should explore how EF training, academic support systems, and flexible learning strategies can enhance AP in students at risk for ADHD, with particular attention to sex-specific patterns.

Although neural activity was not directly measured, our findings align with studies linking OFC to adaptive behavior and AP, especially in men. While our study evaluated OFC functions using neuropsychological tests, not direct neural measures, prior research has linked the OFC to adaptive behaviors in dynamic environments like academic settings[17]. In animal studies, it has been demonstrated that the OFC plays a crucial role in meta-reinforcement learning. This suggests that its conserved functions may regulate distinct mechanisms and timescales, providing additional flexibility and stability in cognition and learning[18], which could ultimately enhance AP.

EF has been consistently associated with academic outcomes from early education[19] to university-level studies[20,21]. It has been observed that EF was an even stronger predictor in the early years of education. This

suggests that during the 1st years of school, other factors such as socioeconomic status, cultural background, rural or urban origin, and academic history are not yet as influential[19]. However, at the university level, sex differences in predictors of academic success have been documented. For instance, self-control and self-monitoring are better predictors of study progress in women than in men[22]. In our findings, EF was associated with AP only in men. This discrepancy may reflect the influence of additional non-cognitive factors in women. For example, conscientiousness and course-taking patterns have been identified as strong predictors of academic achievement in women, particularly in less cognitively demanding academic tasks, such as participation and coursework[23].

Finally, it is important to highlight that a higher risk of ADHD in men is associated with lower EF and DLPFC function. Previous studies have reported impairments in EF and attentional skills in patients with ADHD[24,25]. Furthermore, the DLPFC is associated with decision-making and impulse control[26]. Both of which are altered in ADHD patients, especially those with impulsive symptoms. In our findings, only men exhibited a relationship between ADHD risk, EF deficits, and DLPFC dysfunctions. This may be attributed to gender differences as reported in the literature. Men tend to show more pronounced hyperactivity symptoms, whereas girls more commonly present inattentive and emotional symptoms[27]. Furthermore, compared to women, men with ADHD tend to show greater impairments in WM, and educational functioning, as well as more severe deficits in social functioning and mood regulation[28], highlighting the importance of more extensive and complete studies to identify gender differences in the EF of university students with ADHD risk.

## Conclusion

The results of this study indicate a notable presence of undiagnosed ADHD symptoms among university students, accompanied by measurable EF deficits. Neuropsychological assessment revealed reduced performance in tasks associated with the DLPFC, particularly affecting WM, planning, and cognitive flexibility. These difficulties were more pronounced in women, who nonetheless demonstrated higher AP than men, suggesting the use of compensatory strategies that merit further exploration. In contrast, men showed a stronger association between ADHD risk, DLPFC dysfunction, and lower academic achievement. Moreover, OFC functioning was positively related to AP, especially among male students, pointing to its possible role in adaptive learning and behavioral regulation. These findings reinforce the value of early ADHD screening and comprehensive EF assessment in higher education settings. Future research should further investigate sex-specific cognitive profiles and the interaction between neuropsychological performance and academic adaptation to guide the development of targeted and effective support strategies for students at risk.

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The authors declare that this work was carried out with the authors' resources.

## Conflicts of interest

The authors declare that they have no conflicts of interest. The authors declare that D. Romero-Zavala and Y. Sánchez-Cervantes contributed equally to this work and share first authorship.

## Ethical considerations

**Protection of human subjects and animals.** The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

**Confidentiality, informed consent, and ethical approval.** The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

**Declaration on the use of artificial intelligence (AI).** The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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REVIEW ARTICLE

# Optic neuritis associated with COVID-19 vaccine: a systematic review for clinical characteristics of an uncommon side effect

*Marlon R. Dionisio*[1,2], *Juan C. Martínez-Lazcano*[1], *and Graciela Cárdenas*[3]*

[1]*Laboratorio de Neurofarmacología Molecular y Nanotecnología, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City;* [2]*Facultad de Medicina, Universidad Lamar, Guadalajara, Jalisco;* [3]*Departamento de Neurología, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City. Mexico*

## Abstract

*To characterize the clinical presentation of optic neuritis (ON) associated with COVID-19 vaccination. Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement, a search was performed in PUBMED, Google Scholar, and SciELO database using the keywords "COVID-19 vaccination" AND "optic neuritis." Only articles written in English were included. A total of 126 articles were retrieved, of which 33 corresponded to cases of ON. Because 15 (13 patients) of the 33 articles had comorbidities, these were excluded. The mean age of the included patients was 42 years, the incidence was 79% in women versus 29% in men, and 27 of the cases were unilateral versus 17 bilateral. Treatment consisted of steroids in 37 of the cases, steroids plus plasmapheresis in 7 cases. Vaccines associated with ON were vector type in 18 of the cases, genetic type in 22 cases, and inactivated type in 4 cases; no association with ON was reported for viral and protein attenuated vaccine types. As in the case reported by our group, evidence in the literature indicates that bilateral ON is rare but requires prompt plasmapheresis as an adjunct to intravenous methylprednisolone to reduce neurological sequels.*

***Keywords:*** *COVID-19. Vaccine. Optic neuritis.*

## *Neuritis optica asociada a vacunas COVID-19: características clínicas de un efecto secundario poco común*

## Resumen

*Caracterizar la presentación clínica de la neuritis óptica asociada a la vacunación con COVID-19. Siguiendo la declaración Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) se realizó una búsqueda en PUBMED y Google Scholar utilizando las palabras clave «COVID-19 vaccination» y «optic neuritis». Se incluyeron solo artículos escritos en inglés. Se recuperó un total de 126 artículos, de los cuales 33 correspondían a casos de neuritis óptica (ON). Se excluyeron 15 (13 pacientes) de los 33 artículos porque presentaban comorbilidades. La edad media de los pacientes incluidos fue de 42 años, la incidencia fue del 79% en mujeres frente al 29% en hombres, y 27 de los casos fueron unilaterales frente a 17 bilaterales. El tratamiento consistió en esteroides en 37 de los casos, esteroides más plasmaféresis en 7 casos. Las vacunas asociadas a la ON fueron de tipo vectorial en 18 de los casos, de tipo genético en 22 casos y de tipo inactivado en 4 casos; no se observó ninguna asociación con la ON en los tipos de vacuna vírica y proteica atenuada.*

***Correspondence:**
Graciela Cárdenas
E-mail: gcardenas@innn.edu.mx

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*Al igual que en el caso reportado por nuestro grupo, la evidencia en la literatura indica que la ON bilateral es rara, pero requiere plasmaféresis rápida como complemento de metilprednisolona intravenosa para reducir las secuelas neurológicas.*

***Palabras clave:*** *COVID-19. Vacuna. Neuritis óptica.*

## Introduction

Since its emergence and rapid global spread, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been associated with high rates of hospitalization and mortality. Efforts to control the disease have included the development of specific antiviral drugs and safe vaccines. Since the mid-2020s, several clinical trials of antiviral drugs and vaccines have been announced. CanSino Biologics was the first vaccine to be approved by a national authority in China for limited use in military personnel. BioNTech/Pfizer, Moderna, the Gamaleya Institute, and Oxford University reported promising results in vaccine trials by November 2020, and several countries approved the use of Pfizer-BioNTech's COVID-19 vaccine for emergency use by December 2020. Other vaccines were approved by the World Health Organization shortly thereafter[1,2].

Mexico was the first country in Latin America to import and apply vaccines against COVID-19, following a five-stage vaccination program[3-34]. Health care workers and the elderly were the first to be vaccinated. As vaccination progressed globally, several adverse reactions, including neurologic disorders, were reported[35]. Several studies in this regard have also been published in Mexico[36-40]. According to these reports, the most common adverse events were headache, fatigue, and myalgia. Neuro-ophthalmic complaints, although rare, have been reported both in SARS-CoV-2 infection and after vaccination against COVID-19[41,42].

Optic neuritis (ON) is an inflammatory condition that affects one or both optic nerves. Typical ON is a clinical manifestation of central nervous system (CNS) inflammation, usually characterized by unilateral pain on ocular movement, mild to moderate decrease in visual acuity (VA), and dyschromatopsia in young adults. Atypical ON (AON), more common in patients older than 50 years or younger than 12 years, is characterized by bilateral involvement, severe visual loss (20/200), and severe optic disc inflammation[43]. Considering that ON is a rare side effect of COVID-19 vaccines, we present a review of cases of ON after COVID-19 vaccination reported in the literature is also presented.

## Epidemiology

A subset demonstrated the incidence of neuro-ophthalmic sequelae after COVID-19 disease is far greater than after vaccination against the virus[44,45]. ON was the neuro-ophthalmic sequelae most frequently reported after COVID-19 infection and vaccination, and before the onset of the pandemic, it is known to occur at a stable rate in the general population[46].

## Associated

The neurotropism of SARS-CoV-2 virus is poorly elucidated; access of the virus to the CNS through the olfactory bulb, crossing the blood–brain barrier following viremia, transport through infected leukocytes is a probable mechanisms[47].

While the phenomenon is poorly studied, previous studies have suggested molecular mimicry between myelin basic protein and viral proteins, epitope spreading, bystander activation, and superantigen activation as potential mechanisms[48].

## Materials and methods

A systematic search was conducted in PubMed, Google Scholar using the terms using the keywords "COVID-19 vaccination" AND "optic neuritis." Two clinicians (C.G. and M.A.R.D.) conducted a full-text review of the articles and extracted all relevant data on ON associated with COVID-19 vaccination. Inclusion criteria included a complete clinical characterization of ON, identification of vaccines administered, and time of onset of clinical symptoms in adult patients. Only articles written in English were included. Articles with insufficient data to confirm clinical ON were excluded.

### *Statistical analysis*

Data were analyzed using the Statistical Package for the Social Sciences 23 (IBM Inc., Somers, NY, USA). Qualitative variables were reported as percentages and compared using the Chi-squared ($\chi^2$) test with Yates

**Table 1.** Characteristics of studies included in our systematic review corresponded to cases of isolated ON

| Author | Publication type | Age | Gender | Time* | Vaccine associated | Affected eye | Type of ON | Treatment |
|---|---|---|---|---|---|---|---|---|
| Arnao et al., 2022[3] | LE | ND | Female | 2.00 | Vector-based vaccine | Both | Bilateral | Steroids |
| Estrada et al., 2022[4] | CR | 19 | Female | 1.00 | Vector-based vaccine | Left | Unilateral | Steroids |
| | | 27 | Female | 1.28 | Vector-based vaccine | Left | Unilateral | Steroids |
| Roy et al., 2022[5] | CS | 48 | Female | 0.71 | Vector-based vaccine | Left | Unilateral | Steroids |
| | | 40 | Male | 1.71 | Vector-based vaccine | Right | Bilateral | Steroids |
| Tarcha et al., 2023[6] | CR | 22 | Male | 1.42 | Genetic | Both | Bilateral | Steroids and immunoglobulin |
| Elnahry et al., 2023[7] | CR | 69 | Female | 2.28 | Genetic | Both | Bilateral | Steroids |
| | | 32 | Female | 0.85 | Vector-based vaccine | Left | Unilateral | Steroids |
| Shemer et al., 2023[8] | CR | 54 | Male | 24.00 | Genetic | Right | Unilateral | Steroids |
| | | 38 | Female | 8.00 | Genetic | Left | Unilateral | Steroids |
| | | 42 | Female | 3.00 | Genetic | Left | Unilateral | Steroids |
| | | 14 | Male | 9.00 | Genetic | Left | Unilateral | Steroids |
| Saluja et al., 2023[9] | LE | 35 | Male | 0.28 | Vector-based vaccine | Both | Bilateral | Steroids |
| Pirani et al., 2023[10] | CR | 31 | Female | 0.85 | Genetic | Right | Unilateral | Steroids |
| | | 46 | Female | 1.14 | Genetic | Right | Unilateral | Steroids |
| Shah et al., 2022[11] | CR and review | 39 | Female | 4 weeks (first doses) | Genetic | Right | Unilateral | Steroids with plasmapheresis |
| **1 week (second doses)** | | | | | | | | |
| Motegi et al., 2022[12] | CR | 86 | Male | 1.14 | Genetic | Right | Unilateral | Steroids |
| Wang et al., 2022[13] | CR | 21 | Female | 3.00 | Inactivated | Right | Unilateral | Steroids |
| | | 38 | Female | 3.00 | Inactivated | Right | Unilateral | Steroids |
| Tugizova et al., 2023[14] | CC | 65 | Female | 0.71 | Genetic | Right | Unilateral | Steroids and immunoglobulin |
| | | 67 | Male | 0.14 | Genetic | Left | Bilateral | Steroids |
| Lee, 2022[15] | CR | 28 | Female | 0.28 | Vector-based vaccine | Right | Unilateral | Steroids |
| Liu and Lee 2022[16] | CR | 49 | Female | 2.00 | Vector-based vaccine | Both | Bilateral | Steroids |

*(Continues)*

**Table 1.** Characteristics of studies included in our systematic review corresponded to cases of isolated ON *(continued)*

| Author | Publication type | Age | Gender | Time* | Vaccine associated | Affected eye | Type of ON | Treatment |
|---|---|---|---|---|---|---|---|---|
| Saxton et al., 2023[17] | CR | 28 | Female | 1.00 | Genetic | Right | Unilateral | Steroids |
| Zhang et al., 2023[18] | CR | 58 | Female | 0.01 | Genetic | Left | Unilateral | Steroids |
| Natung et al., 2023[19] | CR | 44 | Female | 0.57 | Vector-based vaccine | Both | Bilateral | Steroids |
| Badeeb et al., 2024[20] | CC | 66 | Female | 1.42 | Genetic | both | Bilateral | Steroids |
| Katayama et al., 2022[21] | CR | 63 | Male | 1.50 | Genetic | Both | Bilateral | Steroids |
| Donaldson and Margolin, 2023[22] | CC | 54 | Male | 3.00 | Vector-based vaccine | Right | Bilateral | Steroids |
| Raxwal et al., 2022[23] | CR | 47 | Female | 1.14 | Genetic | Left | Unilateral | Steroids |
| Huang et al., 2023[24] | CC | 47 | Female | 4.00 | Vector-based vaccine | Both | Bilateral | Steroids |

*Time between vaccination and optic neuritis development (weeks).
CP: case report; LE: letter to the editors; CC: clinical correspondence, ON: optic neuritis.

correction. Differences between continuous variables were assessed using Student's t-test; $p < 0.05$ was considered significant.

## Results

A total of 126 articles were retrieved. Of these, only 14 (32 patients) corresponded to cases of isolated ON (Table 1); 6 articles (12 patients) reported ON associated with autoimmune diseases, optic neuromyelitis, encephalomyelitis, and other causes (Table 2). The PRISMA flow chart is presented in figure 1.

### *General characteristics of patients*

A total of 44 patients (32 with isolated ON and 12 with ON associated with autoimmune disease) were included in this analysis. Considering that bilateral optic nerve involvement or AON are more severe conditions, a descriptive analysis was performed comparing bilateral versus unilateral optic nerve involvement. Female patients were more frequently affected (33/44) than males (11/44) ($\chi^2$, $p = 0.056$). Unilateral ON was more frequent in the included patients (27/44). According to the logarithm of the minimum angle of resolution (LogMAR chart) values, the left eye was most affected (non-parametric test, $p = 0.004$). The mean time between vaccination and onset of symptoms was 1.72 ± 1.07 weeks for AON and 4.7 ± 6.7 weeks for unilateral ON; no significant differences were found between the two groups (Table 3).

### *Association to vaccines*

Generic messenger ribonucleic acid (mRNA) vaccines were most associated with ON (22 cases), 62.9% of which were unilateral ON, followed by vector-based vaccine (18 cases), which accounted for 64.7% of bilateral ON cases. Finally, inactivated vaccines were most frequently associated with bilateral involvement.

### *Treatment administered*

Intravenous corticosteroids were the most common treatment, used in 37 cases. All other patients received combined treatment with corticosteroids and plasma exchange (PLEX) (Table 3)[3-34].

Bivariate correlations were found between ON type (unilateral or bilateral) and sex ($p = 0.04$, $R = -0.367$), and severity of vision loss in the left eye ($p = 0.005$, $R = -0.511$).

**Table 2.** Characteristics of studies included in our systematic review corresponded to cases with autoimmune disease

| Author | Publication type | Age | Gener | Time* | Vaccine associated | Affected eye | Type of ON | Treatment |
|---|---|---|---|---|---|---|---|---|
| Shemer et al., 2023[8] | CR | 38 | Male | 18.00 | Genetic | Left | Unilateral | Previous retrobulbar ON |
| | | 29 | Female | 24.00 | Genetic | Right | Unilateral | Esclerosis múltiple |
| | | 45 | Female | 6.00 | Genetic | Right | Unilateral | Disclosed MS with 2 episodes of ON |
| Leber et al., 2021[25] | CR | 32 | Female | 0.07 | Inactivated | Both | Bilateral | Tiroiditis |
| Shirah et al., 2023[26] | CR | 31 | Female | 2.00 | Genetic | Left | Unilateral | Lupus |
| Nagaratnam et al., 2022[27] | CR | 36 | Female | 2.00 | Vector-based vaccine | Both | Bilateral | Encefalomielitis aguda |
| Kang et al., 2023[28] | CR | 42 | Female | 1.00 | Genetic | Left | Unilateral | SLE |
| Yildiz 2022[29] | CR | 32 | Male | 2.00 | Inactivated | Right | Unilateral | 1. Tumor |
| | | | | | | | | 2. Graves' disease |
| Richardson-May et al., 2022[30] | CR | 71 | Female | 1.00 | Vector-based vaccine | Right | Unilateral | Guillain-Barre syndrome |
| Chu et al., 2023[31] | CR | 60 | Female | 2.14 | Vector-based vaccine | Left | Unilateral | Stem cell transplant |
| Shukla et al., 2022[32] | CR | 56 | Female | 1.71 | Vector-based vaccine | Both | Bilateral | Sarcoidosis |
| Helmchen et al., 2022[33] | LE | 40 | Female | 2.00 | Vector-based vaccine | Both | Bilateral | Esclerosis Múltiple |
| Levi-Strauss et al., 2022[34] | LE | 72 | Female | 3.00 | Genetic | ND | ND | Neuromielitis |

*Time between vaccination and optic neuritis development (weeks).
CR: case report; LE: letter to the editors, ON: optic neuritis, SLE: systemic lupus erythematosus.

## Clinical report

A 59-year-old female patient, previously healthy, reported receiving the COVID-19 vaccine 22 days before the onset of clinical symptoms. The patient progressively developed moderate to severe left hemicrania with periorbital involvement; over the next 48 h, left VA decreased to amaurosis. Bilateral ON was observed over the next 72 h. The patient consulted a physician, and magnetic resonance imaging was performed. Patchy inflammatory hyperintensities were observed in the optic nerves, with greater anterior (papillary) involvement. Cerebrospinal fluid cytochemistry (glucose, 57 mg/dL; protein, 23 mg/dL, 3 cells $mm^3$) and cytology were performed, along with determination of oligoclonal bands and detection of AQP4 and anti-myelin oligodendrocyte glycoprotein antibodies (both negative), as well as microbiological culture and staining. AON was considered at diagnosis and the patient received a bolus of methylprednisolone for 5 days, followed by 5 sessions of PLEX. At the end of treatment, bilateral VA was 20/70. Additional tests included a rheumatologic profile (anti-Smith, antinuclear, anti-DNAdc, anti-SSA, anti-SSB, and anticardiolipin Immunoglobulin G and Immunoglobulin M, C3 and C4 proteins, rheumatoid factor, and *Mycobacterium tuberculosis* GenXpert) with negative results.

## Discussion

Vaccine side effects have been extensively reported (especially with viral agents), including ocular side effects. In such cases, it is imperative to assume an association between vaccination and the development

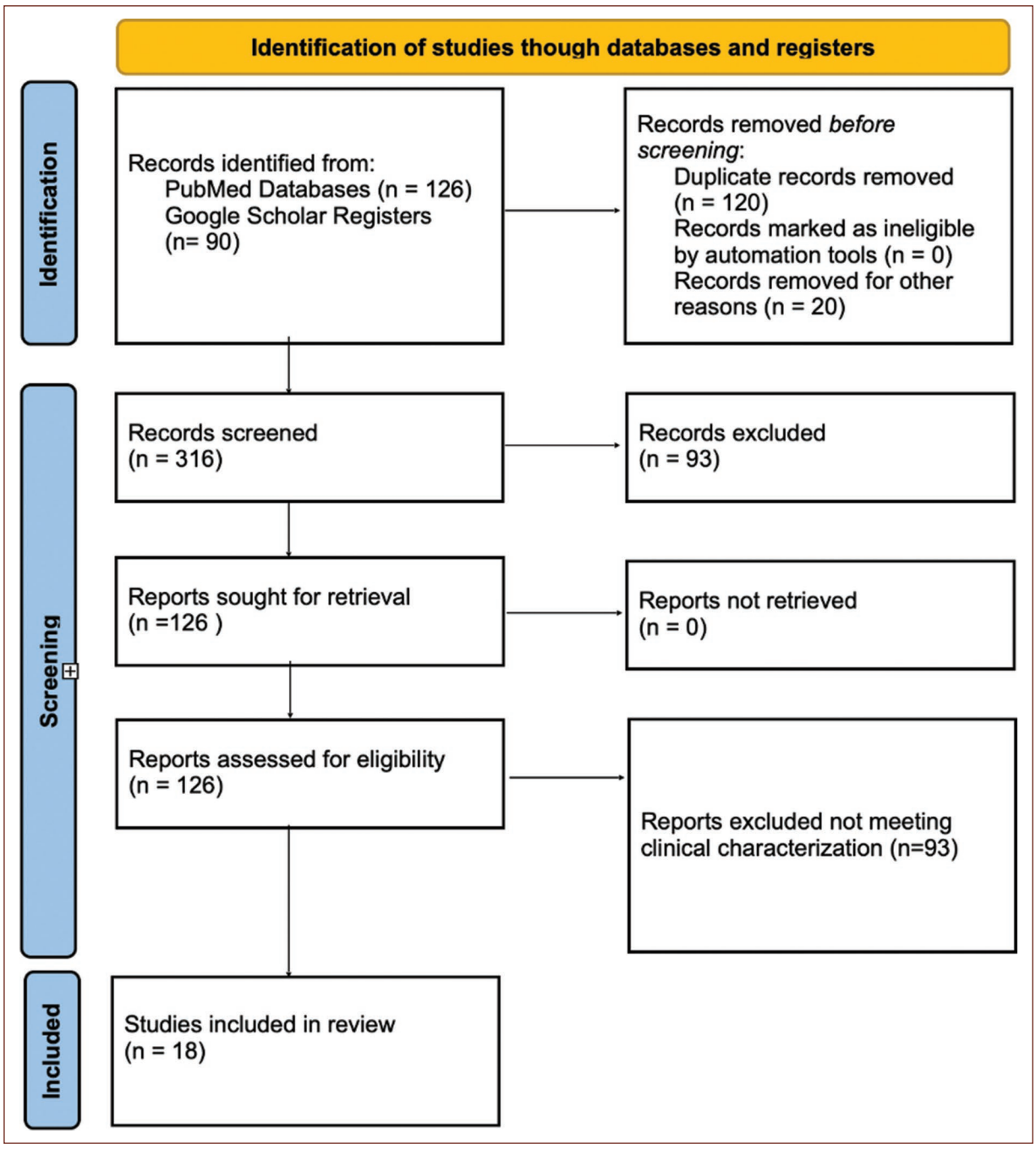


**Figure 1.** Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram depicting the flow of information through the different phases of a systematic review.

of complications to establish causality[48,49]. ON, one of the most serious ocular diseases can be caused by a variety of inflammatory and infectious conditions. According to their clinical presentation, cases of ON can be classified as typical (unilateral visual loss, retroorbital pain on extraocular movement, dyschromatopsia, and higher prevalence in younger patients) or atypical (bilateral onset, refractory to corticosteroid treatment, and optic nerve head/peripapillary hemorrhage)[43].

In this study, we present a case of ON associated with COVID-19 vaccination (ChAdOx1-2 vaccine) and a literature review of ON cases reported as associated with COVID-19 vaccination in the PUBMED and Google

**Table 3.** General characteristics of the included patients

| General data | Bilateral optic neuritis (n = 17) | Unilateral optic neuritis (n = 27) | p |
|---|---|---|---|
| Age (years) | 48.6 ± 14 | 41.07 ± 16.1 | 0.07 |
| Time elapsed between vaccination and ON onset (weeks) | 1.72 ± 1.07 | 4.5 ± 6.7 | 0.6 |
| Isolated ON, n (%) | 13 (40.6) | 19 (59.4) | 0.7 |
| ON plus autoimmune disease, n (%) | 4 (33.3) | 8 (66.7) | |
| Female, n (%) | 11 (33.3) | 22 (66.7) | 0.2 |
| Male, n (%) | 6 (54.5) | 5 (45.5) | |
| Type of vaccine administered, n (%)<br>Vector-based vaccine<br>Genetic<br>Inactivated | <br>11 (61.1)<br>5 (22.7)<br>1 (25) | <br>7 (38.9)<br>17 (77.3)<br>3 (75) | <br>0.03 |
| Abnormal fundoscopy, n (%) | 12 (46.2) | 14 (53.8) | 0.1 |
| Visual acuity, n (%)<br>Mild to moderate<br>Severe | <br>5 (23.8)<br>10 (52.6) | <br>16 (76.2)<br>9 (47.4) | <br>0.1 |
| LogMAR score<br>Right eye<br>Left eye | <br>0.66 ± 0.8<br>0.98 ± 0.9 | <br>0.51 ± 0.73<br>0.3 ± 0.65 | <br>0.3<br>0.004 |
| Serum antibodies, n (%)<br>AQP4<br>MOG | <br>2 (50)<br>3 (50) | <br>20 (50)<br>3 (50) | <br>1 |
| Treatment, n (%)<br>Corticosteroid monotherapy<br>Corticosteroids plus PLEX | <br>14 (37.8)<br>3 (42.9) | <br>23 (62.2)<br>4 (57.1) | <br>1 |

ON: optic neuritis; PLEX: plasma exchange; MOG: myelin oligodendrocyte glycoprotein.

Scholar databases. Our results suggest that the incidence of ON associated with SARS-CoV-2 vaccines is low (only 44 patients were retrieved); moreover, a significant proportion of these patients (38.6%) had autoimmune diseases associated with ON. The vaccines most frequently associated with ON were those of genetic origin (mRNA), and females were the most affected sex.

To date, the mechanism of vaccine-related ON is not clearly understood, but some hypotheses have been proposed, such as molecular mimicry with viral proteins, immune cross-reactivity with human tissues, activation of NLRP3 inflammation, and/or microthromboembolism formation[44-47].

Despite limitations related to the small sample size and its retrospective design, our work showed interesting results. We suggest long-term follow-up of these patients, especially those with associated autoimmune disease, to prevent visual dysfunction.

## Conclusion

Clinicians should be aware of the risk of ocular side effects of COVID-19 vaccines, especially in patients with functional neurological compromise, to promptly initiate immunomodulatory treatment (corticosteroids plus PLEX) and prevent further complications.

### *Limitations of the study*

It is important to consider that only two databases were used: PubMed and Google Scholar. A third database, SciELO, could not be included, mainly because this database contains studies reported in languages other than English. Another important limitation is that only one neurological referral center was included: the National Institute of Neurology and Neurosurgery, a public neurological referral center. During the period of preparation of this manuscript, the number of cases of NO has increased considerably; however, many of the reported cases have been attributed to the COVID-19 Omicron variant.

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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 considerations

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

**Confidentiality, informed consent, and ethical approval.** This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

**Declaration on the use of artificial intelligence (AI).** The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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REVIEW ARTICLE

# Neuropsychiatric manifestations as an initial presentation of cerebral venous thrombosis: two case reports and literature review

*Gerardo Arrieta-Limón*[1], *Andrea Salgado-Alvear*[1], *Natalia Dávalos-Cabral*[1], *Raymundo Solís-Gómez*[1]*, *Laura M. Reyes-Martínez*[1], *Ana V. Herrera-Hernández*[1], *and Fabiola E. Serrano-Arias*[1,2]

[1]*Direction of Education;* [2]*Stroke Clinic. Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City, Mexico*

## Abstract

*Cerebral venous thrombosis (CVT) is the involvement of the venous sinuses due to the formation of clots that occlude the cerebral veins. It is a rare cause of cerebrovascular disease, accounting for 0.5-1% of cases, with a higher frequency in women under 50 years of age. The most common symptoms are headache, papilledema, seizures, motor and sensory deficits, cranial nerve paresis, and alterations in mental status. Cases with neuropsychiatric manifestations, such as delirium, cognitive impairment, and mutism, have been reported as isolated presentations, although these are limited. Two cases of CVT are presented, both of which exhibited neuropsychiatric manifestations characterized by erratic behavior, aggression, disorientation, depressive, and catatonic symptoms. Treatment for CVT includes addressing the underlying cause, controlling symptoms, and initiating anticoagulation, which has significantly reduced mortality. CVT presenting with mental status alterations without focal neurological deficits is uncommon. In these cases, a temporal association between symptoms and vascular pathology was observed. Although neuropsychiatric manifestations are rare, CVT should be considered in atypical presentations of common diseases.*

**Keywords:** *Intracranial thrombosis. Stroke. Cognitive dysfunction. Delirium. Catatonia.*

## *Manifestaciones neuropsiquiátricas como presentación inicial de la trombosis venosa cerebral: dos reportes de caso y revisión de la literatura*

## Resumen

*La trombosis venosa cerebral (TVC) es la afectación de los senos venosos por la formación de coágulos que ocluyen las venas cerebrales. Es una causa infrecuente de enfermedad vascular cerebral con 0.5 al 1% de los casos, con mayor frecuencia en mujeres menores de 50 años. Los síntomas más frecuentes son cefalea, papiledema, crisis epilépticas, déficits motores y sensitivos, paresia de los nervios craneales y alteraciones del estado mental. Se han reportado casos con manifestaciones neuropsiquiátricas como manifestaciones aisladas, representadas por delirium, deterioro cognitivo y mutismo, sin embargo, son limitados. Se presentan dos casos de trombosis venosa cerebral que presentaron manifestaciones neuropsiquiátricas caracterizadas por conducta errática, agresividad, desorientación, síntomas depresivos y catatónicos. El tratamiento de la TVC incluye abordar la causa subyacente, controlar síntomas e iniciar anticoagulación, lo que ha reducido*

***Correspondence:**
Raymundo Solís-Gómez
E-mail: ray.sogo99@gmail.com

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*la mortalidad significativamente. La presentación de la TVC con alteraciones del estado mental sin déficits neurológicos focales es poco común. En estos casos, se observó una asociación temporal entre los síntomas y la patología vascular. Aunque las manifestaciones neuropsiquiátricas son inusuales, el diagnóstico de TVC debe considerarse en presentaciones atípicas de enfermedades comunes.*

***Palabras clave:*** *Trombosis intracraneal. Infarto cerebral agudo. Deterioro cognitivo. Delirio. Catatonia.*

## Introduction

Cerebral venous thrombosis (CVT) is a rare but potentially serious condition that involves the formation of a blood clot in the veins draining the brain. Although its incidence is relatively low compared to other cerebrovascular disorders, CVT accounts for 0.5% to 1% of patients with cerebrovascular disease[1]. In Mexico, the National Mexican Registry of Cerebrovascular Disease reported a prevalence of 3%[2].

The dural venous sinuses are large trabecular channels lined with endothelium that collect blood from the brain's surface, deep regions, and the posterior fossa, due to their intracranial course. Specifically, the dural venous sinuses (such as the superior sagittal sinus) drain into the lateral sinuses and ultimately into the internal jugular veins. In addition, these sinuses facilitate the removal of cerebrospinal fluid (CSF) via arachnoid granulations. When clots form in these sinuses, it is referred to as dural venous sinus thrombosis[3].

The most common age of onset for CVT is before 50 years, with a higher incidence in women[4]. The risk factors for developing CVT can be divided into acquired and genetic predisposition categories. Acquired risk factors include the use of oral contraceptives, pregnancy, puerperium, infections, neoplasms, vasculitis, traumatic brain injury, and central nervous system disorders. Genetic risk factors include hereditary thrombophilias or genetically heavier neoplasms. Approximately 85% of patients with CVT have an underlying prothrombotic condition[5].

The clinical presentation of CVT differs from that of more common forms of arterial origin cerebral infarction[5,6]. Four typical patterns of presentation have been identified, in order of frequency: (1) Focal neurological alterations (including focal seizures); (2) Isolated intracranial hypertension; (3) Subacute encephalopathy; (4) Cavernous sinus syndrome[7]. Less frequently, atypical presentations such as transient ischemic attack, chronic progressive optic neuropathy without associated headache[8], and psychiatric symptoms are observed. Neuropsychiatric manifestations in CVT patients are rare. In the International Study of Cerebral Vein and Dural Sinus Thrombosis, 22% of patients exhibited mental status alterations. Behavioral symptoms such as delirium, dementia, and mutism have also been reported as isolated manifestations[9].

Therefore, two cases of patients with CVT presenting with neuropsychiatric manifestations are described below.

## *Case 1*

A woman in her third decade of life, without any risk factors. She began with a decrease in sleep requirements and erratic behavior. This was followed by verbal and physical aggression, along with increased purposeful activity. Her speech became disorganized, and she was admitted to the neuropsychiatry unit. Upon initial evaluation, she exhibited psychomotor agitation, disorganized speech, and soliloquy. Neurological examination showed no focal sensory-motor deficits. The brain computed tomography scan was reported as normal. CSF analysis revealed an opening pressure of 30 cm $H_2O$, glucose 72, protein 24, and 1 cell. Initial treatment consisted of olanzapine 20 mg/day and lorazepam 6 mg/day. Venous magnetic resonance imaging (v-MRI) showed filling defects in the left lateral sinus, extending to the ipsilateral sigmoid and jugular sinuses, consistent with thrombosis (Fig. 1), and thus management with enoxaparin 80 mg every 12 h was initiated, progressing to oral anticoagulation with acenocoumarin. At 30 days, the patient showed improvement, with oxcarbazepine 450 mg/day as a mood stabilizer and acenocoumarin 4 mg/day. Control v-MRI at 6 months did not show recanalization of the thrombotic sinus; however, there were no changes in the cerebral parenchyma (Fig. 1). Other studies performed to investigate etiology were normal. During the 12-month follow-up with neuropsychiatry, complete remission of the symptoms was maintained.

## *Case 2*

A man in his second decade of life, without significant medical history related to the current condition. He presented suddenly with temporospatial disorientation,

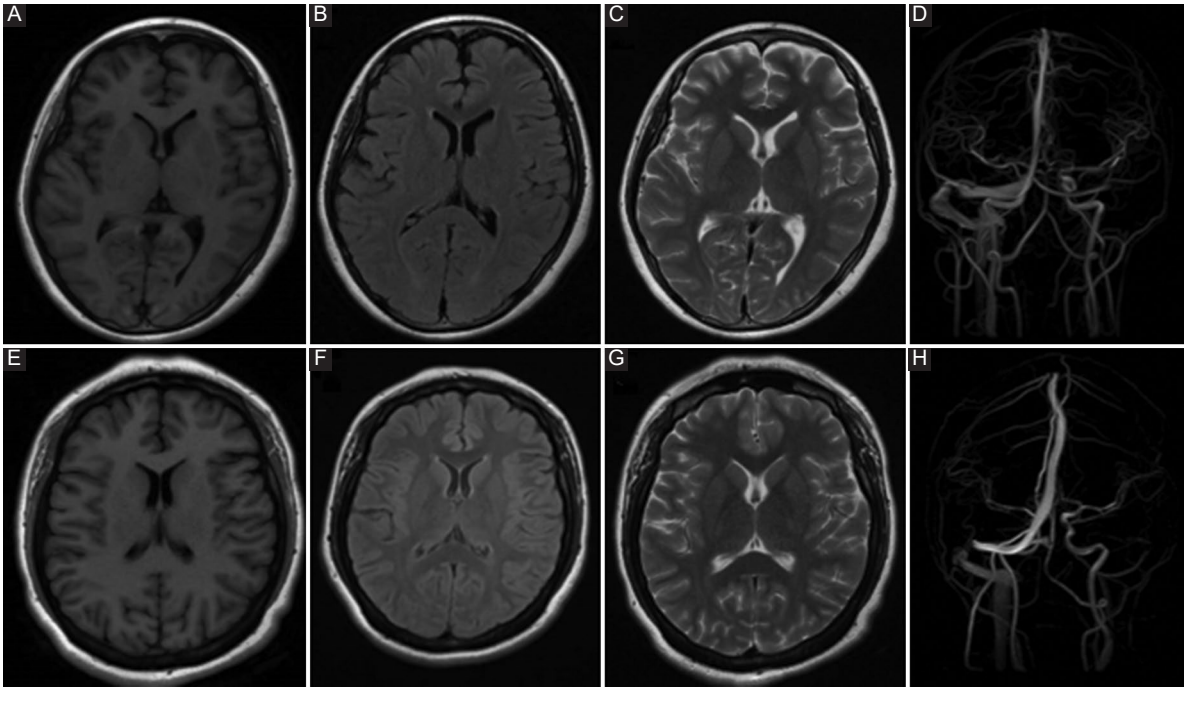


**Figure 1.** Magnetic resonance imaging (MRI) scans of two patients. **A-D** correspond to patient 1. **A:** magnetic resonance imaging (MRI) patient 1. **B:** T1 FLAIR. **C:** T2 FLAIR. **D:** T2W with no evident parenchymal lesions. **E-H** correspond to patient 2. **E:** venous MRI (v-MRI) shows absence of left lateral sinus in patient 2. **F:** T1 FLAIR. **G:** T2 FLAIR. **H:** T2W with no evident parenchymal lesions. v-MRI shows the absence of the left lateral sinus.

bradyphasia, hypophonia, sad mood, and bradykinesia. During his hospitalization, he developed catatonic symptoms, including mutism and maintenance of fixed postures. Additional signs included fixed gaze, catalepsy, and withdrawal. Routine laboratory studies and a simple cranial CT scan were normal. A lumbar puncture was performed, revealing an opening pressure of 320 mm $H_2O$, protein 29, glucose 54, and two leukocytes. Due to the finding of intracranial hypertension, v-MRI was performed, showing thrombosis of the left lateral sinus (Fig. 1). Treatment with enoxaparin 60 mg every 12 h was initiated, followed by oral anticoagulation with acenocoumarin 4 mg/day. Fluoxetine 20 mg/day and modafinil 400 mg/day were started, resulting in psychiatric symptom improvement 1 month later. To determine the etiology of venous thrombosis, prothrombotic studies and an immunological profile were performed with negative results. The control v-MRI at 6 months demonstrated partial recanalization of the left lateral sinus (Fig. 1).

## Discussion

The presentation of CVT with mental status alterations, in the absence of focal neurological deficits, is rare[10]. In a series of 62 patients with isolated lateral sinus thrombosis, a 5% prevalence of mental status alterations was reported, suggesting an atypical presentation[11].

In older individuals with thrombosis of the deep cerebral venous system, the most commonly reported mental status changes are somnolence and acute confusional state, with no cases reported in younger patients[12,13]. This study describes two cases of young patients with neuropsychiatric manifestations as the initial presentation of lateral sinus thrombosis. Both patients presented with an acute onset of symptoms, including intracranial hypertension and either a manic or catatonic presentation. Bousser et al. reported that patients with neuropsychiatric manifestations tend to have a better prognosis[14].

Most cases of mania associated with cerebrovascular disease occur in lesions of the right hemisphere, seen in up to 68% of cases, whereas only 15% are associated with lesions in the left hemisphere[14]. In contrast, the presentation of catatonia is often linked to lesions within the anterior circuit cingulate[15]. In the cases presented, the temporal association between the onset of symptoms and vascular pathology is

clear, though it is important to note that no parenchymal lesions were observed, and the left lateral sinus was affected (Fig. 1). In both cases, thrombosis of the lateral sinus, which drains blood from the cerebellum, brainstem, and the posterior part of the cerebral hemispheres, was identified. The venous thrombosis likely resulted in reduced venous drainage, contributing to dysfunction in these regions and potentially causing symptoms such as bradyphasia, temporospatial disorientation, and disturbances in the sleep-wake cycle. Literature has described neuropsychiatric disorders, including delusions, disorganized behavior, and visual hallucinations, following remote cerebellar strokes[16], symptoms which were also observed in the present cases.

In more severe cases, impaired venous drainage leads to visible vasogenic edema in imaging studies, accompanied by venous infarctions and associated hemorrhages. The diagnosis of CVT should be considered in patients presenting atypically, once more common causes have been excluded[17].

## Conclusion

There is limited literature on neuropsychiatric manifestations in CVT. This review presents two patients diagnosed with CVT who exhibited only neuropsychiatric symptoms as their clinical presentation, manifesting as disturbances in the sleep-wake cycle, bradykinesia, and mood alterations. The diagnosis of CVT can be challenging and sometimes delayed due to the variability in clinical presentation. Psychiatric symptoms can be disabling and misleading in diagnosis, highlighting the need for early recognition and treatment.

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REVIEW ARTICLE

# The link between gut health and neurodegenerative disorders: the importance of the microbiota

*Kevin L. López-Simental*[1], *Karen P. Camarillo-Cárdenas*[2]*, *and Leonel A. Cantú-Martínez*[3]

[1]*School of Chemical Sciences, Universidad Autonoma de Nuevo Leon, San Nicolas de los Garza;* [2]*Independent Researcher, Monterrey;* [3]*Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Instituto de Neurología y Neurocirugía, Centro Médico Zambrano Hellion, TecSalud, San Pedro Garza Garcia. Nuevo León, Mexico*

## Abstract

*The gut microbiota, a complex ecosystem of microorganisms, plays an essential role in human health by influencing metabolism, immune function, and the gut-brain axis. Emerging evidence links gut dysbiosis (imbalance) to neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease. Mechanistic pathways include the propagation of amyloidogenic proteins, production of neurotoxic metabolites such as trimethylamine N-oxide, and intestinal permeability disruption. This review highlights key mechanisms and explores therapies such as fecal microbiota therapy, probiotics, and lifestyle changes to modulate the microbiota and slow neurodegeneration. Despite significant advances, further research is essential to fully understand the microbiota's role in neurodegeneration and to develop microbiota-targeted therapies for clinical application.*

***Keywords:*** *Gut microbiota. Neurodegenerative diseases. Gut-brain axis. Bacterial amyloid. N-óxido de trimetilamina. Microbiota-targeted therapies.*

## *El vínculo entre la salud intestinal y los trastornos neurodegenerativos: la importancia de la microbiota*

## Resumen

*La microbiota intestinal, un ecosistema complejo de microorganismos, desempeña un papel esencial en la salud humana al influir en el metabolismo, la función inmunológica y el eje intestino-cerebro. Evidencia reciente vincula la disbiosis intestinal (desequilibrio) con enfermedades neurodegenerativas como la enfermedad de Alzheimer (EA), la enfermedad de Parkinson (EP), la esclerosis lateral amiotrófica (ELA) y la enfermedad de Huntington (EH). Entre los mecanismos propuestos se incluyen la propagación de proteínas amiloidogénicas, la producción de metabolitos neurotóxicos como el N-óxido de trimetilamina (TMAO) y la alteración de la permeabilidad intestinal. Esta revisión destaca los mecanismos clave y explora terapias como el trasplante de microbiota fecal (TMF), los probióticos y los cambios en el estilo de vida para modular la microbiota y retrasar la neurodegeneración. A pesar de los avances significativos, es esencial continuar con la investigación para comprender plenamente el papel de la microbiota en la neurodegeneración y desarrollar terapias dirigidas a la microbiota para su aplicación clínica.*

***Palabras clave:*** *Microbiota intestinal. Enfermedades neurodegenerativas. Eje intestino-cerebro. Amiloide bacteriana. TMAO. Terapias dirigidas a la microbiota.*

***Correspondence:**
Karen P. Camarillo-Cárdenas
E-mail: karencamarillo01@gmail.com

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## Introduction

The gastrointestinal tract hosts a large community of microorganisms, including bacteria, fungi, yeast, archaea, and viruses. Symbiosis among humans and communities of microorganisms is highly relevant due to the benefits it provides to our health. These microbes are fundamental for the proper functioning of our gut by metabolizing macronutrients such as carbohydrates and proteins, primarily in the cecum and distal colon, where microbial populations are most abundant. This type of microorganism is well known as gut microbiota. The gut microbiota thrives on undigested food and mucus shed from the intestine, promoting tissue growth and intestinal immune development. This community is capable of producing metabolites that can promote or inhibit the progress of different pathologies such as diabetes, obesity, colitis, Crohn's disease, and even neurodegenerative diseases[1].

The gut-brain axis, primarily mediated by the vagus nerve, enables bidirectional communication between the gut microbiota and the central nervous system. Metabolites such as short-chain fatty acids, endotoxins, and key neurotransmitters (e.g., dopamine and gamma-aminobutyric acid) influence neuronal function[2].

Gut microbiota metabolites can also reach the brain through systemic circulation, although two barriers, the intestinal barrier and the blood–brain barrier, limit their access. The intestinal barrier has a mucus layer, a glycoprotein biofilm that protects the intestinal epithelium. A low fiber diet or the presence of inflammatory mediators can weaken this barrier. The blood–brain barrier, composed of tightly packed endothelial cells, regulates the entry of substances into the brain and has specific transporters that limit the passage of harmful molecules.

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) are major global health concerns with limited therapeutic options. Increasing evidence links gut microbiota to these diseases, suggesting that microbial alterations may influence protein aggregation, neuroinflammation, and neuronal death. This review explores the interplay between gut microbiota and neurodegenerative diseases, highlighting potential mechanisms and therapeutic interventions.

## Gut microbiota development and composition

Throughout life, humans are exposed to a wide variety of microorganisms that colonize the gastrointestinal tract, promoting either health or disease. The diversity of gut microbiota is mostly influenced by factors such as mode of delivery, diet, and exposure to microorganisms from infancy to adulthood. The observation of bacteria in the placenta and amniotic fluid supports that microbial colonization begins even before delivery[3], with distinct microbial communities established based on the delivery method: vaginal delivery promotes *Lactobacillus*, *Prevotella,* and some fecal microbe colonization, while cesarean sections favor *Staphylococcus* and *Corynebacterium*[4]*.* Breastfed infants have a more diverse gut microbiota than infants fed with formula[5], primarily due to human milk oligosaccharides, which are a group of complex carbohydrates that improve the gut microbiota's development[6].

In adulthood, the gut microbiota stabilizes, with *Bacteroidetes* and *Firmicutes* predominating. However, its composition can be altered by diet, stress, and antibiotics[7].

These compositional shifts set the stage for gut-brain axis perturbations reviewed below.

## Gut microbiota and neurodegenerative mechanisms

In recent decades, researchers around the globe have been striving to uncover the mechanisms underlying neurodegenerative diseases. Although the precise mechanisms remain unclear, increasing evidence suggests that gut microbiota may play a significant role in neurodegeneration. The main characteristic of these diseases is the aggregation of proteins known as amyloids, which are toxic and lead to neuronal death. Each neurodegenerative condition is associated with a specific protein, such as alpha synuclein in PD and Lewy body dementia and amyloid beta (Aβ) and tau proteins in AD, among others[8].

## AD

AD is the most prevalent form of dementia, accounting for 60-70% of cases globally, with aging as the primary risk factor[9]. Its hallmark pathological features include the extracellular accumulation of Aβ plaques and the intracellular aggregation of hyperphosphorylated tau protein, forming neurofibrillary tangles. These aggregates disrupt neuronal signaling, induce synaptic loss, and ultimately lead to widespread neuronal death, manifesting as progressive cognitive decline and memory loss, a link between gut dysbiosis and AD pathogenesis[10]. Inflammatory bowel diseases, such as ulcerative

colitis and Crohn's disease, have been linked to a 2.54-fold increased risk of dementia, highlighting the gut's influence on neurodegenerative processes[11].

## PD

PD is a leading neurodegenerative disorder worldwide, with its global burden increasing significantly over the past decades[12]. It is clinically characterized by motor symptoms such as bradykinesia, postural instability, rigidity, and resting tremor. These symptoms arise due to progressive loss of dopaminergic neurons in the substantia nigra and noradrenergic neurons in the locus coeruleus. Lewy bodies, observed in post-mortem evaluations, are a hallmark of PD. These are formed by the accumulation of misfolded alpha-synuclein fibrils[13].

One of the most important hypotheses regarding the origin of PD is Braak's hypothesis. In his study published in 2004, Braak observed Lewy bodies in the gastrointestinal tracts of PD patients during post-mortem analysis. This finding suggested that α-synuclein aggregation might begin in the gut before propagating to the brain. This was supported by a study carried out in 2007, where researchers observed that α-synuclein, which is mostly expressed in the brain, is also expressed in enteroendocrine cells of the intestinal epithelium[14].

As intestinal cells can produce α-synuclein, researchers propose that it may travel to the brain through the vagus nerve in a prion-like manner[15].

Experimental evidence supports this mechanism. In a mouse model, pathological α-synuclein preformed fibrils were injected into the gut. The results showed that truncal vagotomy (severing the vagus nerve) and α-synuclein knockout reduced neurodegeneration by limiting α-synuclein aggregation and propagation[16].

## ALS

ALS is a progressive neurodegenerative disease primarily affecting motor neurons. It is characterized by weakness in the limbs and bulbar muscles (mouth or throat), leading to difficulties in movement, speech, and swallowing. The average life expectancy after diagnosis is 3-5 years.

Several factors contribute to ALS pathogenesis, including genetic mutations (*SOD1*, *FUS*, *C9orf72,* and *TRADBP*), as well as gender, age, and nutritional status. The disease's physiopathology is mediated by excitotoxicity, protein aggregation, mitochondrial dysfunction, and disruption of axon transport processes. ALS affects 5.20/100,000 habitants in North America[17].

Patients with ALS often experience gastrointestinal disorders, such as delayed gastric emptying, constipation, and stool incontinence.

Evidence suggests that disruption of the intestinal barrier may play a role in disease progression. For example, one study detected inflammatory markers in the majority of stool samples from ALS patients, while another reported the presence of bacterial endotoxins (lipopolysaccharides) in the blood, with higher levels observed in advanced disease stages[18].

## HD

HD is an autosomal dominant neurodegenerative disorder characterized by progressive motor and cognitive impairment, along with neuropsychiatric symptoms. It is caused by an expansion of cytosine-adenine-guanine repeats in the *huntingtin* gene, resulting in a mutant protein with toxic properties that lead to neuronal dysfunction and cell death. The median survival time of patients diagnosed with HD is approximately 18 years, and the global incidence is 2.71 cases/100,000 people[19].

Similar to other neurogenerative diseases, HD patients often experience gastrointestinal symptoms, including diarrhea, disruption of the intestinal epithelium, gastritis, and nutrient deficiencies. The exact association between gastrointestinal symptoms and disease progression is unclear; however, evidence suggests that gut microbiota alterations may play a significant role in HD pathogenesis. Certain bacterial populations in the gut have been observed to influence inflammatory and metabolic pathways, potentially contributing to disease progression[20]. Further research is needed to elucidate these mechanisms and their clinical implications.

## Role of the microbiota in neurodegeneration

Studies have shown that patients with neurodegenerative disorders present variation in their gut microbiota compared to healthy controls. In a study of colonic bacterial composition, an increase of proinflammatory and a reduction of anti-inflammatory bacteria were observed in American PD patients, suggesting that this dysbiosis could be related to neurodegeneration[21]. The alteration of gut microbiota, increasing the presence of pathological bacteria, can disrupt the intestinal barrier by augmenting proinflammatory cytokines, promoting the pass of bacterial metabolites to the circulation, leading to a weakening of the blood–brain barrier[22].

## Amyloid-producing bacteria and cross-seeding

The presence of amyloids produced by gut bacteria may facilitate protein aggregation by cross-seeding[23]. *Escherichia coli* produces curli, a functional bacterial amyloid that interacts with host proteins (CsgA and CsgB). Those proteins form a biofilm that helps bacteria to attach to the intestinal epithelium[24]. *Salmonella* Typhimurium and *Citrobacter koseri* can also produce curli, and their interactions, along with cross-seeding, contribute to the formation of interspecies biofilm[25].

Even though curli was the first protein described as a bacterial amyloid, there are other proteins that are also linked with neurodegenerative diseases, such as FapC, a functional amyloid produced by *Pseudomonas* sp. in the formation of a biofilm called amyloid-like fimbriae[26]. Experimental studies have demonstrated that oral exposure to curli-producing bacteria enhances α-synuclein aggregation in the gut and brain, supporting Braak's hypothesis of PD pathogenesis.

## Bacterial amyloids and neurodegenerative diseases

### *Curli*

The capacity of bacterial amyloids for cross-seeding *in vivo* has triggered a series of studies with amyloids associated with neurodegeneration. It has been observed an enhance in the accumulation of α-synuclein in the intestine, hippocampus, and striatum of Wild-type rats after weekly oral administration of curli-producing bacteria compared with controls[27].

### *FapC*

In a study using FapC obtained from *Pseudomonas aeruginosa*, researchers found that FapC promotes Aβ aggregation through a series of complementary experiments. *In silico:* Discrete molecular dynamics simulations demonstrated the molecular interactions between FapC and Aβ. *In vitro:* Thioflavin T assays were used to analyze amyloid kinetics, while stimulated emission depletion microscopy provided insights into the interaction between Aβ and FapC. *In vivo*: A zebrafish model of AD was used to assess the effects of FapC on Aβ aggregation through immunohistochemistry and behavioral tests[28].

In addition, *E. coli* is particularly relevant due to its natural presence in the healthy human gut microbiota, unlike other amyloid-producing bacteria[29]. Studies have shown that *E. coli* is more prevalent in the gut microbiota of patients with neurodegenerative diseases such as PD and AD, suggesting a potential role in disease pathogenesis[21,30].

## Trimethylamine N-oxide (TMAO)

TMAO is a gut microbial metabolite associated with several pathologies, including neurodegenerative diseases like AD[31]. Choline and L-carnitine are obtained by the consumption of red meat, eggs, dairy, and saltwater fish metabolized by the gut microbiota obtaining trimethylamine (TMA). This compound can pass through the intestinal barrier to circulation and be converted to TMAO by the enzyme flavin-containing monooxygenase 3 in the liver[32]. TMA is mostly absorbed in the small intestine due to bacteria that use choline and L-carnitine as substrates and is more present than in the large intestine[33]. There is a large diversity of bacteria capable of producing TMA, and *E. coli* is the most common TMA-producing bacteria[34]. It has been observed in studies that TMAO is elevated through age progression and it is related to neuronal plasticity deficits by inducing endoplasmic reticulum stress through PERK- EIF2α-ER. This was identified in the hippocampus tissue of mice models[35]. In other study using Alzheimer's models (APP/PS1) fed with choline and probiotics (*Lactobacillus plantarum*), researchers observed that there was a decrease in beta-amyloid levels in the hippocampus as well as in plasmatic TMAO in the group fed with probiotics, suggesting that TMAO is involved in disease progression[36].

Recently, TMAO plasma levels were correlated with PD progression and the need for an increment in medication (levodopa). Moreover, it was observed that PD patients present lower TMAO plasma concentration compared with healthy controls, a need for dose increment, and a higher risk of dementia conversion was observed in the patients with lower levels of TMAO[37]. It was also observed that PD patients present lower levels of TMA and TMAO than healthy controls in fecal samples[38].

## Therapeutic approaches targeting gut microbiota

Several strategies have been proposed to modulate gut microbiota and potentially mitigate neurodegenerative disease progression. These include:

### *Inhibition of bacterial amyloid aggregation*

Epigallocatechin gallate (EGCG), a small molecule with reported neuroprotective properties, has been

**Table 1.** Gut microbiota alterations and therapeutic strategies in neurodegenerative disorders

| Disease | Microbiota changes | Key mechanisms | Evidence | Interventions |
|---|---|---|---|---|
| AD | ↓*Firmicutes/Bacteroidetes*<br>↑*Escherichia coli* | FapC cross-seeds Aβ/tau<br>TMAO induces ER stress | 28,30,31,35 | Mediterranean diet[46]<br>*Lactobacillus plantarum*[36] |
| PD | ↓*Roseburia*<br>↑*Proteobacteria* | *Curli* enhances α-synuclein<br>Vagus propagation | 16,21,40 | EGCG[39]<br>FMT[44] |
| ALS | ↑Pathobionts<br>↓Barrier integrity | LPS neuroinflammation<br>Cytokine surge | 17,18 | High-fiber diet[48]<br>Butyrate (preclinical) |
| HD | ↓Diversity<br>↓*Bacteroides* | Metabolic dysfunction | 19,20 | Aerobic exercise[50]<br>Personalized probiotics |

↑: indicates increase.
↓: indicates decrease in microbial abundance or function.
AD: Alzheimer's disease; PD: Parkinson's disease; ALS: amyotrophic lateral sclerosis; HD: Huntington's disease; FMT: fecal microbiota transplantation; TMAO: trimethylamine N-oxide; ER: endoplasmic reticulum; LPS: lipopolysaccharide.

shown to reduce the toxicity of alpha-synuclein and amyloid-beta fibrils. *In vitro* studies have demonstrated that EGCG inhibits the formation of CsgA, a key component of bacterial amyloids, by interfering with the assembly of curli subunits on the bacterial outer membrane[39].

A recent study utilizing a PD mouse model (Thy1-aSyn), which overexpresses alpha-synuclein, evaluated the effects of EGCG on pathological alpha-synuclein aggregation and cognitive impairment. Mice administered curli-producing bacteria exhibited increased alpha-synuclein aggregation and cognitive deficits. However, treatment with EGCG significantly reduced both alpha-synuclein aggregates and cognitive impairment compared to the control group, without altering *Escherichia coli* composition in the gut microbiota[40].

### *Fecal microbiota transplantation (FMT)*

FMT has shown promise in restoring microbial balance and improving clinical outcomes[41-43]. In PD patients, FMT significantly alleviated motor symptoms and gastrointestinal dysfunction in randomized trials[44], with minimal adverse effects (e.g., transient diarrhea). Animal studies further demonstrate that FMT from young donors reduces neuroinflammation and extends lifespan[42], suggesting its potential as a disease-modifying therapy.

### *Lifestyle interventions: diet and exercise*

Lifestyle modifications, including diet and exercise, synergistically modulate gut microbiota composition and function[45]. Adherence to a Mediterranean diet, rich in polyphenols, fiber, and unsaturated fats, reduces neuroinflammation and amyloid aggregation, with meta-analyses showing a 13% lower incidence of PD and AD[46]. Fermented foods (e.g., kefir and kombucha) provide probiotics that, combined with high-fiber diets (prebiotics), enhance microbial diversity and short-chain fatty acid production[47,48].

Moderate exercise stabilizes gut microbiota and improves barrier integrity, though excessive intensity may exacerbate intestinal permeability[49,50]. These interventions collectively mitigate neuroinflammation and oxidative stress, critical pathways in neurodegeneration.

## Discussion

The interplay between the gut microbiota and neurodegeneration is complex and multifaceted. While evidence strongly suggests a role for microbiota in disease progression, the exact mechanisms remain to be fully elucidated. As summarized in table 1, disease-specific microbial alterations, key pathological mechanisms, and candidate interventions highlight the potential for microbiota-targeted therapies in neurodegeneration.

These findings underscore the need for personalized approaches, as microbiota composition varies significantly between individuals. For example, while FMT shows promise in PD[44], its efficacy may depend on donor-recipient compatibility. Similarly, the Mediterranean diet's benefits in AD[46] could be mediated by individual differences in microbial metabolite processing.

The current limitations include the lack of large-scale longitudinal studies in humans and the challenge of establishing causality between dysbiosis and neurodegeneration. Most evidence derives from animal models or cross-sectional human studies, which cannot fully capture the temporal dynamics of microbiota-brain interactions. Future research should prioritize microbiota-based biomarkers for early disease detection and randomized controlled trials testing interventions like FMT or targeted probiotics.

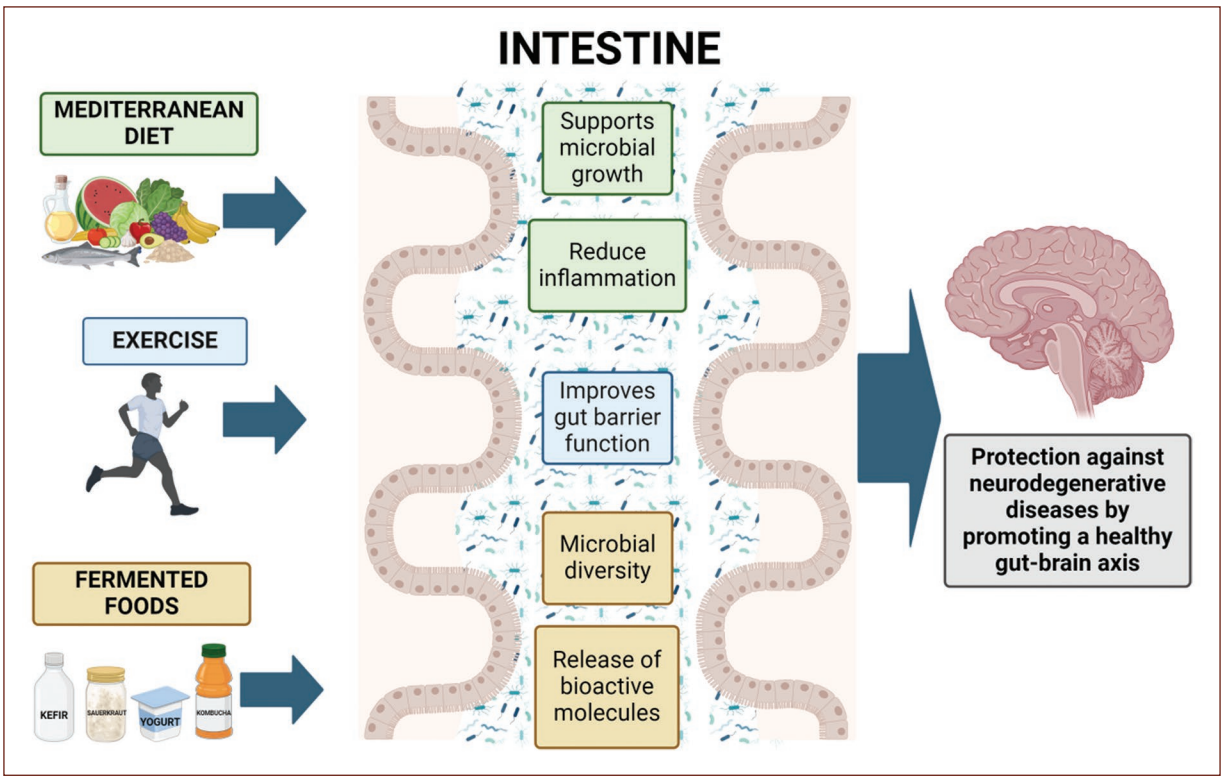


**Figure 1.** Impact of Mediterranean diet, fermented foods, and exercise on the gut. A Mediterranean diet, regular exercise, and the consumption of fermented foods contribute to gut microbiota diversity and stability. These interventions support microbial growth, reduce inflammation, improve gut barrier function, and promote the release of bioactive molecules. Collectively, these changes help maintain a healthy gut-brain axis, which may offer protection against neurodegenerative diseases.

The gut-brain axis offers a unique therapeutic window. Lifestyle modifications, such as combining a Mediterranean diet with aerobic exercise, may synergistically enhance microbial diversity and reduce neuroinflammation[48,50]. Pharmacological strategies (e.g., EGCG and TMAO inhibitors) could complement these approaches by targeting specific pathological cascades[39,35]. However, optimizing dosing, timing, and patient stratification will be critical for clinical translation.

To translate these findings into clinical practice, future work must address:

– Standardization of microbiota-targeted therapies (e.g., optimal probiotic strains and FMT protocols).
– Patient stratification based on microbial profiles and genetic risk factors.
– Long-term safety and efficacy of interventions, particularly in early-stage patients.

By integrating mechanistic insights (Table 1) with actionable lifestyle strategies (Fig. 1), this review highlights the gut microbiota as a modifiable frontier in neurodegenerative disease management.

## Conclusion

The gut microbiota is increasingly recognized as a critical modulator of neurodegenerative diseases. Dysbiosis, bacterial amyloid production, and microbial metabolites such as TMAO may contribute to neurodegenerative pathogenesis via mechanisms involving inflammation and protein aggregation. Targeted interventions, including dietary modifications, FMT, and probiotics, offer promising therapeutic strategies. However, further longitudinal and clinical studies are necessary to elucidate causal relationships and develop effective microbiota-based therapies.

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