

ISSN: 3081-1562

Indexed in: Embase/Excerpta Medica,
EBSCOhost, Scopus, SJCR, CINAHL, SciELO,
Latindex, Biblat, CONAHCYT

Archivos de Neurociencias

Volume 31. Number 1, January-March 2026

www.archivosdeneurociencias.mx



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ISSN: 3081-1562

Ref.: 11744AMEX261

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Psychopathological severity and global functioning in offsprings of parents with bipolar disorder

Gravedad de la psicopatología y funcionamiento global en hijos de padres con trastorno bipolar

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Marcos F. Rosetti^{3,4} , Assad D. Saad-Manzanera¹ , Joanna Jiménez-Pavón⁵ ,
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Abstract

Background: Offspring of parents with bipolar disorder (OPB) are a vulnerable group, with a large psychopathological load and low global functioning. Its association with the polarity and sex of the affected parent has not been explored. **Objective:** To determine the psychopathology and functioning of OPB and its association with the sex and polarity of the affected parent. **Methods:** OPB and the affected parent were invited; instruments and interviews were applied to assess psychopathology, suicidal behavior, and functionality. **Results:** Twenty-eight of 30 (93%) of the OPB presented at least one diagnosis; the average comorbidity was 2.3 diagnoses. OPB of mothers with predominantly manic polarity showed a tendency toward greater suicidal behavior (SB). A significant negative correlation was found between the number of psychopathology dimensions involved and the global functioning ($r = -0.52$, 95% confidence interval = $-0.75-0.21$, $df = 28$, $p = 0.003$). **Conclusion:** OPB constitutes a vulnerable pediatric population with a risk of psychopathology and burden.

Keywords: Psychopathology. Bipolar disorders. Parent-child relations.

Resumen

Antecedentes: Los hijos de padres con trastorno bipolar (HPTB) son un grupo vulnerable, con gran carga psicopatológica y bajo funcionamiento global. Su asociación con la polaridad y el sexo del progenitor afectado no se ha explorado. **Objetivo:** Determinar la psicopatología y el funcionamiento del HPTB y su asociación con el sexo y la polaridad del progenitor afectado. **Método:** Se invitó al HPTB y al progenitor afectado; se aplicaron instrumentos y entrevistas para evaluar psicopatología, conducta suicida y funcionalidad. **Resultados:** Veintiocho de 30 (93%) de los HPTB presentaron al menos un diagnóstico; la comorbilidad promedio fue de 2.3 diagnósticos. Los hijos de madres con polaridad predominantemente maníaca mostraron una tendencia a una mayor conducta suicida. Se encontró una correlación negativa significativa entre el número de dimensiones de psicopatología involucradas y el funcionamiento global ($r: -0.52$; IC 95%: -0.75 a 0.21 ; $gl = 28$; $p = 0.003$). **Conclusión:** Los HPTB constituyen una población pediátrica vulnerable con riesgo de psicopatología y carga.

Palabras clave: Psicopatología. Trastornos bipolares. Relaciones paterno-filiales.

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Date of reception: 05-03-2025
Date of acceptance: 05-03-2025
DOI: 10.24875/ANCE.M25000055

Available online: 18-07-2025
Arch Neurocién (Eng). 2026;31(1):1-6
www.archivosdeneurociencias.mx

Introduction

Bipolar disorder (BD) is a condition characterized by recurrent episodes of mania or hypomania and major depression¹. Mania and hypomania are states of elevated or irritable affect, increased activity, or energy, with mania being more severe. A depressive episode is characterized by a period of at least 2 weeks with a persistent displeasurable mood and loss of interest, along with other symptoms, both being accompanied by functional impairment².

BD has an estimated prevalence ranging from 0.5 to 5% in both sexes and tends to have a higher incidence in younger age groups³. Moreover, BD is considered one of the psychiatric disorders with the highest disease burden, accounting for approximately 5.5 million disability-adjusted life years, representing the total time lost to disability⁴.

Offspring of parents with BD (OPB), defined as children or adolescents with at least one progenitor diagnosed with BD, are considered a vulnerable population⁵. A recent systematic review encompassing 13 articles and 1,859 OPB revealed that although the research was varied, it qualitatively showed that families affected by BD tended to be low in nurturing, exhibited ineffective communication styles, and lacked discipline⁶. These familial traits were identified as risk factors for the development of internalizing disorders (ID⁷), externalizing disorders (ED⁸), and neurodevelopmental disorders (NDD⁹) in OPB, whether considered as categorical diagnoses or integrated into dimensional approaches.

Several studies have explored the presence of psychopathology in OPB. For instance, Chang et al., conducted a narrative review and found that 52% of OPB met the criteria for at least one diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) or its revision (DSM-III-R), compared to only 29% of offspring of healthy controls¹⁰.

Building on this, Carballo (2008) identified suicidal behavior (SB) as a significant clinical indicator of psychopathology, noting an elevated prevalence of SB not only in individuals with BD but also in their offspring, particularly when there was a family history of suicide¹¹.

Later, Mesman et al., conducted a 12-year longitudinal study with 108 participants, reporting several comorbidities with ID and ED. The 33% of OPB presented with unipolar depression (ID), 24% with BD (ID), 34% with anxiety disorders (ID), and 7% with disruptive behavioral disorders (DBD, ED¹²).

Furthermore, historically, onset polarity, defined as the predominant mood state (either manic or

depressive) at the first episode of BD, has been a predictor of BD outcome, influencing the likelihood of subsequent depressive or manic episodes and the risk of SB or psychotic symptoms in OPB¹³.

Further expanding this research, Lau et al., performed a meta-analysis including 17 studies with 2,098 OPB aged 2-30 years compared to a control group. The analysis revealed that 56% had a psychiatric diagnosis vs. 27.4% in the control group. Specific risk rates for OPB were 8.97 for BD, 2.43 for non-BD disorders (including ID and ED), 2.59 for attention deficit hyperactivity disorder (ADHD, NDD), and 2.48 for DBD¹⁴.

Similarly, Sandstrom et al., evaluated 378 OPB aged 4-22 years for depressive disorders and schizophrenia, using semi-structured interviews. They discovered that 82 had significantly higher rates of ADHD (B = 0.54, NDD), oppositional defiant disorder (ODD; B = 0.57, ED), and anxiety disorders (B = 0.25, ID) compared to offspring of parents with depressive disorders or schizophrenia¹⁵.

In addition, Bastos et al.¹⁶, conducted a systematic review with a meta-qualitative synthesis on the personality features of OPB of mothers with BD, integrating 10 studies with 2,638 participants. They concluded that maternal neglect and violence were associated with DBD symptoms in their offspring and a high incidence of Axis-I non-specified disorders according to the DSM, Fourth Edition.

Finally, Helmink et al., conducted a systematic review focused on the global functioning of OPB. Their analysis revealed that individuals older than 16 years exhibited worse functioning compared to younger age groups. The review included 49 studies, although only 19 of these were controlled for psychopathology¹⁷.

Research in Latin America has shown that OPB displays a higher incidence of ID, ED, NDD, and worse global functioning in comparison with offspring of parents who do not have BD⁵. In addition, findings from our group highlighted a significant, tenfold increase in the risk for diminished global functioning among OPB when conditions such as major depressive disorder (MDD), ADHD, or ODD were present¹⁸. Moreover, SB is recognized as a critical clinical indicator of psychopathology, other research has identified an elevated prevalence of SB not only in individuals with BD but also in their offspring, particularly when there is a family history of suicide or are faced with personal stressors¹⁹.

In summary, these studies demonstrated that nearly half of OPB present with psychopathology, regardless of the specific diagnosis or dimension. Considering the above, to our knowledge, no research has analyzed the polarity or sex of the affected parent with BD and its

association with psychopathology and global functioning in their offspring, specifically in Mexican children and adolescents. Therefore, this study aimed to establish (a) the presence of psychopathology and global functioning in OPB, and (b) the associations among the OPB's psychopathology dimensions (ID, ED, and NDD), SB, and global functioning with the affected parent's sex and polarity.

Methods

Participants

Children and adolescents aged 6-17 years old, whose parents had been diagnosed with BD at the Affective Disorders Clinic of the National Institute of Psychiatry Ramón de la Fuente Muñiz (ADC-INPRFM), participated in the study. Their inclusion was contingent upon their willingness to participate and the parents' agreement, as evidenced by signing an informed assent/consent form.

Instruments

The Brief Psychiatric Rating Scale for Children and Adolescents – 29 Items Version (BPRS-CA-29) was used as a semi-structured clinical interview with the child or adolescent and their parent, facilitating the establishment of categorical and dimensional diagnoses. SB was evaluated using item nine of the BPRS-CA-29, with responses categorized on a scale from 0 = no information, 1 = mild, 2 = moderate, and 3 = severe SB. This item specifically includes several questions where the clinician assesses ideation, planning, and behaviors. Diagnoses were obtained by a certified child and adolescent psychiatrist with more than 15 years of experience, using BPRS-CA-2 as a clinical guide. We decided to present diagnoses in terms of dimensions, we grouped participants considering the main and comorbid diagnosis, into ID, ED, and NDD.

Global functionality was measured using the global assessment of functioning scale (GAF), a validated tool that measures this construct on a scale from 100 to one in groups and has been previously used in pediatric populations²⁰; in addition, we also used the clinical global impression scale (CGI) as a tool to establish clinical severity²¹. Information on the onset and predominant polarity in the affected parent was gathered from the parents' clinical records, based on diagnoses made at the ADC-INPRFM.

Procedure

The treating psychiatrist at the ADC-INPRFM invited parents to participate alongside their offspring. Interested parties were then referred to the principal researcher for a detailed debriefing session. This session, conducted either through video/audio calls or in person, provided a thorough explanation of the study's specific details, and the informed assent/consent documents were provided either directly or by email. This ensured that both the participants and their legal guardians had a comprehensive understanding of the process. The BPRS-CA-29, GAF, and CGI evaluations were conducted with the child or adolescent and one or both parents during a 90-min in-person or online interview.

Statistical analysis

For categorical variables, percentages were used; for continuous variables, means accompanied by standard deviations (SD) were employed. χ^2 tests (χ^2) were used to examine associations between the three dimensions of psychopathology and SB with the sex or polarity of the affected parent. Wilcoxon tests (Z) were applied to compare the number of diagnoses and the levels of global functioning; this approach aimed to minimize the number of comparisons and thus enhance statistical power. Pearson correlations (r) were used to identify associations between diagnoses and global functioning. A multiple regression analysis (β) was conducted to measure potential predictor variables regarding the number of dimensions obtained through the BPRS-CA-29. Significance was established at $p < 0.05$; all tests were two-tailed.

Ethical considerations

The institutional research ethics committee authorized the study under number CEI/C/011/2023. Free and prolonged psychiatric follow-up (up to 5 years) was offered to participants who exhibited psychopathology.

Results

Sociodemographic and clinical characteristics

A total of 30 dyads were recruited. The sex distribution showed 16 males (53.33%) and 9 females (30.00%). The mean age of the OPB was 13.2 years (SD = 2.89; range 6-17 years). All dyads had at least one parent diagnosed

with BD, and $n = 2$ had both parents diagnosed with BD (6.67%). The mean age of diagnosis in the parents was 23.9 years ($SD = 6.42$; range 15-40 years). Most parents, $n = 28$ (93%), had the same onset and predominant polarity. The proportion of predominant polarity was: manic in $n = 14$ (47%), depressive in $n = 16$ (53%), and mixed in $n = 1$ (3.33%). The severity of BD in parents was distributed as: moderate in $n = 17$ (56.67%), severe in $n = 8$ (26.67%), and mild in $n = 5$ (16.67%).

Categories and dimensions of psychopathology

We found an average of 4.45 diagnoses (range one to 6) across 15 different categories, NSSI and LPE. Based on the multiple regression analysis, being female emerged as a predictor for the number of diagnoses: $\beta = 0.92$ ($SE = 0.48$, $t = 1.93$, $p = 0.03$). Regarding dimensional diagnosis, ID was present in $n = 12$ participants (40.00%), ED in $n = 8$ cases (26.67%), and NDD in $n = 18$ cases (60.00%). Details on categorical, dimensional diagnoses and sex distribution are presented in table 1.

SB

SB was present as mild in $n = 8$ (26.67%), moderate in $n = 1$ (3.33%), and severe in $n = 1$ (3.33%) participants. SB was absent in $n = 20$ cases (66.67%). OPB of mothers with predominantly manic polarity presented a tendency toward higher SB ($\chi^2 = 3.28$, $df = 1$, $p = 0.07$).

Parent polarity

We found a correlation tendency between more diagnosis when depressive polarity $r = 0.22$ ($p = 0.07$) and a significant correlation when manic polarity $r = 0.35$ ($p = 0.05$) were presented. There were no significant correlations between BD predominant polarity in parents and any of the categorical or dimensional diagnoses.

Clinical severity and global functioning

The CGI had a mean of 2.4 ($SD = 1.04$; range 1-5), while the GAF had a mean of 77.3 ($SD = 11.42$; range 60-90).

The GAF in the OPB did not differ by sex ($Z = 100$, $p = 0.62$) or by the affected parent polarity ($Z = 144$, $p = 0.16$). However, a significant negative correlation was found between the number of categorical diagnoses and the global functioning ($r = -0.52$, 95% confidence interval = $-0.75-0.21$, $df = 28$, $p = 0.003$).

Table 1. Diagnoses and sex distribution

Diagnosis	Dimension	Males n (%)	Females n (%)	Total n (%)
ADHD	NDD	10 (62.5)	9 (64.29)	19 (63.33)
ASD	NDD	1 (6.25)	0 (0.00)	1 (3.33)
SLD	NDD	1 (6.25)	0 (0.00)	1 (3.33)
IED	ID	4 (25.00)	1 (7.14)	5 (16.66)
ODD	ID	3 (18.75)	1 (7.14)	4 (13.33)
NSSI	ID	0 (0.00)	3 (21.43)	3 (10.00)
GAD	ED	4 (25.09)	10 (71.43)	14 (46.66)
SAD	ED	0 (0.00)	2 (14.29)	2 (6.66)
SP	ED	0 (0.00)	2 (14.29)	2 (6.66)
SepAD	ED	2 (12.50)	2 (14.29)	4 (13.33)
PTSD	ED	0 (0.00)	1 (7.14)	1 (3.33)
MDD	ED	1 (6.25)	7 (50.00)	8 (26.66)
ED	ED	0 (0.00)	1 (7.14)	1 (3.33)
RLS	ID	0 (0.00)	1 (7.14)	1 (3.33)
LPE	ID	4 (25.00)	1 (7.14)	5 (16.66)

ID: impulse disorder; ED: emotional disorder; NDD: neurodevelopmental disorder; ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder, SLD: specific learning disorder; IED: intermittent explosive disorder; ODD: oppositional defiant disorder; NSSI: non-suicidal self-injury; GAD: generalized anxiety disorder; SAD: social anxiety disorder; SP: specific phobia; SepAD: separation anxiety disorder; PTSD: post-traumatic stress disorder; MDD: major depressive disorder; ED: eating disorder; RLS: restless legs syndrome; LPE: limited prosocial emotions.

Discussion

This preliminary report evaluated the psychopathology of OPB from both categorical and dimensional perspectives, as well as its association with the sex and polarity of the affected parent. We found a significant correlation between the number of categorical diagnoses and worse global functioning; SB also tended to be associated with a predominant manic polarity in affected mothers.

Consistent with previous studies²², our findings showed a high prevalence of psychopathology among OPB, with only two participants not meeting the criteria for at least one diagnosis. Notably, ADHD and anxiety disorders were the most common diagnoses. It is essential to highlight that the comorbidity of more than one diagnosis was prevalent among the majority of OPB. This occurrence is common when relying on categorical classifications, which may not reflect the complex interplay of symptoms seen in real-life settings. In response, alternative models like the hierarchical

taxonomy of psychopathology (HiTOP) have been proposed to address these limitations. In addition to HiTOP's spectra of ID and ED, we included a dimension of NDD^{23,24}, considering the sample size and classifying ADHD as an NDD, diverging from its previous categorization under ED.

Despite our efforts to enhance statistical power by grouping diagnoses into dimensions, no associations were found between these and the polarity or sex of the affected parent, possibly due to the low participation rate, as only half of the invited dyads completed the evaluation. This finding is intriguing, considering that 93% of OPB fell into one dimension of psychopathology, yet none were initially seeking mental health assistance. Similar research has shown that a significant proportion of individuals with a disorder (72%) do not seek medical care²⁵, suggesting that parents with BD might fail to recognize their offspring's symptoms²⁶.

In addition, previous research has described that nearly one-third of individuals with BD have a lifetime history of SB²⁷, and that parental SB significantly increases the risk of SB in their offspring. Specifically, maternal depressive predominance polarity in conjunction with SB may be a more potent risk factor than paternal factors²⁷, with children being more vulnerable than adolescents²⁸. In contrast, our analysis indicated a trend toward higher SB in the offspring of mothers with a *manic* predominance polarity. This finding may reflect a wider mental health care gap among Mexican parents with BD²⁹, which may explain the higher SB risk in OPB compared to those with parents with a predominant depressive polarity.

No significant association was found between the sex or polarity of the affected parent and global functioning. This may have been due to the nature of the GAF as an evaluation tool, given its subjective clinical nature rather than relying on self or parent reports. However, a significant negative relationship was observed between more categorical diagnoses and lower global functioning, suggesting the presence of psychopathological burden, which goes in line with previous research in pediatric populations³⁰.

Limitations

The primary limitation of this study was the small sample size and the fact that the BPRS-CA-29 is a semi-structured interview, which may affect the external validity of the study. Therefore, we suggest interpreting our findings with caution, considering them

preliminary results that warrant further investigation in subsequent studies.

Conclusion

OPB constitutes a vulnerable pediatric population with a risk of psychopathology and burden. We found that more categorical diagnoses are associated with worse global functioning. In addition, OPB of mothers with BD and manic predominance polarity tended to report SB. This highlights the need for early diagnosis and treatment in these children and adolescents.

Authors contributions

Conceptualization, project administration and supervision: F.R. de-la-Peña. Data curation, investigation, methodology: H.A. Taboada-Liceaga and M.A. Valderrama-Yapor. Writing – original draft, writing – review and editing: M.F. Rosetti, A.D. Saad- Manzanera, J. Jiménez-Pavón, S. Totxo-Guerrero, L. Santana-Arellano, A. Bazua-Gerez, and J.C. Medina-Rodríguez.

Funding

This research has not received any specific grant from agencies in the public, commercial, or for-profit sectors.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare to have followed the ethical standards of the relevant experimentation committee, according to the World Medical Association and the Declaration of Helsinki. The procedures were approved 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. 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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Child temporal processing assessment task: construction and content validity through expert judgment

Tarea de evaluación del procesamiento temporal infantil: construcción y validez de contenido por juicio de expertos

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Abstract

Background: Temporal processing is an essential skill for adaptation and organization in childhood. However, there are few validated tools that assess this ability in everyday contexts. **Objective:** This study examines the content validity of an instrument designed to assess temporal processing in childhood, based on everyday activities and a parent questionnaire. It evaluates four dimensions: temporal perception, temporal orientation, time management, and temporal autonomy. **Method:** Seven expert judges assessed the clarity, coherence, relevance, and sufficiency of each item and activity using Aiken's V coefficient. The final version of the instrument incorporated expert suggestions to enhance its conceptual precision and alignment with the evaluated constructs. **Results:** Statistical analysis revealed a high level of agreement among the judges (Aiken's V ranging from 0.85 to 1). All four dimensions demonstrated strong validity indicators, with time management and temporal autonomy standing out. **Conclusion:** The results validate the instrument as a reliable tool for assessing temporal skills in childhood, providing valuable insights for clinical neuropsychology and research.

Keywords: Time perception. Time management. Content validity. Temporal skills assessment.

Resumen

Antecedentes: El procesamiento temporal es una habilidad esencial para la adaptación y organización en la infancia. Sin embargo, existen pocas herramientas validadas que evalúen esta capacidad en contextos cotidianos. **Objetivo:** El estudio analiza la validez de contenido de un instrumento para evaluar el procesamiento temporal en la infancia, basado en actividades de la vida cotidiana y un cuestionario para padres. Evalúa cuatro dimensiones: percepción temporal, orientación temporal, gestión del tiempo y autonomía temporal. **Método:** Siete jueces expertos valoraron claridad, coherencia, relevancia y suficiencia de cada ítem y actividad utilizando el coeficiente V de Aiken. La versión final del instrumento incorporó las sugerencias de los expertos para mejorar la precisión conceptual y su alineación con los constructos evaluados. **Resultados:** El análisis estadístico reveló un alto nivel de acuerdo entre los jueces (V de Aiken entre 0.85 y 1). Las cuatro dimensiones mostraron indicadores sólidos de validez, destacándose gestión del tiempo y autonomía temporal. **Conclusión:** Los resultados validan el instrumento como una herramienta sólida para evaluar las habilidades temporales en la infancia, aportando información valiosa para la neuropsicología clínica e investigativa.

Palabras clave: Percepción del tiempo. Gestión del tiempo. Validez de contenido. Evaluación de habilidades temporales.

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Date of reception: 05-03-2025
Date of acceptance: 10-06-2025
DOI: 10.24875/ANC.25000016

Available online: 10-09-2025
Arch Neurocién (Eng). 2026;31(1):7-15
www.archivosdeneurociencias.mx

Introduction

In an increasingly fast-paced world, effective time management has become an essential skill, as greater abilities are required to coordinate and prioritize various activities throughout the day. The importance of measuring time management lies in the ubiquity of this process, given that all individuals experience the passage of time subjectively¹.

The ability to process time is crucial for adequate psychosocial adaptation², as difficulties in time perception can affect various aspects of daily activities³.

Temporal perception and time management involve complex cognitive and executive functions, supported by different brain regions. The primary areas involved include the basal ganglia, particularly the putamen, which acts as a mediator in counting and working memory; the cerebellum, which is related to the timing of short intervals and motor learning tasks; the prefrontal cortex, implicated in attentional processes and the updating of temporal predictions; and the parietal cortex, associated with attentional functions and duration comparison^{4,5}.

In daily life, time management is reflected in the ability to follow routines, adhere to schedules, and effectively distribute time among academic, household, and leisure activities⁶. Present studies indicate that time management has a moderate influence on work and academic performance and an even greater impact on well-being, challenging the common perception that its primary benefit is increased productivity⁶. Consequently, effective time management has been associated with emotional well-being, yielding benefits such as improved concentration, reduced stress, more effective decision-making, timely task completion, greater enjoyment of leisure time, and lower anxiety regarding deadlines^{6,7}.

Time processing consists of three key dimensions: temporal perception, temporal orientation, and time management⁸, described below:

Temporal perception is the ability to experience and estimate the duration and passage of time, fundamental to the construction of reality^{5,9}. Its assessment involves verbal estimation of time and its discrimination in different contexts.

Temporal orientation is the ability to understand and situate oneself in time, recognizing the sequence of past, present, and future events⁸. This is reflected in the capacity to follow schedules and calendars, remember important dates, and plan future activities based on available time.

Time management is the decision-making process involved in structuring, protecting, and adapting time according to changing conditions¹⁰. It is closely related to organizational and planning skills¹¹. Time management refers to the ability to handle, plan, organize, and execute activities based on available time. It involves efficiently managing time and prioritizing tasks according to their importance and urgency⁸.

Despite its relevance, the assessment of temporal processing faces limitations due to the lack of instruments that ecologically and accurately measure this ability in real-life situations.

The Child Temporal Processing Assessment Task, hereinafter referred to as PROTEMPO, has been designed to evaluate time processing and organization in children within the context of daily life. Its objective is to provide a comprehensive evaluation of children's temporal functioning by analyzing their ability to perceive, understand, and manage time, identifying potential difficulties that may affect their daily performance.

In addition to measuring perception, orientation, and time management, PROTEMPO also incorporates a fourth dimension: Temporal autonomy. This aspect is fundamental to personal development and is defined as the ability to organize and manage time independently and responsibly, without external assistance or intervention¹². This learning process begins in early infancy and consolidates throughout different developmental stages, encompassing personal care, household tasks, and responsibility-taking¹³. Autonomy is essential for individual freedom and holistic development. Moreover, it significantly impacts children's daily lives, influencing their academic performance, participation in activities, and ability to achieve long-term goals¹⁴.

However, most existing tests for assessing time processing focus on tasks detached from daily activities or lack validation for their application, limiting their usability in child assessment. Therefore, it is crucial to develop and validate tools that measure time management in real-world contexts.

The multidimensional approach of the PROTEMPO Task enables a comprehensive evaluation of temporal functioning in daily life, addressing the objective perception of time, orientation concerning the temporal sequence of events, and children's ability to manage their time effectively.

This study aims to validate the content of PROTEMPO for Spanish-speaking countries through expert feedback, ensuring that its dimensions adequately reflect the temporal skills to be assessed. This analysis will not only guarantee the relevance and adequacy of the

included activities and items but also provide a robust and reliable tool for evaluating temporal processing in the child population.

Methods

The present study followed the guidelines established by the COSMIN (Consensus-based Standards for the Selection of Health Measurement Instruments) for the evaluation and reporting of studies on measurement properties¹⁵. In particular, the recommended criteria for content validation were applied. Type of study.

This study is descriptive and psychometric in nature, involving a content validation analysis through expert judgment.

Participants

The population consisted of expert judges intentionally selected based on their experience in neuropsychological assessment, cognitive functions, statistics, and the development of psychological evaluation instruments. Potential participants meeting these criteria were identified through colleague recommendations and a review of relevant scientific publications. The intentional sample included seven professionals who voluntarily agreed to participate, five of whom were women and two men. All participants work as university-level professors and researchers. One of the judges held a specialist degree; two had master's degrees, and four held doctoral degrees. All judges were native Spanish speakers from diverse countries: five from Argentina, one from Colombia, and one from Spain.

Instrument

The PROTEMPO task was developed to assess temporal processing in children aged 8-12 years, covering four dimensions: perception, orientation, management, and autonomy.

The instrument is administered individually, with an estimated duration of 20 min. A trained neuropsychology evaluator conducts the test in a controlled environment.

The instrument was developed in Spanish. It is presented in a digital questionnaire format, completed by the evaluator, with the support of printed material to be used by the assessed child. The assessment is conducted individually and consists of seven activities performed by the children and a questionnaire for parents, detailed below:

Tasks for children

TEMPORAL PERCEPTION DIMENSION

Activity 1. Estimation of objective duration

Description: participants are presented with auditory and visual stimuli and are asked to estimate their duration by selecting from pre-defined options. The stimuli were selected from public databases, prioritizing those that were culturally neutral and easily understandable for children aged 8-12 years. Scoring: incorrect answer (0 points); closest approximate answer (1 point); correct answer (2 points).

Activity 2. Duration comparison

Description: pairs of sounds with different durations are presented, and participants are asked to indicate which one they perceive as longer. Scoring: incorrect answer (0 points); correct answer (1 point).

Activity 3. Estimation of task duration

Participants estimate the time required to complete the task of writing their first and last name by choosing from pre-defined options. The actual time taken to complete the task is recorded and compared with their initial estimation. Scoring: incorrect answer (0 points); closest approximate answer (1 point); correct answer (2 points).

TEMPORAL ORIENTATION DIMENSION

Activity 4. Identification of the clock and calendar

Description: participants answer questions related to time concepts, including identifying clock times, daily schedules, dates, days of the week, months of the year, calculating time intervals, and detecting errors. Initially, they respond without consulting a calendar; afterward, they are allowed to use a calendar to locate and verify the days. Scoring: each incorrect answer (0 points); each correct answer (1 point).

Activity 5. Temporal sequencing of events

Description: two sets of shuffled images are presented, each depicting a sequence of activities (one related to a child's morning routine and the other to daily meals). Participants must arrange the images in the correct order and identify any errors. Scoring for sequence order: incorrect response (0 points); correct response (1 point). Scoring for recognition of extra

image: incorrect response (0 points); correct response (1 point).

TIME MANAGEMENT DIMENSION

Activity 6. Time management and decision-making

Description: in this activity, the participant takes on the role of an assistant in organizing a school camp. The objective is to complete three tasks within a maximum time of 3 min. A visible stopwatch and the necessary materials will be provided. The participant will receive an explanation of the three tasks and will be allowed to decide in which order to complete them, always considering the time constraint.

The three tasks the participant must complete are as follows:

- *Tent organization*: this task is presented in a digital format with a list of ‘classmates’ names and three teachers. The participant must assign them to the available tents based on a specific criterion. The available tents include two tents for three people, one tent for four people, and one tent for five people, as well as a designated tent for the teachers. The participant’s task is to correctly allocate each person to the appropriate tent following a pre-determined rule: on the screen, four tents will be labeled with letters corresponding to the initials of the ‘classmates’ names. In addition, there will be a tent specifically for the teachers. The participant must match each name to the corresponding initial and ensure that each person is placed in the correct tent.
- *Camping activity list*: in this task, the participant is required to create a list of five activities to be carried out during the camp days while adhering to specific requirements.
- *Search for essential items*: the participant is given a printed image containing various hidden objects. Their task is to identify and mark five essential items to bring to the camp. The evaluator will record their responses.

At a certain point during the activity, the participant will be presented with an unexpected challenge that they must attempt to resolve within the same time frame.

Scoring: The evaluation of this activity is based on two criteria: accuracy and efficiency. For accuracy, points are awarded according to the correct execution of each of the three tasks: not completed (0 points); completed with errors or partially (1 point); completed correctly (2 points).

For efficiency: did not remain engaged in the task (0 points); did not complete all tasks but continued trying for the full 3 min (1 point); completed all tasks within the 3-min time limit (2 points).

Finally, the response to the unexpected event is evaluated: did not respond correctly or became blocked, failing to manage time effectively (0 points); responded partially and/or with delay, but ultimately succeeded (1 point); responded correctly and promptly, managed time well, and continued with the activity (2 points).

Time distribution in task management is not scored, but it is recorded whether the participant distributed time evenly across tasks or focused excessively on one to the detriment of the others.

TEMPORAL AUTONOMY DIMENSION

Activity 7. Autonomy questionnaire

Description: a Likert scale questionnaire with nine statements related to autonomy in time management is presented. The participant selects the option that best reflects their daily behavior.

The statements refer to temporal autonomy in: personal care activities (e.g., sleep and hygiene), organization of school and extracurricular belongings, household chores and study time management, decision-making regarding leisure time, and response options: always, sometimes, never. The choice of a three-point Likert scale is based on the characteristics of the target population (children aged 8-12), who may find it easier to choose among three response options.

Scoring: does not perform the item independently (0 points); performs the item independently on some occasions but requires assistance (1 point); performs the item fully independently (2 points).

Parent or guardian questionnaire

It consists of 15 items, distributed across the same four previously mentioned dimensions: temporal perception (three items), temporal orientation (four items), time management (three items), and temporal autonomy (five items). It is administered online and must be completed by the child’s parents or guardians. The questionnaire uses a three-point Likert scale with the response options: always, sometimes, never.

Scoring: each item is scored based on the response option selected – always (2 points), sometimes (1 point), and never (0 points). Items that assess difficulties are reverse-scored: always (0 points), sometimes (1 point), and never (2 points). This allows for the calculation of

a score for each dimension as well as an overall score that reflects the child's level of temporal skills, according to the parent's or guardian's perception.

Overall scoring

The maximum score for the child's activities is 73 points, distributed across the four evaluated dimensions. The maximum score for the parent questionnaire is 30 points. A higher score indicates greater ability in the assessed areas, while a lower score may highlight domains in which the child could benefit from support or intervention. The scores obtained from both the child's activities and the parent questionnaire allow for the identification of strengths and difficulties in temporal processing, facilitating the design of personalized strategies to enhance time organization and temporal autonomy in the child.

Procedure

The instrument design was carried out in several stages, following the COSMIN recommendations to ensure its methodological quality. The adopted methodology comprised three phases: (1) the design and development of the task, (2) content validation through expert judgment and statistical analysis, and (3) the implementation of a pilot test.

FIRST PHASE: DESIGN AND DEVELOPMENT

The design process began with a literature review to theoretically define the construct. This search facilitated the establishment of operational definitions of temporal processing. Subsequently, an analysis was conducted on previous instruments used to assess this construct both in the general population and in individuals with pathologies. For the task design, several reference instruments were considered, including the instrument for assessing children's time concept by León¹⁶, the Time Concept Questionnaire¹⁷, the KaTid and KaTid-Youth¹⁸, which assess time processing ability in children and adolescents, and the study by Narbona et al.² on temporal processing in attention-deficit/hyperactivity disorder (ADHD). Based on the review of these instruments, some conceptual and methodological references were incorporated into the task design. However, original tasks and adaptations were also developed to better align with the specific objectives of the study.

Based on this analysis, activities were designed to reflect the operational definitions of temporal

processing. The selected activities were those that exhaustively represented each dimension of temporal processing without ambiguity (i.e., items referred exclusively to one dimension and not to the others). Finally, after a revision process, the task was structured into seven activities.

SECOND PHASE: CONTENT VALIDATION BY EXPERT JUDGMENT AND STATISTICAL ANALYSIS

To validate the instrument's content, an expert judgment evaluation was conducted. Seven specialists were selected based on their experience with the target population and their expertise in the construction, adaptation, and validation of psychological and educational assessment instruments.

The judges were contacted through email, where they were sent an invitation to participate along with an evaluation guide detailing: the objective of the instrument, the theoretical construct of the dimensions to be assessed, a description of the categories and evaluation indicators, and an evaluation template for the PROTEMPO task. The judges evaluated the written version of the test, without observing its actual administration. The judges were requested to return their assessments within 15 days.

The evaluation was conducted using the individual aggregation technique, in which each judge's response is collected independently, without communication between them¹⁹.

The instrument was designed to be flexible and applicable to a wide range of contexts, taking into account cultural, social, and economic differences. The activities were based on everyday routines common across Spanish-speaking countries, such as waking up, getting ready for school, personal hygiene, and daily meals. To ensure its relevance across diverse populations, judges from different backgrounds were selected to confirm that the activities were clear and meaningful regardless of cultural context.

Following the methodological approach of Escobar-Pérez and Cuervo-Martínez²⁰, four criteria were analyzed: clarity, coherence, relevance, and sufficiency, with values assigned on a scale from 1 to 4 to indicate the level of compliance (1: does not comply, 2: low compliance, 3: moderate compliance, 4: high compliance).

In addition, a section for qualitative observations was included.

Based on the judges' feedback, several adjustments were made to improve the clarity and precision of the instrument. The wording of the instructions for Activity

3 was refined, modifications were made to the items in activity 4, and the instructions for activity 6 were revised, including replacing certain words, reorganizing sentence structure, clarifying directives, and removing redundant terms. In addition, in activity 6, a record of the order in which the child completes the tasks was incorporated, as this aspect had not been originally considered. The image used in activity 6 was also modified to enhance the clarity of two elements that could potentially lead to confusion. Furthermore, following the judges' recommendation, a parent questionnaire was added to provide a complementary perspective on children's understanding of time and their ability to organize it.

After these modifications, the revised questionnaire was resent to the judges for reassessment, focusing primarily on the incorporation of the parent questionnaire. The responses received were used for content validity analysis, and no further modifications were made to the original seven activities.

The judges provided minor suggestions regarding the parent questionnaire, which were implemented, including the addition of examples in three items, and clarifications in two items.

Subsequently, a statistical analysis was conducted to evaluate the level of agreement among the judges, using Aiken's V test^{21,22}. This coefficient ranges from 0 (no agreement) to 1 (perfect agreement), with values equal to or > 0.70 considered acceptable²³.

Thus, the final version of the task comprised eight activities, seven for children and one questionnaire for parents or guardians.

THIRD PHASE: PILOT TESTING

A pilot test and comprehensibility evaluation were conducted following COSMIN recommendations to assess the instrument's performance and ensure the clarity and relevance of its items in the target population. A sample of 25 primary school children, with characteristics similar to those of the intended users, participated in the study.

The pilot study sample was selected through convenience sampling at a school with an intermediate socioeconomic level in the city of Mar del Plata, Argentina. Invitations were sent to the parents of children aged 8-12 years, and those who agreed to participate were included in the study, after obtaining informed consent from the parents and assent from the children.

During the evaluation, children completed the task under standard conditions while their response times were recorded to assess cognitive load and feasibility.

Any challenges in executing the activities were documented. After completing the task, participants answered structured questions to evaluate their understanding of the instructions, items, and response options.

Some difficulties were identified, mainly related to prior knowledge and time constraints, such as insufficient time to complete activity 6. However, none of the participants reported difficulties in understanding the instructions, confirming the clarity of the task.

Since the instructions and response options were well understood, no further modifications were necessary.

Results

The results for each activity and each item in the parent questionnaire were subjected to statistical analysis using Aiken's V coefficient, with a 95% confidence interval. [Table 1](#) presents the values corresponding to clarity, relevance, and coherence for all activities and questionnaire items.

Regarding the children's activities, the results indicate a high level of agreement among the judges. In the category of clarity, 57.14% of the activities (four out of seven) obtained an Aiken's V of 1, while 28.57% (two activities) reached a value of 0.95, and 14.29% (one activity) obtained 0.90. In terms of coherence, 28.57% (two activities) achieved an Aiken's V of 1, 42.86% (three activities) obtained 0.95, and the remaining 28.57% (two activities) reached a value of 0.90. Finally, for the category of relevance, 85.71% (six activities) attained an Aiken's V of 1, while the remaining 14.29% (one activity) obtained a value of 0.95.

The parent questionnaire also demonstrated a high level of consensus among the judges across all evaluated categories. For clarity, 53.33% (eight items) obtained an Aiken's V of 1, while 26.67% (four items) reached 0.95, 6.67% (one item) obtained 0.90, and 13.33% (two items) achieved 0.85. In terms of coherence, 86.67% (thirteen items) obtained an Aiken's V of 1, 6.67% (one item) reached 0.95, and another 6.67% (one item) attained 0.90. Regarding relevance, 73.33% (eleven items) obtained an Aiken's V of 1, while 20.00% (three items) reached 0.95, and 6.67% (one item) obtained 0.90.

As illustrated in [figure 1](#), Aiken's V coefficients for clarity, coherence, and relevance show consistently high agreement among the judges for children's activities. The visual distribution confirms the predominance of values equal to or greater than 0.90, reinforcing the quantitative summary presented in [table 1](#).

Table 1. Aiken’s V for clarity, coherence and relevance with a 95% confidence interval for each activity

Activity	Clarity			Coherence			Relevance		
	M	SD	V	M	SD	V	M	SD	V
ACT 1	4.00	0.00	1.00	3.71	0.49	0.90	3.86	0.38	0.95
ACT 2	4.00	0.00	1.00	4.00	0.00	1.00	4.00	0.00	1.00
ACT 3	3.86	0.38	0.95	3.86	0.38	0.95	4.00	0.00	1.00
ACT 4	3.86	0.38	0.95	3.86	0.38	0.95	4.00	0.00	1.00
ACT 5	4.00	0.00	1.00	3.86	0.38	0.95	4.00	0.00	1.00
ACT 6	3.57	0.53	0.90	3.71	0.49	0.90	4.00	0.00	1.00
ACT 7	4.00	0.00	1.00	4.00	0.00	1.00	4.00	0.00	1.00
P.Q. item 1	3.57	0.53	0.85	3.86	0.38	0.95	4.00	0.00	1.00
P.Q. item 2	3.57	0.53	0.85	4.00	0.00	1.00	4.00	0.00	1.00
P.Q. item 3	3.86	0.38	0.95	4.00	0.00	1.00	4.00	0.00	1.00
P.Q. item 4	4.00	0.00	1.00	4.00	0.00	1.00	4.00	0.00	1.00
P.Q. item 5	3.71	0.76	0.90	3.71	0.76	0.90	3.71	0.76	0.90
P.Q. item 6	4.00	0.00	1.00	4.00	0.00	1.00	4.00	0.00	1.00
P.Q. item 7	3.86	0.38	0.95	4.00	0.00	1.00	3.86	0.38	0.95
P.Q. item 8	3.86	0.38	0.95	4.00	0.00	1.00	4.00	0.00	1.00
P.Q. item 9	4.00	0.00	1.00	4.00	0.00	1.00	4.00	0.00	1.00
P.Q. item 10	3.86	0.38	0.95	4.00	0.00	1.00	4.00	0.00	1.00
P.Q. item 11	4.00	0.00	1.00	4.00	0.00	1.00	4.00	0.00	1.00
P.Q. item 12	4.00	0.00	1.00	4.00	0.00	1.00	4.00	0.00	1.00
P.Q. item 13	4.00	0.00	1.00	4.00	0.00	1.00	3.86	0.38	0.95
P.Q. item 14	4.00	0.00	1.00	4.00	0.00	1.00	3.86	0.38	0.95
P.Q. item 15	4.00	0.000	1.00	4.00	0.000	1.00	4.00	0.000	1.00

M: mean; SD: standard deviation.; V: Aiken’s V.; ACT: activity.; P.Q.: parent/guardian questionnaire.

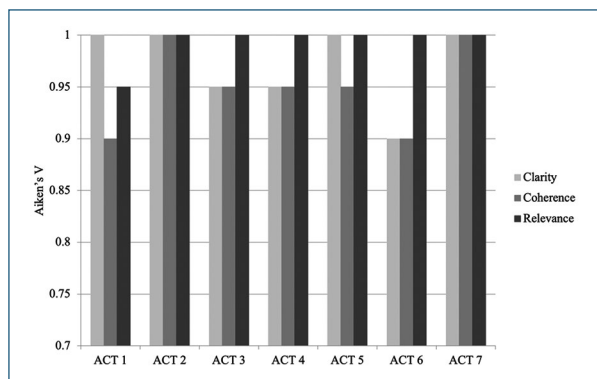


Figure 1. Aiken’s V coefficients for clarity, coherence, and relevance across children’s activities.

For the category of sufficiency (Table 2), the results reflect a high degree of agreement among the judges in both sections of the instrument.

In the children’s activities, the temporal Orientation dimension achieved an Aiken’s V of 1, whereas the temporal perception, time management, and temporal autonomy dimensions obtained a value of 0.95. Similarly, in the parent questionnaire, three dimensions – temporal perception, time management, and temporal autonomy – achieved an Aiken’s V of 1, while the temporal orientation dimension obtained a value of 0.95.

These findings confirm a high level of content validity for PROTEMPO, supporting its adequacy in assessing

Table 2. Aiken's V for the sufficiency category based on the task and questionnaire dimensions

Dimensions	M	SD	V
Child activities			
Temporal perception	3.86	0.38	0.95
Temporal orientation	4.00	0.00	1.00
Time management	3.86	0.38	0.95
Temporal autonomy	3.86	0.38	0.95
Parent questionnaire			
Temporal perception	4.00	0.00	1.00
Temporal orientation	3.86	0.38	0.95
Time management	4.00	0.00	1.00
Temporal autonomy	4.00	0.00	1.00

M: mean.; SD: standard deviation.; V: Aiken's V.

temporal processing skills in children. The strong agreement among judges suggests that both the children's activities and the parent questionnaire effectively capture the dimensions they aim to evaluate, ensuring clarity, coherence, relevance, and sufficiency in their formulation.

Discussion

The analysis of the obtained results demonstrates a high level of agreement among expert judges regarding the clarity, coherence, relevance, and sufficiency of the activities designed for children and the parent questionnaire. The clarity of the items and activities ensures that they are comprehensible for participants, coherence confirms their logical alignment with the evaluated dimensions, relevance indicates that the included elements are essential for assessing the proposed constructs, and sufficiency supports that the number of activities and items is adequate for measuring each dimension.

This high level of judge consensus strengthens the content validity of the instrument, suggesting that both the activities and the parent questionnaire are robust and reliable tools for evaluating temporal aspects in childhood. Content validity is a fundamental criterion in the construction of assessment instruments, as it ensures that they truly measure what they intend to assess, thereby reducing biases and increasing the accuracy of the obtained results.

The findings of this study reinforce the importance of temporal processing as a key skill for psychosocial adaptation and organization in daily life². From an applied perspective, implementing these tools could provide essential information about the development of

time perception and management in children, as well as about parents' knowledge and perspectives on these skills. Previous studies have shown that effective time management not only influences the organization of daily activities but is also closely linked to emotional well-being, stress reduction, and improved decision-making^{6,7}. Therefore, having appropriate assessment tools will make it possible to identify areas for improvement or reinforcement in early education and stimulation, facilitating the development of intervention strategies that promote temporal autonomy and organization in childhood.

Despite the positive results in terms of content validity, this study presents some limitations that should be considered. First, the analysis focused on content validity through expert judgment, which, while providing valuable information on the clarity, coherence, relevance, and sufficiency of the items, does not allow for the evaluation of other essential aspects of the instrument's validity. In this regard, additional studies addressing criterion and construct validity through the application of the questionnaire in larger and more representative samples would be recommended.

Furthermore, although the instrument was designed for use in various Spanish-speaking contexts, cultural factors could influence the interpretation of the items and the way participants respond to them. This highlights the need for cross-cultural studies to confirm its applicability and suitability across different countries and sociocultural settings.

Considering these limitations, future research lines could focus on evaluating the applicability and effectiveness of the instrument in different educational and clinical settings, as well as its adaptation for other key figures involved in child development, such as teachers or healthcare professionals. In addition, it would be relevant to analyze how interventions based on the obtained results can impact the improvement of time perception and management in children, enhancing their performance in both daily and academic activities. Such studies would contribute not only to strengthening the validity of the questionnaire but also to developing evidence-based strategies to optimize the development of temporal skills in childhood.

Conclusion

The findings of this study support the use of these tools for assessing and understanding temporal perception in childhood, providing a foundation for

future research and applications in educational and clinical settings.

Funding

This research has not received any specific grant from public sector agencies, commercial, or non-profit organizations.

Conflicts of interest

The author declares no conflicts of interest.

Ethical considerations

Protection of humans and animals. The author declares that no experiments involving humans or animals were conducted 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. The author declares that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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Predictors of functional outcome at discharge in anterior large vessel occlusion stroke

Predictores del desenlace funcional al alta en infarto cerebral anterior por oclusión de gran vaso

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Abstract

Background: Several patients with anterior large vessel ischemic stroke do not achieve functional independence despite reperfusion therapy. **Objective:** To determine the clinical course, neuroimaging biomarkers, and functional outcome at hospital discharge. **Methods:** Observational retrospective study including seventy-five patients with anterior large vessel stroke admitted to the Fundación Instituto Neurológico de Colombia (2015-2018). Functional outcome at discharge was categorized as favorable (modified Rankin scale [mRS] 0-2) or unfavorable (mRS 3-6). **Results:** At hospital discharge, 32% of patients achieved a favorable outcome. In multivariate analysis, older age (adjusted odds ratio [aOR] 1.06; 95% confidence interval [CI] 1.01-1.11; $p = 0.01$) and higher baseline National Institutes of Health Stroke Scale (NIHSS) (aOR 1.24; 95% CI 1.07-1.44; $p = 0.004$) were independently associated with adverse outcomes. In contrast, intravenous thrombolysis (aOR 4.2; CI 95% 0.96-18.9; $p = 0.05$) was associated with a lower risk of poor outcome. **Conclusions:** Advanced age and greater clinical (NIHSS) severity at admission predict unfavorable functional outcome, while thrombolytic therapy showed a protective effect in patients with anterior large vessel stroke.

Keywords: Core. Imaging biomarker. Large vessel. Magnetic resonance imaging. Reperfusion.

Resumen

Antecedentes: A pesar de las terapias de reperusión en el ataque cerebrovascular de gran vaso anterior, muchos pacientes no alcanzan la independencia funcional. **Objetivo:** Determinar la evolución clínica, los biomarcadores de neuroimagen y el desenlace funcional al alta hospitalaria. **Método:** Estudio observacional y retrospectivo que incluyó 75 pacientes con compromiso de gran vaso anterior, admitidos en la Fundación Instituto Neurológico de Colombia (2015-2018). El desenlace al alta se clasificó como favorable (modified Rankin Scale [mRS] 0-2) o desfavorable (mRS 3-6). **Resultados:** El 32% de los pacientes presentó un desenlace favorable. En el análisis multivariado, la edad avanzada (aOR: 1.06; IC 95%: 1.01-1.11; $p = 0.01$) y un puntaje NIHSS (National Institutes of Health Stroke Scale) basal más alto (aOR: 1.24; IC 95%: 1.07-1.44; $p = 0.004$) se asociaron de manera independiente con desenlaces desfavorables. En contraste, la trombólisis venosa

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Date of reception: 10-02-2025

Date of acceptance: 18-12-2025

DOI: 10.24875/ANC.25000011

Available online: 29-04-2026

Arch Neurocién (Eng). 2026;31(1):16-22

www.archivosdeneurociencias.mx

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(aOR: 0.15; IC 95%: 0.02-0.93; $p = 0.04$) se asoció con una menor probabilidad de desenlaces desfavorables. **Conclusiones:** La edad avanzada y una mayor gravedad clínica (NIHSS) al ingreso se asociaron con un desenlace funcional desfavorable. El tratamiento trombolítico mostró un efecto protector en pacientes con compromiso de gran vaso en la circulación anterior o carotídea.

Palabras clave: Núcleo. Biomarcador de imagen. Gran vaso. Resonancia magnética. Reperusión.

Introduction

Acute ischemic stroke is the second leading cause of mortality and the leading cause of disability worldwide¹. The most significant burden of stroke is observed in low- and middle-income countries¹. In Colombia, cerebrovascular disease is associated with high social and economic costs, as reported by the National Administrative Department of Statistics². In patients with acute anterior circulation stroke due to large vessel occlusion (AIS-LVO), intravenous thrombolysis (IVT) bridging to endovascular thrombectomy (EVT) has markedly improved recanalization rates – ranging from 26.8 to 56.3% with IVT^{3,4}, and from 71 to 83.6% with EVT⁴. However, despite successful recanalization of the occluded vessel, a significant proportion of patients -nearly half experience clinical deterioration and fail to achieve functional independence⁵⁻⁷.

Increasing attention has been directed toward understanding the complex pathophysiology of stroke and the dynamic changes that make each event unique to the individual patient. Identifying prognostic and predictive biomarkers that reflect the pathological features and predispose to poor recovery is crucial⁸. Personalized stroke care requires not only expert clinical assessment but also the integration of multimodal biomarkers – including blood-based measures and neuroimaging – which can provide valuable clues for predicting clinical outcomes. This approach allows all involved parties to be better informed about prognosis and plan long-term care accordingly⁸.

Objective

The objective of the study was to determine clinical characteristics, neuroimaging biomarkers (magnetic resonance imaging [MRI]), and functional outcomes at hospital discharge in patients with AIS-LVO.

Methods

Study design and population

This was a retrospective observational study based on a prospectively collected cohort. A total of 75 patients admitted to the Fundación Instituto Neurológico de Colombia between January 2015 and January 2018

with confirmed anterior circulation ischemic stroke due to large vessel occlusion (AIS-LVO) verified by magnetic resonance imaging were enrolled and retrospectively analyzed. This academic hospital manages an average of 300-400 ischemic stroke cases per year and was certified as an Advanced Stroke Center by the World Stroke Organization/Sociedad Iberoamericana de Enfermedades Cerebrovasculares (SIECV) in 2022.

Inclusion criteria were: (1) age ≥ 18 years, (2) pre-morbid modified Rankin scale (mRS) ≤ 2 , (3) known time of symptom onset, (4) activation of the emergency ischemic stroke code, and (5) diagnosis of anterior AIS-LVO confirmed by brain MRI, with or without gadolinium-enhanced perfusion imaging. Patients were excluded if blood samples were unavailable or if they presented with hemorrhagic infarction.

The study was approved by the Institutional Review Board (IRB) of the hospital (Study # 109; approval date: February 05, 2018; IRB # PE8INV5_PR0016). The requirement for informed consent was waived in accordance with the national legislation and institutional standards. The study adhered to the strengthening the reporting of observational studies in epidemiology checklist for study design and for reporting.

Data collection and measurements

Demographic and clinical variables – including age, sex, vascular risk factors, medication history, systolic and diastolic blood pressure, blood glucose, baseline stroke severity (assessed by the National Institutes of Health Stroke Scale [NIHSS]), and time from symptom onset to emergency department arrival- were recorded at admission. The decision to administer reperfusion therapy, either IVT with recombinant tissue plasminogen activator (tPA, 0.9 mg/kg; max. 90 mg), EVT, or both, was made on an individual basis according to AHA/ASA guidelines⁹. IVT was not administered to patients who presented outside the therapeutic time window or had documented medical contraindications. An experienced neurointerventional surgeon performed EVT, and patients were admitted to the neurocritical care unit for continued management. Successful recanalization was defined as a modified Thrombolysis in

Cerebral Ischemia (mTICI) score of 2b-3. In addition, the time from symptom onset to reperfusion therapy, NIHSS score at discharge, and in-hospital mortality were collected. Functional outcome at discharge was assessed using the mRS and classified as favorable (mRS 0-2) and unfavorable (mRS 3-6).

Baseline MRI was acquired on a Siemens Magnetom Symphony 1.5-T system (Siemens, Germany) using Gadovist as the contrast agent. Slice thickness ranged from 3 to 5 mm. The imaging protocol included diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), fluid-attenuated inversion recovery (FLAIR), susceptibility-weighted imaging (SWI), time-of-flight magnetic resonance angiography (TOF-MRA), and dynamic susceptibility contrast perfusion-weighted imaging (PWI). AIS-LVO was defined by the presence of diffusion restriction on DWI/ADC sequences. MRI data included stroke location, DWI-Alberta Stroke Program Early Score (DWI-ASPECTS), infarct core volume (calculated as $AxBxC/2$), and FLAIR hyperintensity (visually classified as absent, subtle, or bright). TOF-MRA was used to identify occlusion sites, including the supraclinoid or infraclinoid intracranial internal carotid artery (ICA), M1 or proximal M2 segments of the middle cerebral artery (MCA), anterior cerebral artery (ACA), and tandem occlusions (ICA and MCA M1). An experienced neuroradiologist estimated the ischemic core and penumbra without automated software. Perfusion data were analyzed using perfusion maps of cerebral blood volume, cerebral blood flow, mean transit time, and time to peak. The ischemic penumbra was defined as a DWI/PWI mismatch $> 20\%$.

Statistical analysis

Statistical analysis was performed using Jamovi software version 2.4.8. A $p < 0.05$ was considered statistically significant. Categorical variables were presented as frequencies and percentages, and comparisons were made using Fisher's exact test or the Chi-square test. The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed variables were expressed as a mean \pm standard deviation (SD) and compared using Student's *t*-test.

In contrast, non-normally distributed variables were expressed as median and interquartile range (IQR) and compared using the Mann-Whitney U test. Variables that were significantly different between groups were included in a binary logistic regression model. A stepwise forward multiple logistic regression analysis was performed to confirm the findings. Potential confounder

factors previously reported in the literature were also included in the model. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results

Patient characteristics

Seventy-five patients with anterior AIS-LVO met the inclusion criteria and were included in the analysis. The mean age was 63 years (SD \pm 16.6; min 24, max 94), and 41.3% ($n = 31$) were female. The median premorbid mRS score was 0 (IQR 0-0). The most common cardiovascular risk factors were hypertension 54.7% ($n = 41$), smoking 28% ($n = 21$), and diabetes mellitus 18.7% ($n = 14$). Compared with patients in the mRS 3-6 group, those in the mRS 0-2 group had a lower proportion of vascular risk factors. In addition, 21.6% ($n = 16$) of the patients were taking antiplatelet agents, and one patient was on oral anticoagulation before stroke onset.

At admission, the mean NIHSS score was 14 (SD \pm 7; min 0, max 33), and the mean systolic blood pressure was 147 mmHg (SD \pm 24.7; min 86, max 240). The median diastolic blood pressure was 80 mmHg (IQR 74-90; min 44, max 142), and the median blood glucose was 109 mg/dL (IQR 100-103; min 54, max 227). On baseline MRI, the median MRI DWI-ASPECTS was 7 (IQR 4-8), and the median infarct core volume was 26.8 mm³ (IQR 7.4-76.7). FLAIR hyperintensity was absent in 44.6% ($n = 33$), subtle in 20.3% ($n = 15$), and bright in 32.4% ($n = 24$). The most common site of occlusion on TOF-MRA was the M1 segment of the MCA in 53.3% ($n = 40$), followed by the infraclinoid intracranial ICA in 20.0% ($n = 15$), and the M2 segment of the MCA in 17.3% ($n = 13$). Less frequent sites included the supraclinoid intracranial ICA ($n = 5$), the A1 segment of the ACA ($n = 1$), and tandem occlusion ($n = 1$). PWI-MRI was performed in 54 patients, of whom 72.2% ($n = 39$) demonstrated a DWI/PWI mismatch $> 20\%$. Regarding perfusion therapy, 29.3% ($n = 22$) received IVT with rtPA alone, 16% ($n = 12$) received IVT followed by EVT, and 18.7% ($n = 14$) underwent EVT alone (Table 1).

The median time from symptom onset to hospital arrival was 180 min (IQR 120-251; range of 30-720). The median time from arrival to IVT was 75 min (IQR 56-92), and the median time from arrival to recanalization was 115 min (IQR 78.5-135). No statistically significant differences were observed in these times using the Mann-Whitney U test ($p = 0.66$, $p = 0.077$, $p = 0.43$, respectively).

Table 1. Clinical assessment and magnetic resonance imaging biomarker characteristics

Characteristics	mRS 0-2 24 (32%)	mRS 3-6 51 (68%)	p
Age, years, mean (SD)	56.6 (± 14.2)	65.8 (± 17.2)	0.02 ^a
Sex, female, n (%)	7 (29.2)	24 (47.1)	0.14 ^b
Hypertension, n (%)	10 (41.7)	31 (60.8)	0.12 ^b
Hyperlipidemia, n (%)	3 (12.5)	10 (19.6)	0.53 ^c
Diabetes mellitus, n (%)	1 (4.2)	13 (25.5)	-
Coronary heart disease, n (%)	1 (4.2)	6 (11.8)	-
Atrial fibrillation, n (%)	1 (4.2)	9 (17.6)	-
History of stroke, n (%)	3 (12.5)	7 (13.7)	1.00 ^c
Baseline NIHSS score, mean (SD)	8 (± 5.24)	16 (± 6.26)	< 0.00 ^a
SBP (mm Hg), mean (SD)	140 (± 18.7)	148 (± 26.6)	0.15 ^a
DBP (mm Hg), median (IQR)	80 (75-85)	80 (73-90)	0.62 ^d
Blood glucose level (mg/dL), median (IQR)	104.0 (99-109)	120 (101-138)	0.05 ^d
Stroke etiology, n (%)			0.44 ^c
Atherosclerosis	5 (20.8)	18 (35.3)	
Cardioembolism	7 (29.2)	12 (23.5)	
Indeterminate	12 (50)	19 (37.3)	
Other causes	0	2 (3.9)	
IVT rtPA, median (IQR)	11 (45.8)	11 (21.6)	0.03 ^b
DWI-MRI ASPECTS, median (IQR)	7 (6-8)	7 (3-8)	0.07 ^d
Core size, mm ³ , median (IQR)	14.3 (2.8-37.1)	32.6 (12-97.2)	0.01 ^d
FLAIR-MRI, n (%)			0.55 ^c
Bright hyperintensity	9 (12.2)	16 (21.6)	
Subtle hyperintensity	3 (4.1)	12 (16.2)	
No hyperintensity	12 (16.2)	22 (29.7)	
Mismatch > 20%	13 (76.5)	26 (70.3)	0.75 ^c

^aStudent's *t*-test.^bChi-square test.^cFisher's exact test.^dMann-Whitney U test.

SD: standard deviation; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; SBP: systolic blood pressure; DBP: diastolic blood pressure; IQR: interquartile range; IVT: intravenous thrombolysis; rtPA: recombinant tissue-type plasminogen activator; MRI: magnetic resonance imaging; DWI: diffusion-weighted imaging; ASPECTS: the Alberta Stroke program early CT score; FLAIR: fluid-attenuated inversion recovery.

A total of 37.7% (n = 28) of patients underwent subtraction arteriography. The most frequent occlusion sites were the M1 segment of the MCA in 53.6% (n = 15), the supraclinoid intracranial ICA in 21.4% (n = 6), the infraclinoid intracranial ICA in 10.7% (n = 3), and the proximal M2 segment of the MCA in 10.7%

(n = 3), with no statistically significant differences observed between groups according to the Fisher's exact test (p = 0.69). Successful recanalization (mTICI 2b-3) was achieved in 68.8% (n = 22) of patients, with no significant difference between groups according to Fisher's test (p = 0.67). The most common TOAST etiologic subtype was undetermined cause 41.3% (n = 31), followed by extensive artery atherosclerosis 30.7% (n = 23). The median mRS score at hospital discharge was 4 (IQR 2-4), and the median NIHSS score was 8 (IQR 2-15). The in-hospital mortality rate was 16% (n = 12) (Fig. 1).

Predictors of unfavorable functional outcomes

Bivariate analysis showed that older age (OR 1.03; 95% CI 1.003-1.07; p = 0.03), higher baseline NIHSS score (OR 1.30; 95% CI 1.15-1.46; p < 0.001), elevated blood glucose (OR 1.02; 95% CI 1.001-1.05; p = 0.03), and larger infarct core volume (OR 1.02; 95% CI 1.003-1.03; p = 0.01) were significantly associated with unfavorable functional outcome. In contrast, IVT with rtPA (OR 0.30; 95% CI 0.10-0.87; p = 0.02) was independently associated with a lower risk of poor outcome. In the forward stepwise multivariate logistic regression model, older age and higher baseline NIHSS score remained independently associated with unfavorable functional outcome at discharge, while IVT with rtPA maintained a protective effect, with a model fit (Nagelkerke R²) of 55. A strong negative correlation was observed between DWI-ASPECTS and infarct core volume (Spearman's rho -0.90; p < 0.01) (Table 2).

Discussion

This study explored clinical characteristics, MRI biomarkers, and functional outcomes at hospital discharge in patients with AIS-LVO. The main finding was that age, baseline NIHSS score, and the administration of IVT with rtPA were independently associated with functional outcomes, as previously reported in the literature⁵⁻⁷.

Age has consistently been identified as a predictor of poor stroke recovery¹⁰. Older adults often present with greater frailty, pre-existing physical or cognitive impairment, and more advanced atherosclerotic changes, all of which can reduce the likelihood of successful recanalization¹¹. Furthermore, little is known about the age-related biomarkers that may influence prognosis, such as chronic inflammation or renal impairment¹⁰.

The baseline NIHSS score is a well-established predictor of stroke outcome¹². It reflects the severity of

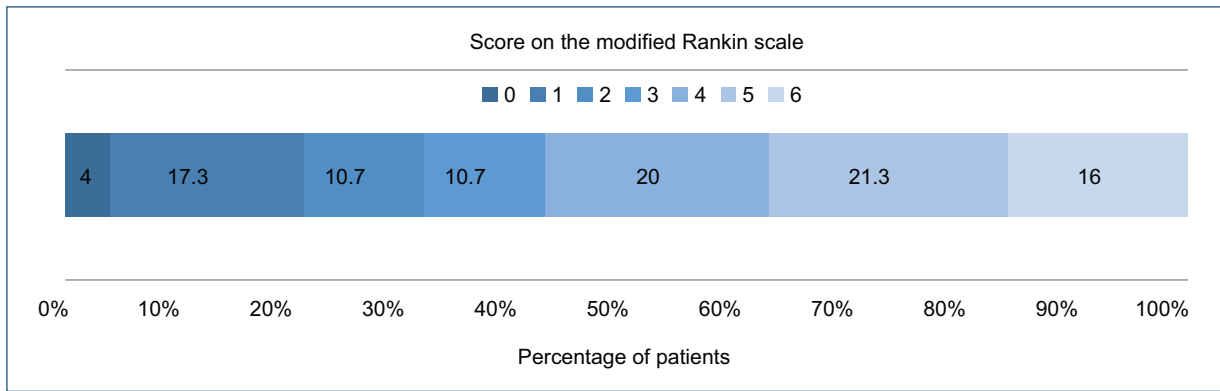


Figure 1. Distribution of modified Rankin scale scores at hospital discharge.

Table 2. Bivariate and multivariate analyses of predictors of functional outcomes at hospital discharge

Predictor	Bivariate			Multivariate		
	OR	CI 95%	p	aOR	CI 95%	p
Age	1.03	1.003-1.07	0.03	1.06	1.01-1.11	0.01
Baseline NIHSS	1.30	1.15-1.46	< 0.00	1.24	1.07-1.44	0.004
Baseline glucose	1.02	1.001-1.05	0.03	-	-	-
DWI core volume	1.02	1.003-1.03	0.01	-	-	-
IVT with rtPA	0.30	0.10-0.87	0.02	0.15	0.02-0.93	0.04

OR: odds ratio; CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale; IVT: intravenous thrombolysis; rtPA: recombinant tissue-type plasminogen activator. Only factors with $p < 0.05$ in the bivariate model were included.

neurological impairment and may correlate with imaging biomarkers. The relationship between NIHSS and neuroimaging findings may enhance precision in lesion-symptom mapping, allowing for segmentation of critical regions involved in functional stroke recovery¹³.

In this study, most patients with favorable functional outcomes received IVT with rtPA, reinforcing the evidence that early treatment with IVT increases the likelihood of successful reperfusion and favorable functional outcomes without increasing the risk of hemorrhagic transformation¹⁴. These findings support the current recommendation that, in the absence of contraindications, patients with LVO should receive bridging therapy with IVT and EVT when eligible^{7,15,16}.

In this study, high admission blood glucose levels and increased infarct core volume on DWI-MRI were also associated with unfavorable outcomes in bivariate analysis, consistent with previous reports^{17,18}. Experimental studies have shown that hyperglycemia with or without a prior history of diabetes may exacerbate ischemic injury, increase infarct volume, and raise the risk of

hemorrhagic complications¹⁹. Hyperglycemia has been associated with disruption of the blood-brain barrier, neurovascular injury, oxidative stress, lactic acidosis, proteolysis, and prothrombotic state²⁰. Despite these associations, multiple clinical trials have failed to demonstrate a significant benefit of normoglycemia in the acute stroke setting.

Ischemic core volume on MRI is one of the most relevant imaging biomarkers in AIS-LVO²¹. However, DWI-derived core estimation alone may not be a sufficient criterion to guide patient selection and treatment decisions. Evaluating early ischemic changes using MRI sequences might provide a more comprehensive assessment of lesion volume, perfusion parameters, and tissue viability^{22,23}. Therefore, it is possible that patients with good physical status and large infarct cores can still achieve favorable functional outcomes following reperfusion therapy and stroke care²⁴.

In clinical practice, patients are diverse, and stroke presentation and evolution may differ from patient to patient, reflecting the potential differences in the

number and convergence of clinical risk factors, blood-based biomarkers, and neuroimaging (MRI) biomarkers. These findings highlight the complexity and heterogeneity of stroke pathophysiology, etiological subtypes, therapy response, and functional outcomes.

Several novel biomarkers have emerged as potential predictors of stroke outcome. Imaging-based markers such as the hypoperfusion intensity ratio (HIR) and the DWI-FLAIR mismatch may provide insights into tissue viability and collateral circulation status²⁵⁻²⁷. Blood-based biomarkers, including platelet indices, the neutrophil-to-lymphocyte ratio, and D-dimer, have been proposed as indicators of incomplete microvascular reperfusion after successful recanalization^{28,29}. Elevated serum creatinine has been associated with fast-progressor phenotypes³⁰, and NT-proBNP levels have been linked to unfavorable functional outcomes and cardiac-thrombogenicity³¹.

This study has several limitations. First, its retrospective design limits the ability to establish causal relationships. Selection bias may be present, as the study was conducted at a referral center, and the patient population may not reflect the broader stroke population. Additionally, the relatively small sample size limited statistical power, and only a subset of patients (n = 30) underwent subtraction arteriography. Finally, essential data on collateral flow status, glycemic control, baseline blood biomarkers, and vascular or cardiac imaging were unavailable, potentially restricting the depth of prognostic modeling.

To improve predictions of functional outcome after AIS-LVO, there is a need to refine a personalized approach to stroke care by integrating routine clinical data with blood-based and neuroimaging biomarkers that reflect dynamic, structural, and physiological changes, accounting for the progression of stroke symptoms and severity^{7,8}. A deeper understanding of these biological signatures may support tailored interventions and better-informed decision-making in acute stroke care.

Conclusion

Age, baseline NIHSS, and administration of IVT with rtPA were independent predictors of functional outcome at hospital discharge in patients with anterior ischemic stroke due to large vessel occlusion.

Authors' contributions

All authors contributed equally to produce this article according to the CRediT taxonomy.

Funding

This research has not received any specific grant from agencies in the public, commercial, or for-profit sectors.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted 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. 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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Unraveling the link between microorganisms and glioma: a scoping review protocol

Desvelando el vínculo entre microorganismos y glioma: un protocolo de revisión de alcance

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Abstract

Glioblastomas, highly malignant primary brain tumors, comprise ~50% of gliomas. Knowledge on their prevention, early detection, and treatment is scarce, making understanding their etiology and therapy resistance crucial. Recent evidence controversially suggests a link between brain microorganisms and cancer development. This protocol outlines a systematic scoping review to identify microorganism species associated with gliomas, potential pathogenetic mechanisms, and analytical procedures employed. Studies will be retrieved from Web of Science, MEDLINE/PubMed, Scopus, and Google Scholar. We will include studies reporting on diagnosed gliomas, microorganism presence in tumors, oncogenic mechanisms (any model), and analyses of biopsies/resected tumors. Exclusions include other brain tumors/body fluids, therapeutic microorganism use, non-original research, articles not in English/Spanish/Portuguese if untranslatable, and irretrievable full texts. A narrative summary will synthesize available data.

Keywords: Glioblastoma. Microorganism-glioblastoma interactions. Microorganism-related mechanisms.

Resumen

Los glioblastomas, tumores cerebrales primarios altamente malignos, constituyen ~50% de los gliomas. El conocimiento sobre su prevención, detección temprana y tratamiento es escaso, y es crucial la comprensión de su causas y resistencia a la terapia. Evidencia reciente sugiere de forma controvertida un vínculo entre los microorganismos cerebrales y el desarrollo del cáncer. Este protocolo describe una revisión sistemática de alcance (scoping review) para identificar especies de microorganismos asociadas con gliomas, posibles mecanismos patogénicos y los procedimientos analíticos empleados. Los estudios se recuperarán de Web of Science, Medline/PubMed, Scopus y Google Scholar. Se incluirán estudios que reporten sobre gliomas diagnosticados, presencia de microorganismos en tumores, mecanismos oncogénicos (cualquier modelo) y análisis de biopsias/tumores resecados. Las exclusiones incluyen otros tumores cerebrales/fluidos corporales, uso terapéutico de microorganismos, investigación no original, artículos no en inglés/español/portugués que no puedan traducirse adecuadamente y textos completos irrecuperables. Un resumen narrativo sintetizará los datos disponibles.

Palabras clave: Glioblastoma. Interacciones microorganismo-glioblastoma. Mecanismos relacionados con microorganismos.

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Date of reception: 04-06-2025
Date of acceptance: 04-09-2025
DOI: 10.24875/ANC.25000037

Available online: 29-01-2026
Arch Neurocién (Eng). 2026;31(1):23-27
www.archivosdeneurociencias.mx

Background

Gliomas, the most common malignant brain tumors, derive from the transformation of glial cells, which provide neurons with homeostatic, structural, and metabolic support. Around 50% of gliomas are classified as glioblastomas (GBMs), a grade 4 astrocytic glioma with wild-type *IDH1/2* genes¹, which are considered the most common and aggressive form of brain cancer. GBMs are characterized by high infiltration, resistance to therapies, and an unfavorable global prognosis^{2,3}.

Despite the massive research efforts and the general improvement witnessed regarding the understanding of glioma formation and progression and the therapeutic approaches, very few progresses have been made in the prevention, early detection, and treatment of GBMs in the past two decades^{2,4}. At present, treatment options consist mainly of surgery and concomitant chemotherapy and radiotherapy⁴. Nevertheless, resistance to therapies and relapses are common, leading to a dismal prognosis⁵.

One of the major challenges in developing effective therapeutical strategies is linked to the fact that the etiology of these tumors and the mechanisms of resistance are still poorly understood⁶.

It has been considered that infectious agents are responsible for about 20% of cancer incidence worldwide⁷, and some findings in this field, along with implemented public health measures, have significantly contributed to the reduction in cancer incidence⁸. Although the presence of resident microorganisms in the healthy human brain remains debatable, the identification of microorganisms in brain tumors supports the notion that these may play a role in cancer development^{9,10}. While a direct causal link between microorganisms and glioma remains to be definitively proven, the available evidence suggests that certain viruses, bacteria, and potentially fungi and protozoa might play a role in glioma development, progression, or response to treatment and the gut microbiome is emerging as a potentially important factor¹⁰⁻¹², but this remains a controversial issue due to contradictory data. Importantly, several impactful publications about the tumor microbiota have awakened the scientific community to revisit some ideas.

This protocol is aligned with United Nations Sustainable Development Goal 3 “Ensure healthy lives and promote well-being for all at all ages” (indicator 3.4.1) and Cochrane’s Scientific Strategy 2025-2030 research priority “Multiple chronic conditions.”

To address the critical gap in our understanding of glioma’s etiology, specifically the potential role of

microorganisms, we propose a comprehensive review encompassing a broad scope of microorganisms putatively linked to its development. Elucidating microbial associations with gliomas and their underlying mechanisms is crucial for improving our knowledge of tumor pathogenesis. This line of investigation will lead to more targeted studies on glioma formation and progression, which may contribute to the development of novel therapeutic strategies. The potential impact of microbial involvement in gliomas is a key area for comprehensive review and further research. In this context, we intend to review the available information on this topic to identify which species have been linked to gliomas, which microorganism-related mechanisms have been proposed to contribute to understanding the pathogenesis of gliomas and which analytical procedures have been used to unravel these processes.

Objectives

The primary objective of this review is to map the existing literature and identify the extent of evidence regarding the relationship between microorganisms and the etiology of gliomas, particularly glioblastoma. The secondary objectives are as follows:

- Understand if microbial-related mechanisms may be an underlying cause of gliomas.
- Identify which microorganisms have been proposed as a possible underlying cause of gliomas.
- Describe the methods and/or techniques that have been used to study microorganism presence and their interactions with gliomas.
- These objectives allowed us to establish the research questions (Table 1), which led us to define the search strategies to be used in the different databases.

Methods

Review design and protocol edition

We used the online tool “Right Review”¹³ to establish the type of review we should do, according to our objectives. The type of revision suggested was a scoping review. We also searched the Cochrane Library, the International Prospective Register of Systematic Reviews, and Open Science Framework (OSF) to verify if there were any reviews or ongoing protocols for systematic or scoping reviews similar to the review for which the present protocol is established. No relevant records were identified (2024, December 10th).

Table 1. Research questions for this systematic review

Question	Framework	Description
Primary research question	PCC	Which microbial-related mechanisms (C) are involved in tumor development (C) in patients with gliomas (P)?
Secondary research question 1	PCC	Which microbial-related mechanisms (C) might be an underlying cause (C) of gliomas (P)?
Secondary research question 2	PCC	Which microorganisms have been proposed (C) as a possible underlying cause (C) of gliomas (P)?
Secondary research question 3	PCC	Which methods and/or techniques have been used (C) to study microorganism interactions (C) with gliomas (P)?

PCC: population, concept, context.

Our review protocol is available at the OSF since December 2024 (creation date: December 16th, 2024, last update: June 2nd, 2025).

The protocol was initially drafted and then revised until this final version, by the research team and is reported according to methodological guidelines including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRSIMA)¹⁴ and the PRISMA extensions for protocols,¹⁵ and for scoping reviews¹⁶.

The team that will carry out the revision includes researchers with different experiences and profiles, as biochemists, biomedical scientists, and experts in evidence synthesis and systematic reviews, which gives us the confidence necessary that we will be able to meet our goals.

Search strategy and screening

Our search strategy is presented here in compliance with PRISMA-S¹⁷. The research team developed the strategy and followed the Peer Review of Electronic Search Strategies guideline¹⁸ and using 2DSearch platform¹⁹. We will retrieve all published studies from MEDLINE/PubMed (National Center for Biotechnology Information, NCBI), Scopus (Elsevier), and databases accessible through the Web of Science from inception to the present date. In addition, Google Scholar results (we will only consider the first one hundred references, after being sorted by relevance, without citations).

Data availability

The information regarding the databases that will be used, their respective hosts (interfaces), coverage dates, and search strategies can be provided upon request to the authors. No limits or filters will be used in the searches.

If necessary, for example, when full texts are not available, corresponding authors will be contacted, but no other sources will be considered.

We will try to include relevant articles written in languages other than English, Spanish, and Portuguese. We will either use adequate translations made by digital tools (DeepL²⁰ and/or Google Translator²¹) or ask researchers who know the languages in which the articles are written to help us translate them to English, Spanish, or Portuguese. Duplicated references will be identified through Rayyan²² and complemented with the Zotero²³ deduplication features. Duplicates will also be manually revised and eliminated.

Two independent researchers will evaluate the eligibility of all references according to predefined criteria also using Rayyan²². Divergent opinions will be solved by a third member of the research team. Screening will be carried out in two steps: first title/abstract screening, followed by full text screening of the articles included in the previous step. The screening stage will be preceded by a pilot test, run with 50 randomly selected references, to determine the assessment agreement between the reviewers. Finally, studies selected for inclusion will be checked out for possible retractions (using the Retraction Watch database²⁴) and if any retracted studies are identified, they will be excluded.

The bibliographic searches will be rerun after 12 months of the initial searches or before the elaboration of the final draft to identify recent studies for their possible inclusion in future updates. Results from these processes will be described using a PRISMA flow diagram.

Eligibility criteria

INCLUSION CRITERIA

In the review, we will include:

- Original research articles, including randomized controlled trials if available. Comments and letters to the editor will also be included if they present a description of an original study
- Studies reporting the analysis of diagnosed gliomas, regardless of the World Health Organization (WHO)

classification in place at the time of publication, and the methodology used for diagnosing

- Studies reporting the presence of any type of microorganism, including viruses and helminths, in the human tumors analyzed; studies that intentionally implement methods to determine the presence of any type of microorganism and report their absence will also be included
- Studies reporting any type of microbiological analyses conducted on biopsies or tumors following surgical resection
- Studies reporting possible oncogenic mechanisms induced by microorganisms in any biological model (cell lines, rodents, non-human primates, or others)
- Studies written in English, Portuguese, Spanish, or another language in which a reliable translation can be obtained using tools.

EXCLUSION CRITERIA

For this review we will exclude:

- Reviews, meta-analyses, and other types of articles which do not report original research
- Studies reporting the analysis of other types of brain tumors or of body fluids
- Studies using microorganisms for cancer treatment
- Studies whose full texts could not be retrieved

These criteria may be adjusted during screening. Adjustments will be applied to all studies and reported accordingly.

Data extraction and synthesis

The data extraction step will be preceded by a pilot test, run with 10-15% of the included references, to determine the agreement between the reviewers. Two independent researchers will extract data using an extraction form specifically developed in Excel for this purpose. Discrepancies will be solved by a third member of the research team. Data will be extracted only from studies reporting original results.

Extracted data include the following parameters: (1) study characterization (last name of the first author, year of publication, journal, country where the study was carried out (in its absence, we will extract the country of the affiliation of the first author), type of study, objectives of the study); (2) tumor characterization (diagnosis date, IDH1/2 mutation (presence/absence); methodology used in the diagnostic, WHO classification); (3) microbiological analyses (type of

sample (biopsy or tumor resection); sampling conditions; storage conditions; time between sampling and analysis; method(s) used to identify the microorganism(s); control samples); (4) microorganisms (presence/absence; type(s) of microorganisms identified); (5) oncogenic mechanisms (biological model(s)); description); and 6) study limitations as reported by the authors.

Given the variables of interest, it is not expected that unit conversions will be necessary. No unclear information will be included.

The extracted data will be presented in tables, figures, or graphics, as suitable. A narrative synthesis will include all studies. Statistical analysis will not be carried out for this study.

Expected results

With this review, we aim to identify precisely which microorganisms have been found in gliomas and understand the possible ways they might influence the growth of these cancers, gathering the available information on the mechanisms associated with glioma development. At this stage, we are still retrieving the available information, but as far as we could observe, the studies are very heterogeneous, reporting, for example, results regarding the diagnosis of infections in glioma as a post-surgical complication or difficulties to diagnose glioma versus infectious cysts and other pathologies. Although these are interesting studies, they are not specifically related to the goal of the scoping review, they need to be carefully analyzed considering the established eligibility criteria, which poses a major challenge. While extracting the data, we will carefully focus on studies' limitations so we can consider them when mapping the facts and gaps identified in the available literature.

Potential relevance

By mapping out what is known about the putative role of microorganisms in the development of gliomas, we can pinpoint specific areas for future investigation. Understanding the mechanisms by which microbes could contribute to glioma development might open doors to entirely new strategies for prevention or treatment like it was previously found, for example, for Human Papillomavirus and cervical cancer. Ultimately, this research offers a new avenue of exploration and potentially brings new hope to those affected by this challenging disease.

Strengths and limitations

Our research question complies with systematic frameworks. The search strategy was peer-reviewed and consistent with the systematic questions. An effort will be made to include all studies despite their language. Furthermore, the multidisciplinary research group will provide complementary perspectives considering the different areas of specialty. However, only a narrative analysis of the evidence will be considered.

Authors' contributions

M. Teotónio-Fernandes: conceptualization. M.D. Estêvão, I. Perez-Neri: methodology. M.D. Estêvão, M. Teotónio-Fernandes: writing – original draft. M.D. Estêvão, I. Perez-Neri, and M. Teotónio-Fernandes: writing – review and editing.

Funding

The present research has not received any specific grants from agencies in the public, commercial, or for-profit sectors.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted 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. 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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Two unpublished cases of prosopagnosia from Justo Gonzalo y Rodríguez-Leal's archive

Dos casos inéditos de prosopagnosia del archivo de Justo Gonzalo y Rodríguez-Leal

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Abstract

Throughout history, cases have been described of neurological patients who are unable to recognize familiar faces after suffering a brain injury. This disorder is called prosopagnosia. This article presents two previously unpublished clinical cases of this particular condition, located in the archive of Dr. Justo Gonzalo y Rodríguez-Leal (1910-1986). Both are part of a series of veterans of the Spanish Civil War (1936-1939) examined by this Spanish neuroscientist in the early 1950s at the Cerebral Physiopathology Laboratory of the former San Carlos Faculty of Medicine (Madrid, Spain). The first is a 32-year-old man, struck by a rifle bullet in the left occipital region during the Battle of Teruel. The second is a 20-year-old man with a bilateral occipital injury caused by a rifle bullet during the Battle of the Ebro.

Keywords: Perception. Face. Prosopagnosia. Physiognomic agnosia. Spanish Civil War.

Resumen

A lo largo de la historia, se han descrito casos de pacientes neurológicos que son incapaces de reconocer rostros familiares tras sufrir una lesión cerebral. Este trastorno recibe el nombre de prosopagnosia. En este trabajo se presentan dos casos clínicos inéditos, referentes a esta particular afección, localizados en el archivo del Dr. Justo Gonzalo y Rodríguez-Leal (1910-1986). Ambos forman parte de la serie de veteranos de la Guerra Civil Española (1936-1939), explorados por este neurocientífico español a principios de la década de 1950 en el Laboratorio de Fisiopatología Cerebral de la Antigua Facultad de Medicina de San Carlos (Madrid, España); el primero es un varón de 32 años, alcanzado por un proyectil de fusil en la región occipital izquierda durante la Batalla de Teruel. El segundo, un varón de 20 años con una lesión occipital bilateral causada por un proyectil de fusil en el transcurso de la Batalla del Ebro.

Palabras clave: Percepción. Cara. Prosopagnosia. Agnosia fisonómica. Guerra Civil Española.

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Date of reception: 20-09-2025
Date of acceptance: 02-12-2025
DOI: 10.24875/ANCE.M25000069

Available online: 29-04-2026
Arch Neurocién (Eng). 2026;31(1):28-31
www.archivosdeneurociencias.mx

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Introduction

Humans are highly skilled at determining a person's age, sex, or familiarity from their face. Patients with neurological disorders may sometimes lose this ability: they know that what they are looking at is a face, but they are unable to determine to whom it belongs (is it a man or a woman? Is it someone I know or a stranger?). The first mention of this singular deficit can be found in the description by Thucydides of the plague that struck Athens between 430 and 429 BC: "Others, in fact, upon recovering, suffered total amnesia and did not know who they were nor recognize their relatives"¹. The first detailed contemporary description is attributed to Quaglino and Borelli (1867)². Hoff and Pötzl (1937)³ proposed that this alteration is a specific form of visual agnosia, specifically an agnosia of human physiognomies (Agnosie der menschlichen Physiognomien). In 1947, Bodamer⁴ proposed the term "prosopagnosia" for this selective disorder of visual perception.

This article aims to present 2 previously unpublished clinical cases of prosopagnosia located in the family archive of Justo Gonzalo y Rodríguez-Leal. Both cases are part of the series of nearly 200 veterans of the Spanish Civil War (1936-1939) examined by this Spanish neuroscientist between 1951 and 1953 in the Laboratory of Cerebral Pathophysiology of the former School of Medicine of San Carlos (Madrid, Spain)⁵.

Justo Gonzalo y Rodríguez-Leal was born on March 2nd, 1910, in Barcelona (Spain). In 1933, after completing his medical studies, he traveled to Vienna, where he trained in clinical neurology and animal experimentation with Hans Hoff, and in cerebral cytoarchitecture with Otto Pötzl. He later completed a stay at the Universitäts Nervenlinik de Frankfurt with Karl Kleist. In 1935, he returned to Spain and shortly after the outbreak of the Spanish Civil War, he was appointed consulting neurologist at the Hospital General de Madrid. In the summer of 1937, he was sent to the Republican front as a war physician, and at the beginning of 1938 he began working at the Hospital de Sanidad Militar de Godella (Valencia) under the direction of Gonzalo Rodríguez Lafora. After the end of the war, he returned to Madrid and presented a report with the first results of his research on brain-injured patients to the Consejo Superior de Investigaciones Científicas (CSIC). In 1942, he was appointed head of the Laboratory of Cerebral Pathophysiology at the Instituto Cajal (a center integrated into the CSIC). Four years later, he initiated administrative procedures to examine brain-injured patients registered in the Benemérito

Cuerpo de Mutilados de Guerra por la Patria. His *opus magna*, entitled *Dinámica cerebral. La actividad cerebral en función de las condiciones dinámicas de la excitabilidad nerviosa*, was published in 1945 (Volume 1) and 1950 (Volume 2). He died on September 28th, 1986, in Madrid⁶.

Case #71

A 32-year-old man who in December 1937 was struck by a rifle projectile during the Battle of Teruel. The projectile caused a wound with an entry point in the right occipital region and an exit through the left temporal region (Fig. 1). He remained practically blind for 2 months; vision was gradually recovered. Initially, he was unable to speak or understand spoken language; he was also unable to read or write.

Gonzalo examined him on June 2nd and 3rd, 1952 (at that time, the veteran was 47 years old). He complained of visual difficulties, some language problems, and tinnitus in the left ear. Examination revealed right hemianopsia and leukoma in the left eye. There was narrowing of the visual field in the right eye (field up to 35° or 40-45° on the nasal side, with variability) and in the left eye (field up to 20° on the temporal side, more stable than the right eye). A marked elevation of the auditory threshold was also observed. Regarding touch, distal deficit was present in the right hand (more pronounced in the little finger). Semantic aphasia, alexia, acalculia, and right-left disorientation were also identified. He presented marked visual agnosia, showing prolonged response latency when attempting to identify figures. He was able to recognize banknotes, but only by size, shape, or color. Regarding face recognition, notes preserved in the family archive state: "he complains of not remembering people's physiognomy. He does not recognize anyone, not even himself in photographs." Another note indicates that "he could not find his children if they were among others."

Case #78

A 20-year-old man struck by a rifle projectile during the Battle of the Ebro (exact date unknown). The projectile caused a wound with an entry point at the left occipital level and an exit through the right occipital region (Fig. 1). He presented immediate loss of consciousness, which he did not regain until 4 days later. Subsequently, he remained completely blind for several days.

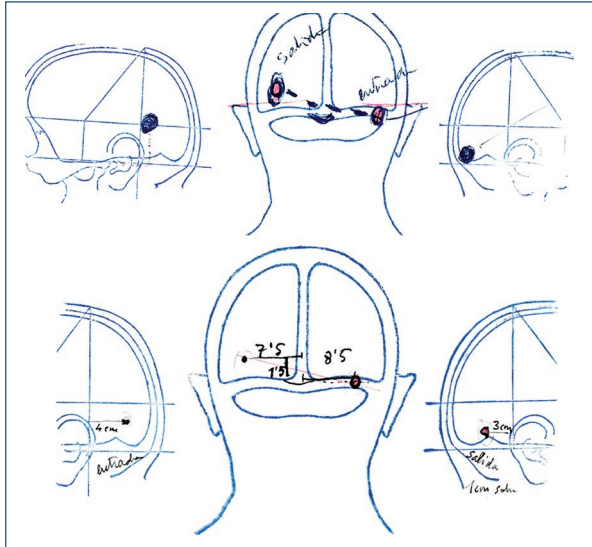


Figure 1. Upper part: case #71. Diagram showing the location of the cranial scars of projectile entry and exit. Lower part: case #78. Diagram showing the location of the cranial scars of projectile entry and exit (photomontage produced by AGM from unpublished illustrations from the family archive of Justo Gonzalo).

Gonzalo examined him on June 10th and 11th, 1952 (at that time, the veteran was 33 years old). He exhibited moderate symmetric concentric reduction of the visual fields (right eye field up to 50° and left eye up to 45°), with similar visual acuity in each eye, micropsia and distance metamorphopsia (“he sees a cow as the size of a dog”), and visual fatigue. Regarding touch, distal deficit was recorded in both hands. The veteran reported difficulty using the fingers of both hands to roll a cigarette, and in winter to move and use them. Acalculia was also present. He showed visual agnosia. Regarding face recognition, Gonzalo wrote in the notes preserved in the family archive: “He complains of not recognizing people. Even at small gatherings. When attending festivities, he searched for his girlfriend among the crowd unsuccessfully.” Another note states: “He has great difficulty distinguishing photographs of different faces, he incorrectly matches physiognomies, but correctly identifies when one is seen from behind.”

Final comment

In Volume 1 of *Dinámica cerebral*⁷, Gonzalo proposed that there are no absolute differences between the different types of visual agnosia. He also indicated that they form part of the same fundamental disorder of visual sensory field organization, in which

elementary sensory defects originate from the “central” lesion. The result is a dynamically reduced sensory field due to a deficit in nervous excitability, with the most complex functions (those with higher physiological demand) being the most affected; among them, the schema function. In this sense, according to Gonzalo, visual agnosia involves a disintegration (dissolution) of the schema function, in which both altered perception of forms – resulting in diffuse and metamorphic vision – and an inability to construct the schema are involved. The schema dissolves into more concrete or accessory activities, without organization beyond juxtaposition, lacking a general framework or ideation. This conceptualization likely explains why Gonzalo did not use the term “prosopagnosia” in this work to refer to the inability or difficulty in recognizing faces.

Currently, prosopagnosia is conceived as a selective visual agnosia that may present in two main forms: apperceptive and associative (or amnesic). Apperceptive prosopagnosia, linked to lesions in the right inferior occipitotemporal cortex – the fusiform gyrus – entails the inability to perceive structural differences between faces. Associative prosopagnosia, on the other hand, results from right anterior temporal lesions and involves the inability to identify familiar (or known) faces⁸.

Authors’ contributions

Both authors contributed equally to the production of this article, according to the CRediT taxonomy.

Funding

This research did not receive any specific grant from public, commercial, or for-profit funding agencies.

Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments were conducted on humans or animals for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal data, clinical records, or human biological samples; therefore, it does not require ethical approval. The SAGER guidelines were not applied.

Declaration on the use of artificial intelligence.



The authors declare that no generative artificial intelligence was used in the writing or content creation of this manuscript.

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Leukoencephalopathy with evanescent white matter in a pediatric patient: a case report

Leucoencefalopatía con sustancia blanca evanescente en paciente pediátrico: un reporte de caso

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Abstract

Leukoencephalopathy with disappearance of the white matter is an autosomal recessive genetic disorder characterized by progressive loss of the white matter of the brain, triggered by factors such as infections or minor trauma. This report describes the case of a pediatric patient with a confirmed diagnosis of leukoencephalopathy with white matter disappearance associated with the homozygous c.338G>A variant in the EIF2B5 gene. The patient presented with generalized hypotonia, gait disturbances and slow speech after mild trauma, accompanied by typical MRI findings, including hyperintense lesions in the periventricular white matter and involvement of subcortical fibers. Multidisciplinary management included neurological rehabilitation therapies and pharmacological treatment to delay functional deterioration. This case emphasizes the relevance of early diagnosis based on imaging studies and genetic analysis, highlighting the need for further research to develop effective therapeutic and preventive strategies.

Keywords: Leukoencephalopathies. Leukoencephalopathy with evanescent white substance. Disappearing substance disease.

Resumen

La leucoencefalopatía con desaparición de la sustancia blanca es un trastorno genético autosómico recesivo caracterizado por la pérdida progresiva de la sustancia blanca del cerebro, desencadenada por factores como infecciones o traumatismos menores. Este reporte describe el caso de un paciente pediátrico con diagnóstico confirmado de leucoencefalopatía con desaparición de la sustancia blanca asociado a la variante homocigota c.338G>A en el gen EIF2B5. El paciente presentó hipotonía generalizada, alteraciones en la marcha y lentitud en el habla después de un traumatismo leve, acompañado de hallazgos típicos en resonancia magnética, incluyendo lesiones hiperintensas en la sustancia blanca periventricular y compromiso de fibras subcorticales. El manejo multidisciplinario incluyó terapias de rehabilitación neurológica y tratamiento farmacológico para retrasar el deterioro funcional. Este caso enfatiza la relevancia del diagnóstico temprano basado en estudios de imágenes y análisis genético, destacando la necesidad de investigaciones adicionales que permitan desarrollar estrategias terapéuticas y preventivas efectivas.

Palabras clave: Leucoencefalopatías. Leucoencefalopatía con sustancia blanca evanescente. Desaparición de la enfermedad de la sustancia blanca.

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Date of reception: 28-01-2025
Date of acceptance: 01-05-2025
DOI: 10.24875/ANCE.M25000057

Available online: 05-02-2026
Arch Neurocién (Eng). 2026;31(1):32-36
www.archivosdeneurociencias.mx

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Introduction

Vanishing white matter (VWM) leukoencephalopathy is an autosomal recessive hereditary disorder that primarily affects the brain's white matter. Although it predominantly manifests in childhood, it can present in neonates, adults, and individuals of all ages; however, its exact incidence rate remains unclear^{1,2}. This disorder is associated with mutations in the *EIF2B5* and *EIF2B2* genes, located on chromosomes 3q27 and 14q24, which encode the epsilon and beta subunits of the eukaryotic translation initiation factor 2B (EIF2B)^{3,4}.

Although mutations in any of the five EIF2B subunits (α , β , γ , δ , and ϵ) can disrupt the regulation of protein synthesis and amplify the cellular stress response, contributing to the pathophysiology of the disorder, this mechanism remains poorly understood⁵⁻⁷. The most common variant, c.338G>A in *EIF2B5*, results in substitution of histidine with arginine and is present in approximately 56-70% of cases⁸.

The disease follows a chronic and progressive course, characterized by abrupt neurological deterioration triggered by stressors such as fever, infections, or minor head trauma⁹. Diagnostic criteria include symptoms such as cerebellar ataxia, spasticity, vision loss, and mild seizures in childhood, while in adults, cognitive and psychiatric dysfunctions predominate. Both groups are susceptible to sudden neurological decline and unexplained comas¹⁰⁻¹². Magnetic resonance imaging (MRI) is essential to identify characteristic patterns such as confluent lesions in the white matter and periventricular cavitations, which are key for diagnosis, confirmed by genetic testing¹³.

This report presents a case of VWM leukoencephalopathy in a pediatric patient with compound homozygous variants in the *EIF2B5* gene, highlighting its clinical, imaging, and genetic characteristics in the context of the diagnostic and therapeutic approach to this rare condition (Fig. 1).

Case presentation

The patient was a male child, product of the first gestation of a non-consanguineous couple, with adequate prenatal care and normal ultrasound findings. He was born preterm at 36 weeks of gestation by emergency cesarean section due to fetal bradycardia due to umbilical cord compression. No neonatal complications attributable to this event were documented, and the

bradycardia had no subsequent relevant clinical consequences.

He did not require neonatal intensive care. Newborn screening ruled out conditions such as phenylketonuria, congenital hypothyroidism, cystic fibrosis, and other metabolic or genetic diseases. He was discharged on the second day of life with age-appropriate vaccinations and regular pediatric follow-up. During infancy, his psychomotor development was age-appropriate, achieving the main developmental milestones within the expected range: head control at 3 months, sitting at 7 months, standing at 12 months, and independent walking at 14 months.

He did not exhibit any signs of neuroregression in his early years, which is notable given that patients with VWM leukoencephalopathy often experience abrupt neurological deterioration during stressful events, although outside of such episodes, the course may be stable. However, at 5 years of age, progressive behavioral changes were observed, characterized by irritability, attention deficit, and increased skin pigmentation. These changes were not associated with acute episodes but were reported by parents to worsen during stress or intercurrent illnesses.

At 7 years and 5 months, he suffered a fall from standing height with mild traumatic brain injury, without loss of consciousness, seizures, or external bleeding. Eleven days later, he developed generalized weakness and was taken to the emergency department of a level IV hospital. Neurological examination revealed generalized hypotonia, dragging gait, tendency to varus, and bradykinesia. A simple brain MRI identified confluent hyperintensities in the periventricular white matter with involvement of subcortical fibers and temporal lobes, findings compatible with vanishing white matter leukodystrophy (Fig. 2). Cerebrospinal fluid studies were unremarkable.

The diagnosis was confirmed by molecular panel, identifying the pathogenic homozygous variant c.338G>A; p.Arg113His in the *EIF2B5* gene, widely described in cases of VWM type 5.

Management was led by a multidisciplinary team including pediatric neurology, physiatry, genetics, and psychology, with physical, speech, and pharmacological therapies. Seizure disorders were ruled out by 12-hour video telemetry, which was normal. Neuropsychological evaluation (Wechsler Intelligence Scale for Children, version V [WISC-V]: full-scale IQ 85) showed difficulties in reading and writing, slow processing speed, and attention deficit.

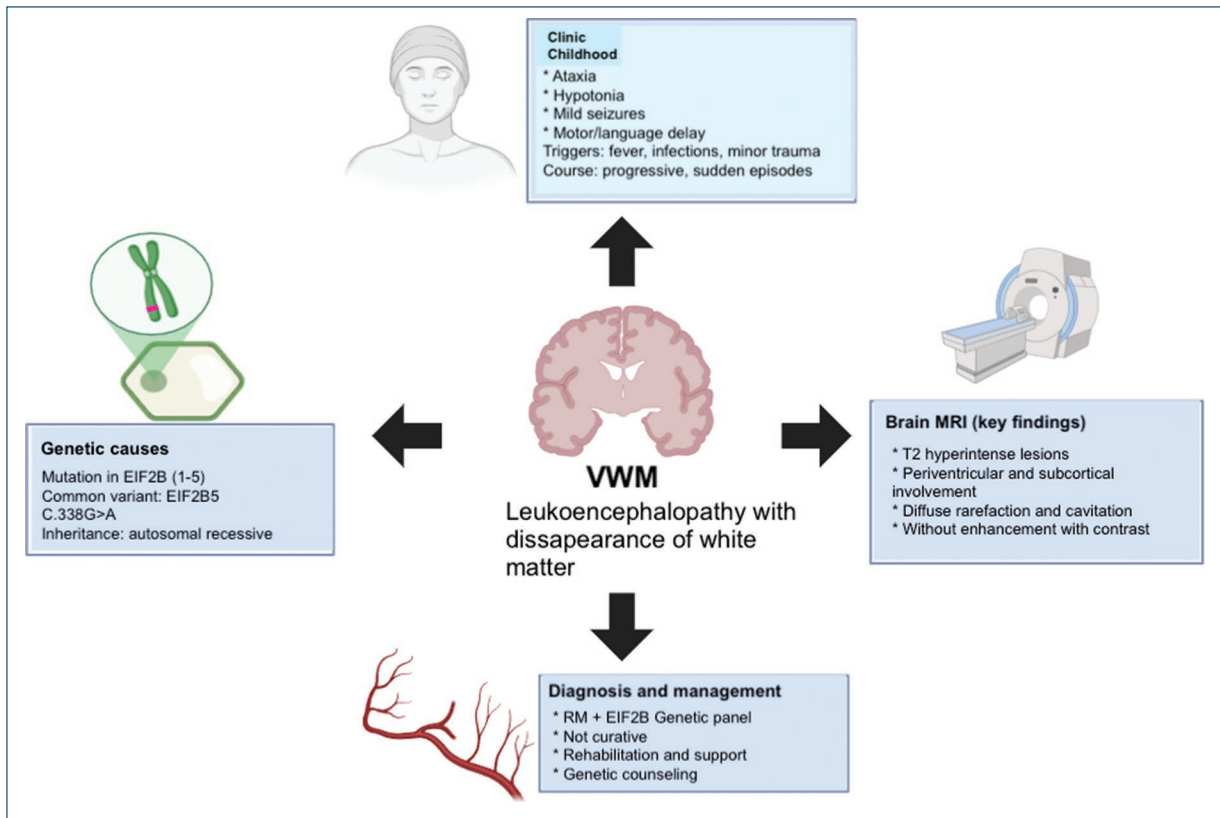


Figure 1. Key aspects of VWM leukoencephalopathy. This figure illustrates the main clinical, genetic, and imaging elements associated with VWM leukoencephalopathy. The clinical presentation includes progressive neurological signs precipitated by stressful events. Typical MRI findings show diffuse involvement of the white matter. Diagnostic confirmation is achieved by identifying mutations in the *EIF2B* genes, with the c.338G>A variant in *EIF2B5* being one of the most frequent. VWM: vanishing white matter.

Pharmacological treatment included: Quintessens® (coenzyme Q10 [10 mg], vitamin C [30 mg], thiamine [9.854 mg], and riboflavin [12.3 mg]) one tablet orally once daily, and Myoessens® (magnesium citrate [333 mg], potassium citrate [365 mg], and magnesium oxide [87.2 mg]) one tablet orally once daily.

Genetic testing of the parents identified them as heterozygous carriers of the same variant. The neurological prognosis was explained as unfavorable, with expected progression toward motor and cognitive deterioration. Although the disease course is highly variable, life expectancy is reduced, with progression to severe disability in the second decade of life. No curative treatments are available; management focuses on supportive care and prevention of triggering factors.

Associated conditions were ruled out, such as seizure syndrome through 12-hour video telemetry, and a neuropsychological evaluation (WISC-V: Full-Scale IQ 85) revealed difficulties in reading and writing, slow

processing speed, and attention deficit. Neuropsychiatric and endocrinological follow-up was recommended to detect comorbidities, such as adrenal insufficiency, which may occur in some cases of VWM leukoencephalopathy.

At the 10-month follow-up, the patient remained under strict multidisciplinary monitoring. Rehabilitation therapies were adjusted as his functional status evolved. Although he partially reintegrated into daily and school activities, these were limited by the need for constant supervision and curricular adaptations to optimize performance and minimize risks.

Discussion

VWM leukoencephalopathy is an autosomal recessive disorder characterized by progressive loss of cerebral white matter, precipitated by stressors such as infections, fever, or minor trauma. Van der Knaap et al.

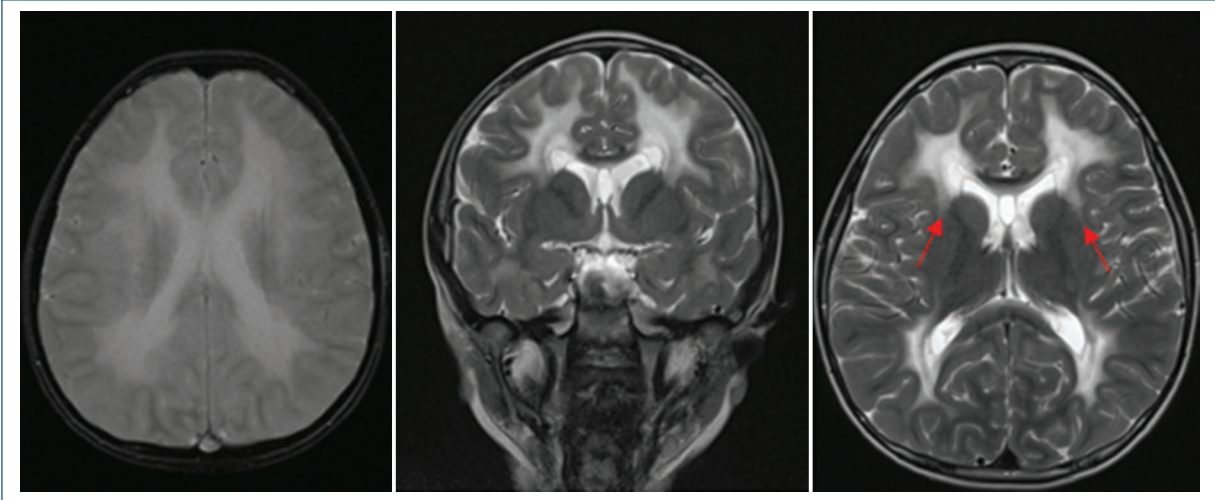


Figure 2. Brain magnetic resonance imaging in a patient with VWM leukoencephalopathy. Axial T2 sequence showing symmetric, confluent hyperintensities in the periventricular white matter (white arrows), with extension into subcortical fibers and temporal lobes. No contrast enhancement is observed. These findings are characteristic of vanishing white matter leukoencephalopathy.

first described the characteristic findings of this disease, including cystic rarefaction of white matter on MRI, resembling cerebrospinal fluid in advanced stages. These criteria guide early diagnosis, particularly in patients with sudden, unexplained neurological episodes, highlighting the need for molecular studies to confirm specific *EIF2B* mutations^{11,12}.

Recent studies have identified *EIF2B5* mutations as the most prevalent in VWM patients, underscoring the utility of next-generation sequencing in expanding knowledge of the genetic variants involved. In our patient, identification of the homozygous c.338G>A variant in *EIF2B5* confirmed the diagnosis and distinguished it from other leukodystrophies with similar presentations. Genetic studies have emphasized the importance of these tools in atypical cases, where VWM leukoencephalopathy may be confused with other neurologic disorders such as multiple sclerosis. In the case described, although the imaging findings were consistent with VWM, molecular confirmation allowed the establishment of the definitive diagnosis, avoiding possible diagnostic errors and facilitating appropriate therapeutic management and prognosis^{14,15}.

Age of onset has been shown to be a key factor in disease progression. Patients with early onset, as in this case, tend to have faster neurological deterioration and greater cystic rarefaction of the white matter. By contrast, in late-onset cases, atrophy and gliosis

predominate, altering clinical course and imaging findings. Our patient's pediatric presentation with progressive impairment supports these observations and highlights the importance of early diagnosis for neuroprotective management strategies¹³.

Genotype-phenotype correlation studies in *EIF2B*-related disorders have shown that the homozygous p.Arg113His mutation is associated with milder forms of the disease vs. other genetic combinations. In our patient, identification of this variant allowed prediction of a less aggressive clinical course compared with more severe mutations, though still with an unfavorable long-term prognosis¹⁶.

Adult-onset VWM leukoencephalopathy cases have been reported, some initially misdiagnosed as multiple sclerosis. These cases illustrate the diagnostic challenges when clinical and radiologic features are ambiguous. Multiple sclerosis typically presents with focal demyelinating white matter lesions, periventricular involvement on neuroimaging, contrast enhancement in active lesions, and temporal and spatial dissemination on MRI, along with cerebrospinal fluid oligoclonal bands¹⁷.

In contrast, VWM leukoencephalopathy presents with a more diffuse, symmetric white matter involvement, progressive cystic rarefaction, and absence of contrast enhancement-findings evident in our patient. The absence of oligoclonal bands in cerebrospinal fluid and progressive course without remissions guided

diagnosis toward a leukodystrophy. Genetic confirmation definitively distinguished it from demyelinating pathologies with similar MRI findings, avoiding diagnostic delays. Once again, this demonstrates the value of genetic testing as a fundamental diagnostic tool and underscores the importance of considering VWM in the differential diagnosis of demyelinating disorders, particularly in atypical cases¹⁵.

Conclusions

VWM leukoencephalopathy is a rare disease with significant clinical implications, whose diagnosis requires a multidisciplinary approach combining clinical, imaging, and genetic findings. This case highlights the importance of considering VWM leukoencephalopathy in the differential diagnosis of progressive neurologic disorders, particularly in pediatric contexts, where early recognition can optimize management and mitigate triggering factors. Although no curative treatment exists, identification of *EIF2B* mutations, such as the homozygous c.338G>A variant in *EIF2B5* described here, provides a strong foundation to advance understanding of its pathophysiology and explore future therapeutic options. Further studies are needed to evaluate long-term impact and develop preventive strategies to improve quality of life in affected patients.

Authors' contributions

ME Obando-Gerron: conceptualization, drafting of the original manuscript, and development of the methodology. CA Castro-Galvis: supervision, formal analysis, and critical review and final editing of the manuscript. JS Serna-Trejos: research, initial drafting, and overall project coordination. SG Bermúdez-Moyano: participation in data collection and drafting of the original manuscript. E Agudelo-Quintero: support in formal analysis and methodological contributions.

Funding

This research did not receive any specific grant from public, commercial, or not-for-profit funding agencies.

Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors followed their institution's confidentiality protocols, obtained informed consent from the patient's guardians, and received approval from the Ethics Committee. The recommendations of the SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence tools were used in the writing of this manuscript.

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Effect of proprioceptive neuromuscular facilitation on independence and assisted gait in Miller-Fisher syndrome. A case report

Efecto de la facilitación neuromuscular propioceptiva en la independencia y marcha asistida en el síndrome de Miller-Fisher. Reporte de caso

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Abstract

A descriptive case study of a single 16-year-old subject diagnosed with Guillain-Barré syndrome, Miller Fisher variant, with a 2-year history of onset. The intervention technique was proprioceptive neuromuscular facilitation (PNF), which was applied for 30 sessions 50 min over a 10-week period. Pre- and post-intervention analyses were performed to assess the results. The following were evaluated: joint range of motion, muscle strength, deep tendon and pathological reflexes, dermatomes, and movements; as well as the application of the functional independence scale and biomechanical gait analysis using Kinovea 2023 version 1.1 software, assessing the following temporal and spatiotemporal variables: toe-off angle, foot elevation, step length, and gait speed. The intervention resulted in an increase in muscle strength and complete movements, as well as joint and dermatome ranges within the norm. Regarding the biomechanical analysis, there was a decrease in foot elevation on the right side and an increase on the left side, resulting in a difference of 7.45 cm compared to the initial evaluation. There was a decrease in step length bilaterally, a decrease in foot angles bilaterally, and an improvement in speed with a difference of 0.1524 m/s. It is concluded that PNF can generate favorable changes in the temporal and spatiotemporal.

Keywords: Proprioceptive neuromuscular facilitation. Physical therapy. Miller Fisher syndrome. Guillain-Barré. Exercise.

Resumen

Estudio de caso con diseño descriptivo de un único sujeto de 16 años con diagnóstico de Guillain-Barré en la variante de Miller-Fisher con dos años de evolución. La técnica de intervención se realizó por medio de la facilitación neuromuscular propioceptiva (FNP) la cual se aplicó durante 30 sesiones de 50 minutos, por un periodo de 10 semanas, realizando análisis previo y posterior a la intervención para el análisis de resultados. Se evaluaron: rango articular, fuerza muscular, reflejos osteotendinosos y patológicos, dermatomas y mudanzas. También se aplicó la escala de independencia funcional (FIM) y se realizó análisis biomecánico de la marcha mediante el software Kinovea 2023 versión 1.1, valorando las variables temporales y espaciotemporales: ángulo de despegue de pie, elevación de pie, longitud de paso y velocidad de la marcha. Como resultados de la intervención se registró un aumento de la fuerza muscular y mudanzas completas, así como rangos articulares y dermatomas dentro de la norma. En cuanto al análisis biomecánico, hubo una disminución de elevación del pie de lado derecho y aumento del lado izquierdo, dando una diferencia de 7.45 cm respecto a la evaluación inicial, disminución en la longitud de paso de manera bilateral, disminución del ángulo de pie de manera bilateral y mejorando la velocidad con

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Date of reception: 27-03-2025
Date of acceptance: 17-07-2025
DOI: 10.24875/ANC.25000020

Available online: 29-01-2026
Arch Neurocién (Eng). 2026;31(1):37-41
www.archivosdeneurociencias.mx

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una diferencia de 00.15.24 m/s. Se concluye que la FNP puede generar cambios favorables en los parámetros temporales y espaciotemporales de la marcha, así como mejora de la funcionalidad e independencia en un paciente con síndrome de Miller-Fisher con estas características.

Palabras clave: *Facilitación neuromuscular propioceptiva. Fisioterapia. Síndrome de Miller-Fisher. Guillain-Barré. Ejercicio.*

Introduction

Guillain-Barré syndrome is an immune-mediated polyradiculopathy that accounts for an estimated 100,000 new cases annually worldwide¹. In most patients, the acute onset of neurological symptoms is preceded by an infectious disease followed by progressive limb deterioration, inducing an aberrant autoimmune response targeting peripheral nerves and their spinal roots². Guillain-Barré syndrome requires close monitoring for disease progression, particularly for bulbar weakness, respiratory failure, and autonomic dysfunction². Most studies estimating incidence rates were conducted in Europe and North America, showing a similar range of 0.8-1.9/100,000 persons/year¹. The annual incidence rate of Guillain-Barré syndrome increases with age (0.6/100,000/year in children and 2.7/100,000 in people over 80 years of age), being more common in men³.

Miller Fisher syndrome (MFS) consists of the triad of ophthalmoplegia, ataxia, and areflexia without any weakness⁴. Most patients with MFS present with at least two features, the most common being ataxia and areflexia⁵. It is of immunological origin and is correlated with upper respiratory tract infection, which is considered the most common (56-76%), followed by gastrointestinal infection (4%), typical of classic GBS, and isolated fever (2%)⁶⁻¹⁰.

The concept of proprioceptive neuromuscular facilitation (PNF) has been used to improve movement gestures so that the patient can perform them in a more coordinated manner from the perspective of strength, mobility, stability, and programming, which should allow for more precise adaptation to the task and the situation in which the activity is performed¹¹. Considering that it stimulates the patient's central and peripheral nervous system to achieve functional activity¹².

Gait is divided into cycles; a step phase and a swing phase, requiring balance, coordination, kinesthetic sense, proprioception, and integrated muscle action^{13,14}. PNF improves function and increases muscle activity, flexibility, and balance during gait by stimulating proprioceptors within muscles and tendons, thereby improving motor function^{15,16}.

This work was carried out in accordance with the Case Report Guidelines (CARE) 2013 checklist for case reports.

Case presentation

A 16-year-old male attended the Physical Therapy Clinic with a medical diagnosis of Guillain-Barré Syndrome, atypically Miller Fisher variant, which had been present for 1 year and 10 months. Symptoms began on April 27, 2022, presenting with paresis in the lower limbs, beginning in the toes and progressing to the pelvic girdle, causing limitations when changing positions. He was admitted to a public institution in León, Guanajuato, on April 27, where he began receiving evaluations. Hours later, he experienced bilateral ophthalmoplegia, blurred vision, weakness in the neck, trunk, and upper and lower limbs, resulting in quadriplegia. During his hospital stay, he was treated with immunoglobulins, and subsequently discharged on May 4, 2022, after being referred to physical therapy for a period of 2 months. He presented with plegia of the axial axis, upper and lower limbs, bilateral ophthalmoplegia, and blurred vision. He also had no past medical history, either familial or personal.

In May 2023, an electromyography (EMG) study was performed, revealing a motor and sensory axonal polyneuropathy predominantly in the lower limbs. The interpretation details the following:

- Motor neuroconduction, which shows decreased amplitudes with decreased nerve conduction velocity in the peroneal and tibial nerves bilaterally.
- Sensory neuroconduction, which shows absent sensory potentials in the sural nerves bilaterally, also the patient demonstrates sensory preservation in the upper limbs.
- Needle electromyography (EMG), which demonstrates active denervation, generating axonal damage after the study of positive waves and fibrillations.

Given the aforementioned interpretation, a symmetrical axonal motor and sensory polyneuropathy predominantly in the lower limbs was concluded, leading to a diagnosis of Guillain-Barré syndrome with Miller

Fisher variant superimposed on axonal form of AMSAN (acute motor and sensory axonal neuropathy).

He attended the physical therapy clinic for an initial wheelchair assessment on February 28, 2024. The following variables were assessed: joint range of motion (ROM), muscle strength, muscle tone, recumbency movements, dermatomes, and deep tendon reflexes. The patient presented the following data: full range of motion in the upper limbs performed voluntarily, full range of motion in the lower limbs performed only passively; muscle strength according to the Daniel's Scale was 3 in the upper limbs and 2 in the lower limbs; muscle tone was present with hypotonia in the lower limbs; and complete recumbency movements to asymmetrical handstand were incomplete, with incomplete movements on all fours, crawling, sitting in a monoischiatric position, kneeling, kneeling transfer, standing stance, and walking. Dermatomes were found to be unimpaired, and deep tendon reflexes were hyporeflexia.

Evaluation

The assessment was performed using the following variables: joint range of motion using a goniometer, muscle strength using the Daniel's scale, and recumbency changes observed; as well as the application of the functional independence scale (FIM) and biomechanical gait analysis using Kinovea 2023 version 1.1 software, assessing the temporal and spatiotemporal variables: foot take-off angle, foot elevation, step length, and gait speed.

Therapeutic intervention

The intervention technique was PNF, which was applied for 30 sessions of 50 min every session over a period of 10 weeks. Patients attended therapy 3 times a week. Pre- and post-intervention analyses were performed to analyze the results.

The results show an increase in muscle strength, joint movements, and range of motion were recorded. Regarding the temporal and spatiotemporal results, relevant differences were observed: left foot elevation (initial result: 15.57 cm) and result: 23.02 cm, obtaining a difference of 7.45 cm; and initial gait speed: 0.57.56 m/s and final speed: 0.42.32 m/s, obtaining a difference of 00.15.24 m/s (Table 1).

The results obtained according to the FIM showed a difference in 4 of the 6 items, referring to the fact that a higher score indicates greater independence. In the self-care item, an initial score of 18 points was obtained

Table 1. Temporal and spatio-temporal results

Variable	Initial analysis	Final analysis	Difference
Right foot elevation	21.17 cm	23.82 cm	2.65 cm
Left foot elevation	15.57 cm	23.02 cm	2.65 cm
Right step length	71.46 cm	66.82 cm	4.64 cm
Left step length	70.52 cm	69.87 cm	0.65 cm
Right step angle	141.1°	136.9°	4.2°
Left step angle	158°	153.4°	4.6°
Gait velocity	00.57.56 m/s	00.42.32 m/s	00.15.24 m/s

and a final score of 40 points out of a total of 42; in mobility, an initial score of 6 points was obtained and a final score of 18 points out of a total of 21; in social knowledge, an initial score of 13 points was obtained and a final score of 21 points out of a total of 21; in ambulation, an initial score of 4 points and a final score of 12 points out of a total of 14. The remaining items: sphincter control and communication, maintained scores within the norm from the beginning of the application. (Fig. 1)

Regarding the biomechanical analysis performed using Kinovea 2023 version 1.1 software, markers were placed in the areas of the lateral epicondyle, femoral condyle, and external malleolus. Figure 2 shows the patient's pre-intervention standing and gait. Head and trunk tilt are observed, with no pelvic girdle control, no scapulae dissociation, and inadequate weight-bearing on the lower limbs. The patient also required a fixed support to facilitate standing and subsequently walking. Post-intervention standing and gait (Fig. 3) showed head and trunk straightening, improved pelvic girdle control, adequate scapulae dissociation, and adequate weight-bearing on the lower limbs. The patient also replaced the fixed support with dynamic support.

Discussion

Gong¹⁷ mentions that there is a greater difference in the training group in the variables of: step length, stance phase, and step time; to which rhythmic exercises using PNF were applied, showing favorable results as presented in the present study.

Cho and Gong (2017)¹⁸ carried out interventions in healthy patients to examine the effects of dynamic exercises using PNF; they formed two groups, a training group and a control group. The training group

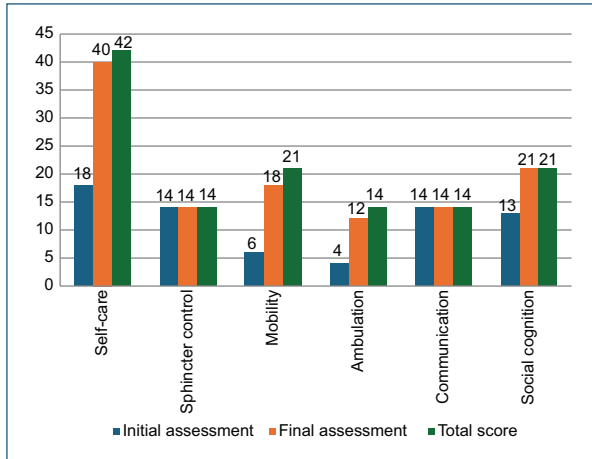


Figure 1. Functional independence scale results.

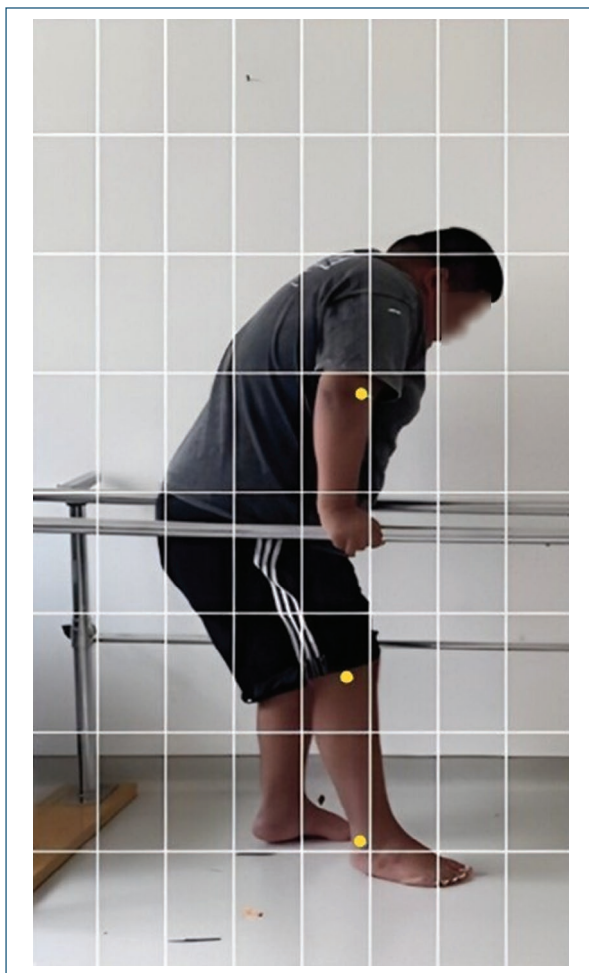


Figure 2. Standing and gait before intervention.

showed a significant change in the variables of: trunk tilt, pelvic position, pelvic movement, pelvic rotation, and scapula position, while the control group did not

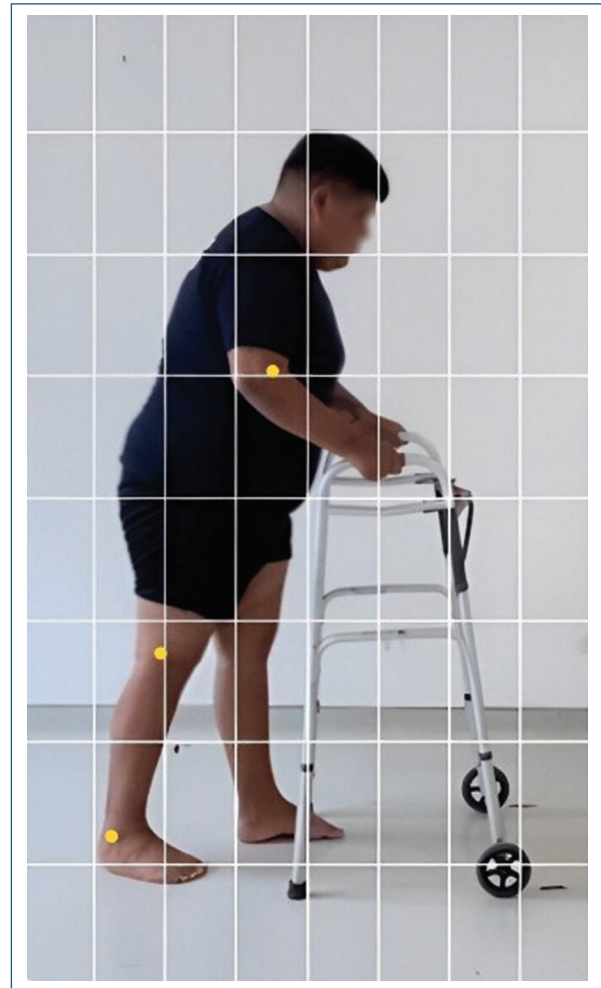


Figure 3. Standing and gait post intervention.

have any significant changes in any of the variables.

Considering the pathophysiology of Guillain-Barré syndrome in its Miller Fisher variant, an exercise program that included strength, endurance, and mobility based on increasing muscle strength, flexibility, improving posture, core activation, and lower limb coordination, as well as functional exercises emphasizing trunk, shoulder, and pelvic girdle mobility, center of gravity shifting, and balance exercises, showed positive changes in spatiotemporal gait parameters, functionality, and independence.

Conclusion

It is concluded that PNF can generate favorable changes in the temporal and spatiotemporal parameters of gait as well as improvement in functionality and

independence in a patient with Miller Fisher Syndrome with these characteristics.

Acknowledgments

To the National School of Higher Studies unit leon (ENES LEÓN), UNAM and to the patient for being part of the work.

Authors' contributions

All authors contributed equally to the production of this article according to the CRediT taxonomy.

Funding

This research has not received any specific grant from agencies in the public, commercial, or for-profit sectors.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical considerations

Protection of humans and animals. The authors declare to have followed the ethical standards of the relevant experimentation committee, according to the World Medical Association and the Declaration of Helsinki. The procedures were approved 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. 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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Transfusion in patients with subarachnoid hemorrhage and anemia: in which cases are outcomes improved?

Transfusión en el paciente con hemorragia subaracnoidea y anemia: ¿en qué casos hay mejores desenlaces?

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To the Editor,

Subarachnoid hemorrhage (SAH) is a serious neurological condition characterized by a high rate of morbidity and mortality¹. Anemia is a common problem in these patients and has been associated with adverse outcomes², which raises the need to determine the optimal hemoglobin (Hb) value for blood transfusion in cases where it is required, to improve outcomes³. Although low Hb concentrations have been shown to increase the risk of cerebral ischemia and worsen functional outcomes², the ideal threshold for transfusion remains a topic of discussion³. Hemodilution, which was previously used in the treatment of vasospasm, has not been recommended since 2010-2012 to reduce the risk of vasospasm or delayed cerebral ischemia⁴, in addition to the fact that it can further reduce Hb⁵, which can increase the risk of cerebral hypoxia.

This suggests that managing anemia in patients with SAH is crucial for preventing complications and improving outcomes. However, if the optimal Hb value for transfusion in this context is unknown, it is possible to incur in cases of irrelevant transfusions and trigger adverse consequences⁶.

The most recent meta-analysis to date³, which included 40 studies and 14,701 patients with SAH, and

whose main objective was to determine how the severity of anemia influences cerebral infarction and functional evolution, showed that even mild anemia (Hb < 11.0-11.5 g/dl) during the acute phase or throughout the treatment is independently associated with a higher risk of cerebral infarction and a worse neurological prognosis at discharge and at the follow-up³. In this analysis, the overall prevalence of anemia was close to 40% and transfusion was indicated in one-third of the cases, with thresholds ranging from 7 g/dL to 10 g/dL. The scales used to assess outcomes (Modified Rankin Scale, Glasgow Outcome Scale and SF-36, among others) differed substantially between studies, which limited the direct comparability of their findings³.

From a pathophysiological point of view, the liberal transfusion strategy in scenarios with Hb values \geq 10 g/dL could improve oxygen delivery to the ischemic brain, reduce the metabolic load of the penumbral tissue and attenuate the consequences of vasospasm; however, it also increases blood viscosity, raises intraluminal arterial pressure and exposes the patient to transfusion reactions, fluid overload and immunomodulation⁴. On the contrary, the restrictive strategy (Hb 7-8 g/dL) decreases the risk of complications related to blood products and avoids an excessive increase in

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Date of reception: 20-03-2025
Date of acceptance: 23-05-2025
DOI: 10.24875/ANCE.M2500058

Available online: 04-11-2025
Arch Neurocién (Eng). 2026;31(1):42-43
www.archivosdeneurociencias.mx

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intracranial pressure, but it might not compensate for the oxygen demands of the injured brain, especially in older people, with established vasospasm or with cardiovascular comorbidities⁴. Thus, the decision to transfuse must integrate additional clinical variables: age, clinical predictive factors, timing of anemia (early vs. late), comorbidities, infectious complications or other concurrent hypoxemic lesions.

In view of this, the SAHARA trial⁷, whose objective was to study the effect of the liberal transfusion strategy (Hb level cut-off score ≤ 10 g/dL) compared to the restrictive strategy (Hb level cut-off score ≤ 8 g/dL), during the critical period after an aneurysmal SAH, randomly assigned 742 patients to the two groups. At 12 months, the rate of unfavorable neurological outcome did not differ significantly across the groups (RR, 0.88; 95% CI, 0.72-1.09; $p = 0.22$), nor were there any differences in quality of life, functionality or adverse events. The results suggest that for most cases, shifting the transfusion threshold 2 grams up or down does not modify global outcomes; however, the study did not fully stratify key factors (e.g., initial degree of anemia, advanced age or presence of vasospasm), so the conclusions should be interpreted with caution⁷.

Overall, the available evidence does not establish a single “safe” Hb value. It does indicate that when SAH is accompanied by anemia, the best results are observed with values maintained between 9 and 10 g/dL; this means that it is not necessary to transfuse to exceed 10 g/dL in all patients or to actively reduce those who already present 11-12 g/dL. Transfusion must be individualized, balancing clinical severity and the inherent risks of each strategy.

In Latin America and the Caribbean, strokes are a common scenario that requires the provision of highly specialized health services⁸, which can provide timely and quality care⁹. Complementarily, having a specific protocol that can generate additional benefits in the management of these patients is a valuable initiative⁹.

Especially considering the burden of disease caused by neurological disorders of vascular origin such as these^{8,9}. Therefore, it is necessary to promote new research adapted to the local context, which can explore the optimal Hb threshold for transfusion in this type of patient and in what conditions better outcomes are obtained¹⁰. This type of research ideas is consistent with research policies oriented to health needs. Therefore, they are relevant and pertinent for neuroscience centers and research groups.

Authors' contributions

All authors contributed equally to the conception, research and realization of this work.

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