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EDITORIAL

Advancing together: celebrating achievements and embracing new challenges

Avanzar juntos: celebrar los logros y afrontar nuevos retos

Antonio Arauz-Góngora

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As we step into the promising horizon of 2025, it is with great pride and gratitude that we introduce the first issue of *Revista Mexicana de Neurociencia* for this new year. Over the years, our journal has established itself as a vital platform for the dissemination of high-quality research in neuroscience, not only within Mexico but also across the global scientific community. This success is a testament to the collective efforts of our authors, reviewers, editorial team, and, most importantly, our readers.

A year of milestones

In recent years, *Revista Mexicana de Neurociencia* has experienced significant growth in both visibility and impact. We have seen an increase in submissions from researchers across Latin America, North America, Asia, and Europe, reflecting the broadening recognition of the journal as a reliable venue for cutting-edge neuroscientific work. Our metrics demonstrate a steady rise in readership and citations, indicators that speak to the quality of the work being published and its relevance in the field of neuroscience.

Among the achievements, we celebrate is the diversity of topics we have been privileged to showcase. From groundbreaking clinical studies to innovative basic science research, the journal continues to reflect the full breadth of neuroscience. This commitment to inclusivity and rigor in research has not only elevated our journal's standing but also strengthened our mission to advance scientific knowledge and foster collaboration among researchers.

The journal's adoption of improved digital platforms has further expanded accessibility. Researchers and practitioners worldwide now have streamlined access to our content, enabling faster dissemination of knowledge and greater global engagement. These steps forward are crucial as we aim to amplify the journal's influence on both academic and clinical practices.

Looking ahead: challenges and opportunities

While it is important to celebrate our accomplishments, we recognize that the landscape of scientific publishing continues to evolve, presenting both challenges and opportunities. As we move forward, *Revista Mexicana de Neurociencia* remains committed to adapting to these changes with a steadfast focus on quality, transparency, and innovation.

One of the most pressing challenges is maintaining rigorous peer review while accommodating the increasing volume of submissions. To address this, we will continue refining our editorial processes, enhancing efficiency without compromising the integrity of the scientific review process. The journal will prioritize timely feedback for authors while ensuring that only the highest-quality research finds its way to publication.

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Furthermore, we aim to broaden our scope to embrace interdisciplinary approaches that bridge neuroscience with fields such as artificial intelligence, genetics, novel neurological treatments, and cognitive sciences. These emerging areas hold the potential to revolutionize our understanding of the brain and its disorders, offering new avenues for exploration and collaboration. By fostering cross-disciplinary research, we can position *Revista Mexicana de Neurociencia* as a leader in integrative and translational neuroscience.

Another ongoing priority is ensuring the accessibility and inclusivity of our journal. As a platform serving the scientific community, we have a responsibility to support researchers at all stages of their careers. By offering opportunities for early-career scientists and promoting diversity in authorship, we will contribute to a richer and more equitable scientific dialog.

A call to action: growing together

Our achievements are a reflection of the collaborative spirit that defines the neuroscience community. As we embrace the challenges ahead, we extend a heartfelt invitation to all our readers, contributors, and colleagues: join us in strengthening and expanding *Revista Mexicana de Neurociencia*.

To our authors

Your work is the cornerstone of this journal. We encourage you to continue submitting your manuscripts – whether clinical studies, basic research, or reviews. Share with us your discoveries, your insights, and your innovations. Each submission contributes to the collective progress of neuroscience and inspires further inquiry.

To our reviewers

Your expertise, diligence, and commitment ensure that the journal upholds the highest standards of scientific excellence. Your invaluable contributions shape the quality and integrity of the work we publish, and we thank you for your continued efforts.

To our readers

You are the ultimate beneficiaries and ambassadors of the research we share. By engaging with our content, citing the work, and discussing it within your networks, you amplify the impact of the science we publish. We hope to continue earning your trust and interest with each new issue.

Conclusion: shaping the future of neuroscience

As we look toward the future, the mission of *Revista Mexicana de Neurociencia* remains clear: to serve as a dynamic and inclusive journal for the advancement of neuroscience. The challenges that lie ahead are not merely obstacles but opportunities to innovate, collaborate, and grow.

In this spirit, we reaffirm our commitment to excellence, accessibility, and scientific progress. We are excited about what 2025 holds for our journal and the field of neuroscience as a whole. Together, as authors, reviewers, and readers, we can shape a brighter future for neuroscience, one discovery at a time.

On behalf of the editorial board, I extend my sincere gratitude for your continued support and engagement. Let us work together to make *Revista Mexicana de Neurociencia* a leading force in the global neuroscience community.

With best wishes for a successful and productive year ahead,

Editor-in-Chief
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EDITORIAL

What about acupuncture in Parkinson's disease

La acupuntura en la enfermedad de Parkinson

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Acupuncture is a simple, convenient, cost-effective, safe, and effective treatment method. In this number of RMN, Chávez-Luévanos et al. describe the role of electroacupuncture (EA) as adjuvant therapy in the outcome of non-motor symptoms of patients with Parkinson's disease (PD)[1]. Twenty-five patients were treated with 10 sessions of EA reporting benefits in non-motor symptoms mainly in the mood/cognition domain. This manuscript given us the opportunity to review the role of acupuncture in PD.

In 1995, Ulm[2] from Germany called attention to the potential role of some physiotherapeutic measures in speech defects in Parkinsonian patients including laser acupuncture. These pioneer efforts were non-useful. At the same time, Li published a clinical analysis of patients with PD describing personal experiences in individual cases of PD patients treated by means of traditional chine medicine[3].

Zuang and Wang published their experience treating 29 patients with PD concluding in this small series the improvement in clinical symptoms and signs[4].

Western literature included information about alternative therapies in PD when Rajedran et al. reported alternative therapies in PD until 40% of patients, including EA (in 10%), vitamins, and herbs[5].

A non-blinded, pilot trial was conducted to assess the safety, tolerability, and efficacy of acupuncture for the symptoms of PD[6]. Eighty-five percent of patients reported subjective improvement of individual symptoms but the only objective improvement was in the sleep category, data different from Chavez-Luévanos study.

In the past 5 years, several case series have evaluated the efficacy of acupuncture in patients with PD. One case study documented a 75-year-old male patient with progressive PD symptoms, including limb tremors, rigidity, and bradykinesia. This patient received exclusive acupuncture therapy, demonstrating significant improvements in both motor and non-motor symptoms without the use of antiparkinsonian medication.

The mechanisms underlying the effects of acupuncture remain poorly defined. However, acupuncture can cause a variety of biological responses, as it has been clearly demonstrated by animal and human studies. Using a model mouse of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced PD, Kang et al. propose a neuroprotective effect of EA in PD[7]. However, there are no clinical trials of neuroprotection in PD.

Another case series investigated the effect of acupuncture on motor reaction time after auditory stimuli in PD patients. The results indicated a trend toward more pronounced improvements on the more affected side of the body, suggesting that acupuncture could enhance motor response efficiency in these patients.

Acupuncture may alleviate non-motor symptoms in PD through several mechanisms: modulation of neurotransmitter levels, regulation of immune responses, reduction of oxidative stress, and enhancement of brain electrical activity. By influencing neurotransmitter

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balance, acupuncture can improve mood and cognitive functions. Its immunomodulatory effects may decrease neuroinflammation, while antioxidant properties help mitigate neuronal damage. In addition, acupuncture's impact on brain electrical function can enhance sleep quality and autonomic regulation, collectively contributing to the amelioration of non-motor symptoms in PD patients[8-9].

In 2008, Soo Lee et al. made a systematic review about the effectiveness of acupuncture for PD[10]. A meta-analysis in this review about the comparison of acupuncture plus conventional drugs versus conventional drugs alone suggested additional benefits of acupuncture. In conclusion, the evidence for the effectiveness of acupuncture for treating PD is not convincing.

These studies suggest that acupuncture could serve as a complementary tool in managing PD, particularly in patients who cannot tolerate or decline conventional medication. However, more research with robust designs and larger cohorts is required to draw definitive conclusions about its efficacy and safety[11].

In conclusion, the available evidence has significant limitations, such as small sample sizes, short follow-up periods and a lack of standardisation in the evaluation scales used. These methodological shortcomings make it challenging to draw definitive conclusions about the efficacy of acupuncture in PD. Therefore, further studies with greater scientific rigor, including larger samples and longer follow-up durations, are necessary to better assess the impact of acupuncture in treating PD.

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ORIGINAL ARTICLE

The effects of auditory brainwave entrainment on the psychophysical health of healthcare programs students

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Abstract

Objective: *This pilot study aimed to explore the modulatory potential of auditory Brainwave Entrainment (aBWE) on the emotional and physical well-being of college students enrolled in healthcare programs.* **Methods:** *All enrolled participants from the Seminole State College received the same intervention of daily aBWE sessions over a 12-week period. Evaluations were conducted at the outset (1st week), midpoint (6th week), and conclusion (12th week), utilizing four distinct questionnaires: the Pittsburgh quality of sleep index (PQSI), the perceived stress scale (PSS), the generalized anxiety disorder 7 (GAD-7), and the profile of mood States (POMS).* **Results:** *Twenty-nine participants (mean age of 39.41) completed the study. In the PQSI, reductions were observed in Subjective Sleep Quality ($p = 0.0039$), Sleep Latency ($p = 0.0454$), and the Global Score ($p = 0.0175$). The PSS indicated significant reductions in stress after 6 weeks ($p = 0.0402$) and 12 weeks ($p = 0.0006$). The GAD-7 scale revealed a significant reduction in anxiety by the final evaluation ($p < 0.0001$). Similarly, the POMS questionnaire showed significant decreases in Tension at both midpoint ($p = 0.0259$) and final evaluations ($p = 0.0001$), along with reductions in Total Mood Disturbance (midpoint $p = 0.0485$, final $p < 0.0001$). In addition, significant improvements were noted in Depression ($p = 0.0314$), Anger ($p = 0.0454$), Vigor ($p = 0.0297$), Fatigue ($p = 0.0002$), and Confusion ($p = 0.0019$) by the final evaluation.* **Conclusions:** *We conclude that aBWE presents a promising intervention for enhancing sleep quality, mood states, and reducing stress and anxiety, without any reported adverse effects, indicating its safety.*

Keywords: *Brainwave entrainment. Neuromodulation. Anxiety. Mood. Sleep. Stress.*

Efectos de la inducción auditiva de ondas cerebrales en la salud psicofísica de los estudiantes de programas de atención sanitaria

Resumen

Objetivo: *Este estudio piloto tuvo como objetivo explorar el potencial modulador del arrastre de ondas cerebrales auditivas (aBWE) en el bienestar físico y emocional de estudiantes universitarios matriculados en programas de atención sanitaria.* **Métodos:** *Todos los participantes inscritos en el Seminole State College recibieron la misma intervención de sesiones diarias de aBWE durante un período de 12 semanas. Las evaluaciones se llevaron a cabo al inicio (1.ª semana), a la mitad*

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(6.ª semana) y al final (12.ª semana), utilizando cuatro cuestionarios distintos: el Índice de Calidad del Sueño de Pittsburgh (PQSI), la Escala de Estrés Percibido (PSS), la Escala de Ansiedad Generalizada (GAD-7) y el Perfil de Estados de Ánimo (POMS). **Resultados:** *Veintinueve participantes (edad media de 39,41 años) completaron el estudio. En el PQSI, se observaron reducciones en la Calidad Subjetiva del Sueño (p = 0,0039), la Latencia del Sueño (p = 0,0454) y la Puntuación Global (p = 0,0175). La PSS indicó reducciones significativas del estrés después de 6 semanas (p = 0,0402) y 12 semanas (p = 0,0006). La escala GAD-7 reveló una reducción significativa de la ansiedad en la evaluación final (p < 0,0001). El cuestionario POMS mostró disminuciones significativas en la Tensión tanto en la evaluación intermedia (p = 0,0259) como en la evaluación final (p = 0,0001), junto con reducciones en la Alteración Total del Estado de Ánimo (evaluación intermedia p = 0,0485, final p < 0,0001). Además, se observaron mejoras significativas en Depresión (p = 0,0314), Ira (p = 0,0454), Vigor (p = 0,0297), Fatiga (p = 0,0002) y Confusión (p = 0,0019) en la evaluación final.* **Conclusiones:** *Concluimos que aBWE presenta una intervención prometedora para mejorar la calidad del sueño, los estados de ánimo y reducir el estrés y la ansiedad, sin ningún efecto adverso reportado, lo que indica su seguridad.*

Palabras clave: *Arrastre de ondas cerebrales. Neuromodulación. Ansiedad. Estado de ánimo. Sueño. Estrés.*

Introduction

Mental disorders are on the rise globally, significantly affecting societal well-being. They stand as a leading cause of disability, leading to substantial functional impairments and diminished quality of life. The causes of mental disorders include both biological factors and social or psychological factors. Depression and anxiety, due to their high prevalence, contribute more to the overall disease burden than more severe mental illnesses, such as schizophrenia and bipolar disorder, as noted by researchers[1]. Despite a decrease in the age-standardized burden of mental disorders over the past three decades, Wu and colleagues[1] reported an increase in both the number of new cases and deaths attributed to mental disorders globally, a trend expected to continue. Notably, the incidence of mental disorders tends to be higher in women than in men[1].

Published studies with college health students have shown the prevalence of depression, anxiety, and stress among them, impairing their quality of life[2-4]. Hence, there's a pressing need to find simple interventions to improve such issues in this population. This is especially pertinent considering that health professionals already often face work overload and stressful conditions, frequently experiencing anxiety, depression, insomnia, and a lower quality of life[5-7].

One potential intervention is brainwave entrainment (BWE), which consists of the induction of specific physiological and psychological states through external auditory or visual stimuli at certain frequency bands[8]. Research exploring various frequencies has indicated improvements in anxiety across different contexts[9-11], stress reduction[12-14], sleep enhancement[15,16], and alleviation of depressive symptoms[17]. Moreover, BWE is recognized as a safe and cost-effective alternative[12,18,19]. Therefore, this pilot study was designed to explore the impact of BWE on the emotional and physical well-being of college students in healthcare programs.

Methods

Study design

This was a pilot study that involved college students from Seminole State College (Florida, USA) as participants. It was conducted in a continuous manner from July 2022 until December 2023. Students were informed about the study through e-mail and invited to participate. The inclusion criteria were individuals over 18 years old and enrolled in healthcare programs (Nursing, Respiratory Care, and other Related Disciplines). Participants with hearing disabilities, seizure disorders, epilepsy, or previous experience with BWE were excluded. This study was conducted following ethical standards and the principles from the Declaration of Helsinki. Furthermore, the Seminole State College Ethics Committee approved this study. Participation was entirely voluntary and carried out only after obtaining a signed Informed Consent Form.

Procedure

After enrollment, the study spanned 12 weeks. Participants began by completing a baseline evaluation of the questionnaires online. Subsequently, they participated in daily 20-min auditory BWE (aBWE) sessions (at home) throughout the study duration. Two additional evaluations were conducted online through Google Forms at the midpoint (6th week) and at the conclusion (12th week). Additional emails were frequently sent to increase adherence.

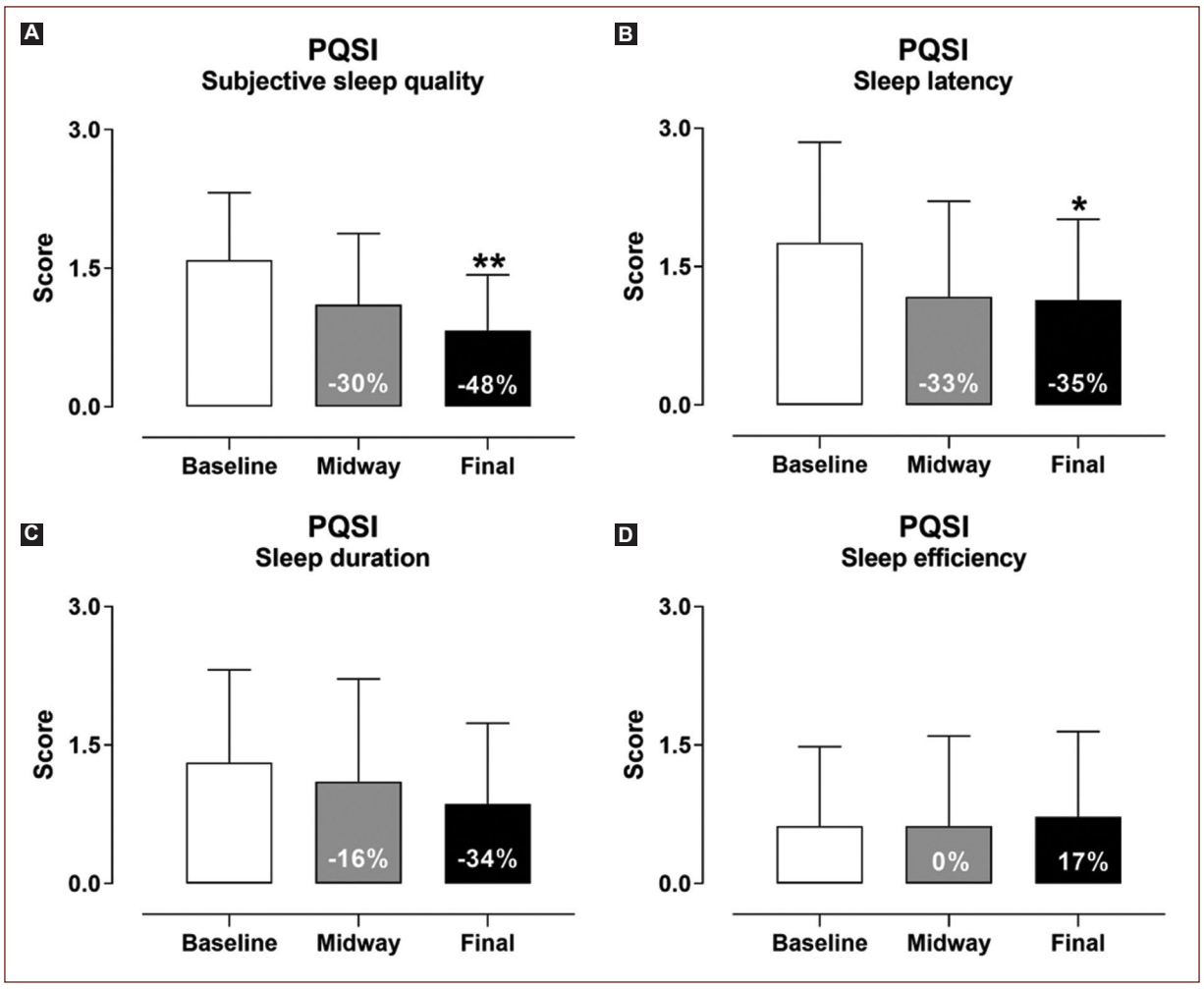

Figure 1. A-D: 12 weeks of Audio Brainwave Entrainment sessions significantly improved the Subjective sleep quality and Sleep latency components. Each point represents the mean of 29 participants and vertical lines show the mean with SD.
*Significant difference of $p < 0.05$ when compared baseline evaluations. The % value is in relation to the baseline. Statistical analysis was performed by Friedmans' test followed by Dunn's multiple comparison test. PQSI: Pittsburgh Quality of Sleep Index; SD: standard deviation.

Audio BWE

Participants engaged in daily 20-min aBWE sessions at home using the BrainTap APP (New Bern, NC, USA) for 12 weeks. The sessions incorporated Binaural Beats and Isochronic Tones designed to entrain brainwave frequencies in specific ranges: α (8-12 Hz) for relaxation and focus, θ (4-7 Hz) for deep relaxation and meditation, and Δ (0.5-3 Hz) for deep sleep and recovery. Binaural Beats were delivered by presenting slightly different frequencies to each ear, which the brain interprets as a single auditory tone, while Isochronic Tones used evenly spaced, sharp sound pulses to synchronize brainwave activity without requiring headphones. However, it was recommended that participants use stereo headphones to maximize the effectiveness of the Binaural Beats.

The sessions were pre-loaded in the app, allowing participants to simply select the session and press play, making it easy to follow the protocol without any additional setup. Participants did not report any issues or difficulties in accessing the app or selecting and playing the sessions, indicating a user-friendly experience throughout the intervention period.

Outcomes evaluation

To assess sleep quality, we chose the Pittsburgh Quality of Sleep Index (PQSI). This self-assessment tool evaluates seven areas (e.g., subjective sleep

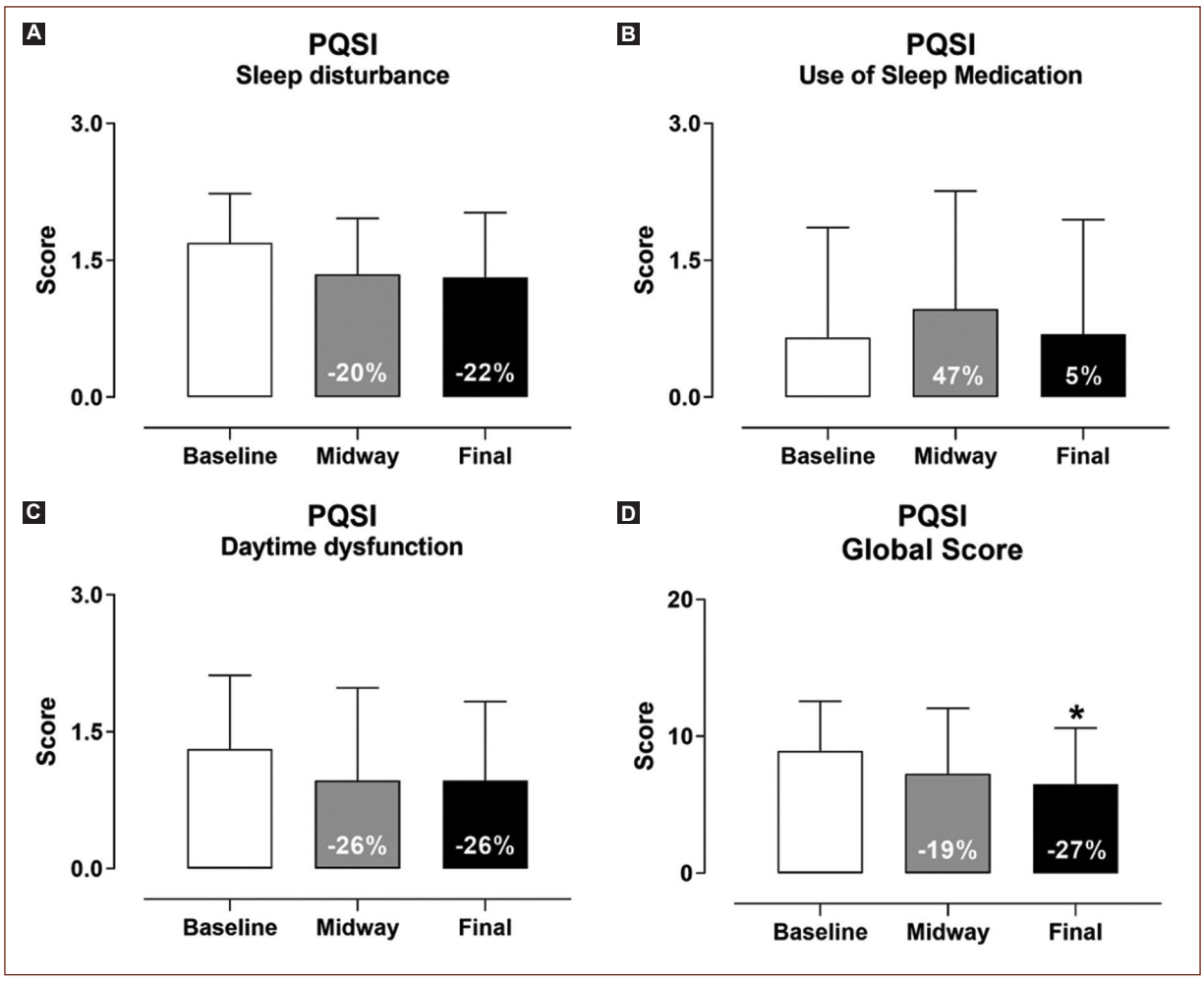

Figure 2. A-D: 12 weeks of Audio Brainwave Entrainment sessions significantly improved the PQSI Global Score. Each point represents the mean of 29 participants and vertical lines show the mean with SD.
*Significant difference of $p < 0.05$ when compared baseline evaluations. The % value is in relation to the baseline. Statistical analysis was performed by Friedmans' test followed by Dunn's multiple comparison test. PQSI: Pittsburgh Quality of Sleep Index; SD: standard deviation.

quality, sleep latency, and daytime dysfunction) over the past month, using a 0-3 scale, with higher scores indicating poorer sleep. The PSQI has shown strong internal consistency and reliability across diverse populations[20,21].

For stress measurement, we used the perceived stress scale (PSS), which assesses stress-related feelings and thoughts over the past month on a 5-point scale (0-4 question). Higher scores suggest increased stress. The PSS-10 has demonstrated good internal consistency (Cronbach's α: 0.71-0.91) and test-retest reliability (typically above 0.70)[22].

To evaluate anxiety levels, we chose the generalized anxiety disorder 7-item (GAD-7) scale. This tool scores 7 items on a 0-3 scale, with cut-off points of 5, 10, and 15 indicating mild, moderate, and severe anxiety. With a threshold of 10, the GAD-7 shows high sensitivity (89%) and specificity (82%) for diagnosing GAD and can also screen for other anxiety disorders[23].

The profile of mood states (POMS) questionnaire was used to assess specific mood states through 65 descriptors rated on a 5-point scale. The POMS has high internal consistency, with Cronbach's α ranging from 0.82 to 0.90 across its subscales[24].

Statistical analysis

We submitted the data to the Shapiro–Wilk test to assess normality. Results were displayed as the mean

plus standard deviation for each evaluation. For datasets failing the normality test, the Friedmans' test was conducted, succeeded by Dunn's multiple comparison test for detailed analysis. In cases where data met normality criteria, a one-way analysis of variance was performed, followed by Tukey's multiple comparison test to evaluate the differences between evaluations. A value of $p < 0.05$ was deemed to indicate statistical significance. Graph Pad Prism® (version 8.0) served as the analytical software for this process. In addition, percentage differences based on the means from the evaluations were calculated utilizing Microsoft Excel®.

Results

Initially, 116 participants were enrolled in the study; however, only 29 completed all three evaluations and were included in the analysis. Of these, 28 were female (sex determined at birth), with an average age of 39.41 years. Some participants dropped out for personal reasons, but the majority was not included in the analysis due to not answering all evaluations in the appropriate time frame.

Quality of sleep

The PQSI revealed statistically significant improvements in sleep quality by the study's conclusion. Specifically, reductions in scores for Subjective Sleep Quality (Fig. 1) ($p = 0.0039$, Fig. 1A) and Sleep Latency ($p = 0.0454$, Fig. 1B) were noted when comparing final evaluation results to baseline values, as depicted in Fig. 1. In addition, as shown in figure 2, there was a significant decrease in the Global Score ($p = 0.0175$, Fig. 2D), indicating an overall improvement in sleep quality since a higher score on this scale is indicative of poorer sleep quality. However, it is possible to observe that there were no statistically significant changes in Sleep Disturbance (Fig. 2A), Use of Sleep Medication (Fig. 2B), or Daytime Dysfunction (Fig. 2C).

Stress

The PSS demonstrated that participants experienced statistically significant decreases in perceived stress following 6 weeks ($p = 0.0402$) and 12 weeks ($p = 0.0006$) of aBWE sessions, as illustrated in figure 3. On this scale, a higher score corresponds to increased perceived stress, indicating that the reductions in scores reflect an improvement in stress levels among the participants.

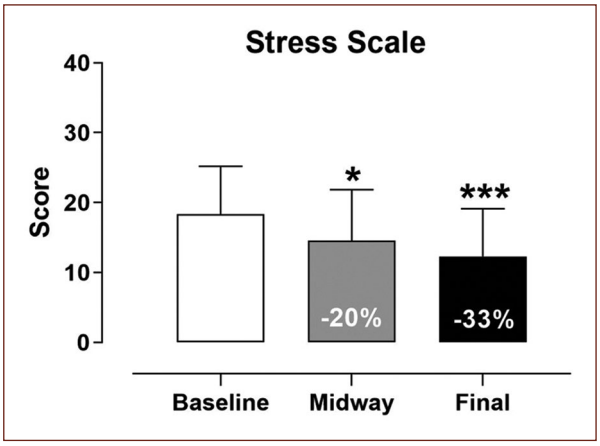

Figure 3. After 6 and 12 weeks of Audio Brainwave Entrainment sessions participants had lower perceived stress. Each point represents the mean of 29 participants and vertical lines show the mean with SD.
*Significant difference of $p < 0.05$ when compared baseline evaluations. The % value is in relation to the baseline. Statistical analysis was performed by RM one-way analysis of variance followed by Tukey's multiple comparison test. RM: repeated measures; SD: standard deviation.

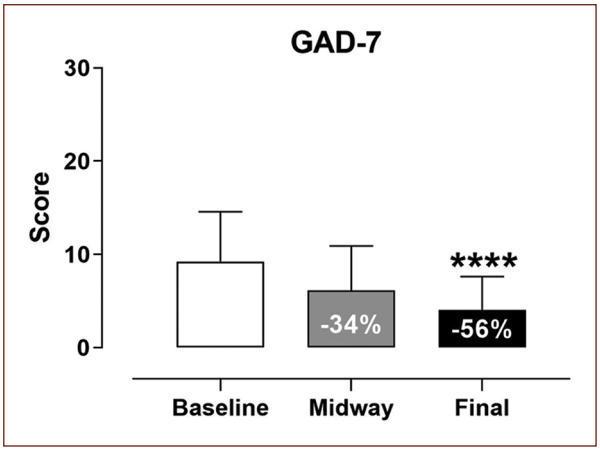

Figure 4. 12 weeks of Audio Brainwave Entrainment sessions significantly reduced participant's anxiety. Each point represents the mean of 29 participants and vertical lines show the mean with SD.
*Significant difference of $p < 0.05$ when compared baseline evaluations. The % value is in relation to the baseline. Statistical analysis was performed by Friedmans' test followed by Dunn's multiple comparison test. SD: standard deviation.

Anxiety

The GAD-7 scale results indicated a statistically significant decrease in generalized anxiety levels in the final evaluation compared to the baseline, with a

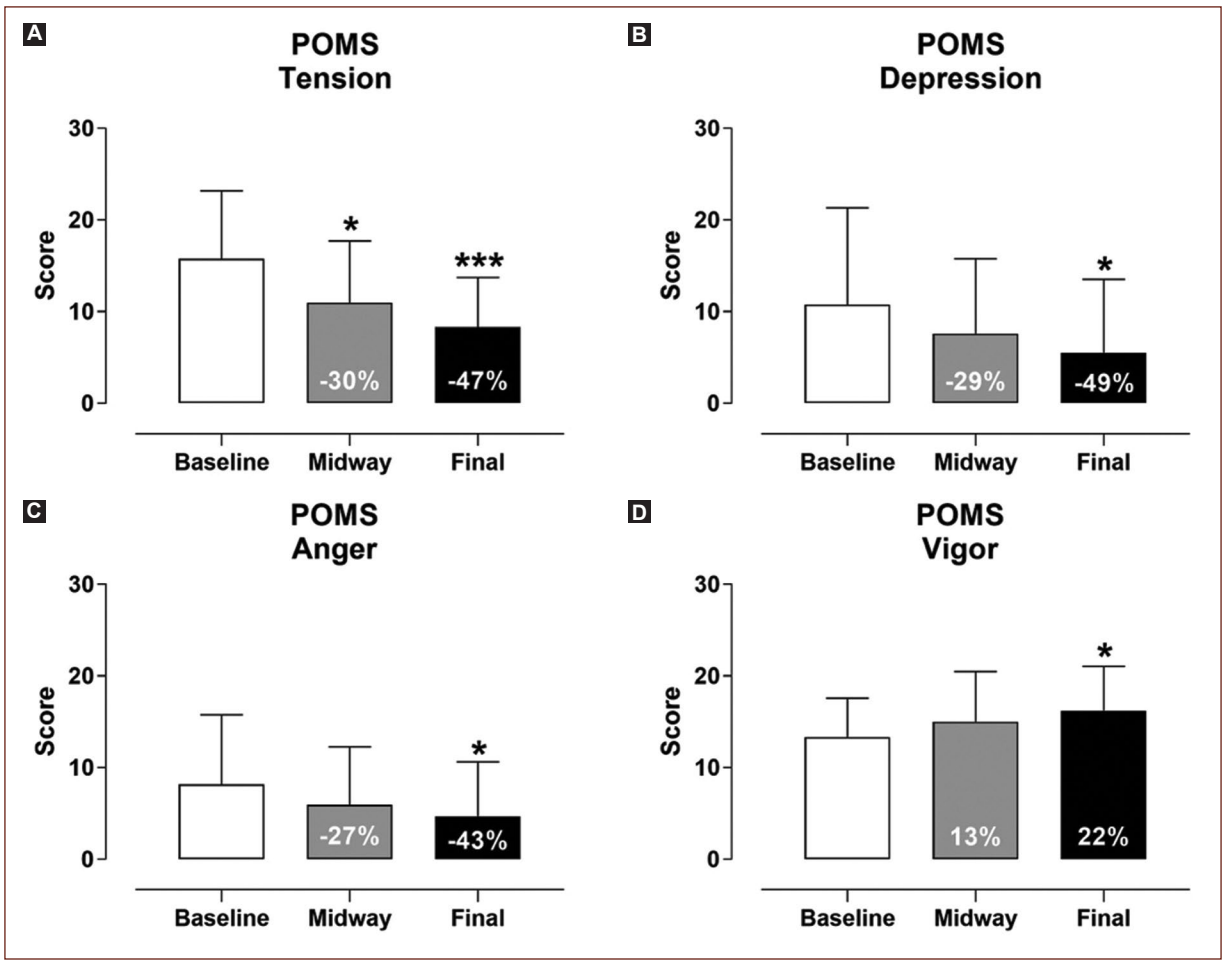

Figure 5. A-D: 6 and 12 weeks of Audio Brainwave Entrainment sessions significantly changes participants mood states. Each point represents the mean of 29 participants and vertical lines show the mean with SD.
*Significant difference of $p < 0.05$ when compared baseline evaluations. The % value is in relation to the baseline. Statistical analysis was performed by Friedmans' test followed by Dunn's multiple comparison test in sub-scales **A, B,** and **C**, and by RM one-way analysis of variance followed by Tukeys multiple comparison test in sub-scale **D.** POMS: Profile of Mood States; RM: repeated measures; SD: standard deviation.

$p < 0.0001$, as depicted in figure 4. This reduction signifies a notable improvement in anxiety symptoms among participants by the end of the study.

Mood states

The POMS questionnaire results revealed statistically significant improvements in mood states. Specifically, reductions in Tension were observed both at the midpoint (Fig. 5) ($p = 0.0259$, Fig. 5A) and in the final evaluations ($p = 0.0001$, Fig. 5A), alongside reductions in Total Mood Disturbance (midpoint $p = 0.0485$, final $p < 0.0001$, Fig. 6C). The final evaluation also showed significant improvements in several mood dimensions, including Depression ($p = 0.0314$, Fig. 5B), Anger ($p = 0.0454$, Fig. 5C), Vigor ($p = 0.0297$, Fig. 5D), Fatigue (Fig. 6) ($p = 0.0002$, Fig. 6A), and Confusion ($p = 0.0019$, Fig. 6B). These findings indicate that the aBWE sessions were effective in positively altering mood states among the participants.

Discussion

Our study hypothesized that aBWE could positively affect sleep and mood while reducing anxiety and stress among college students in healthcare programs (Nursing, Respiratory Care, and other Related Disciplines). This hypothesis was confirmed through significant improvements observed in all measured outcomes after 12 weeks of training. The students improved their

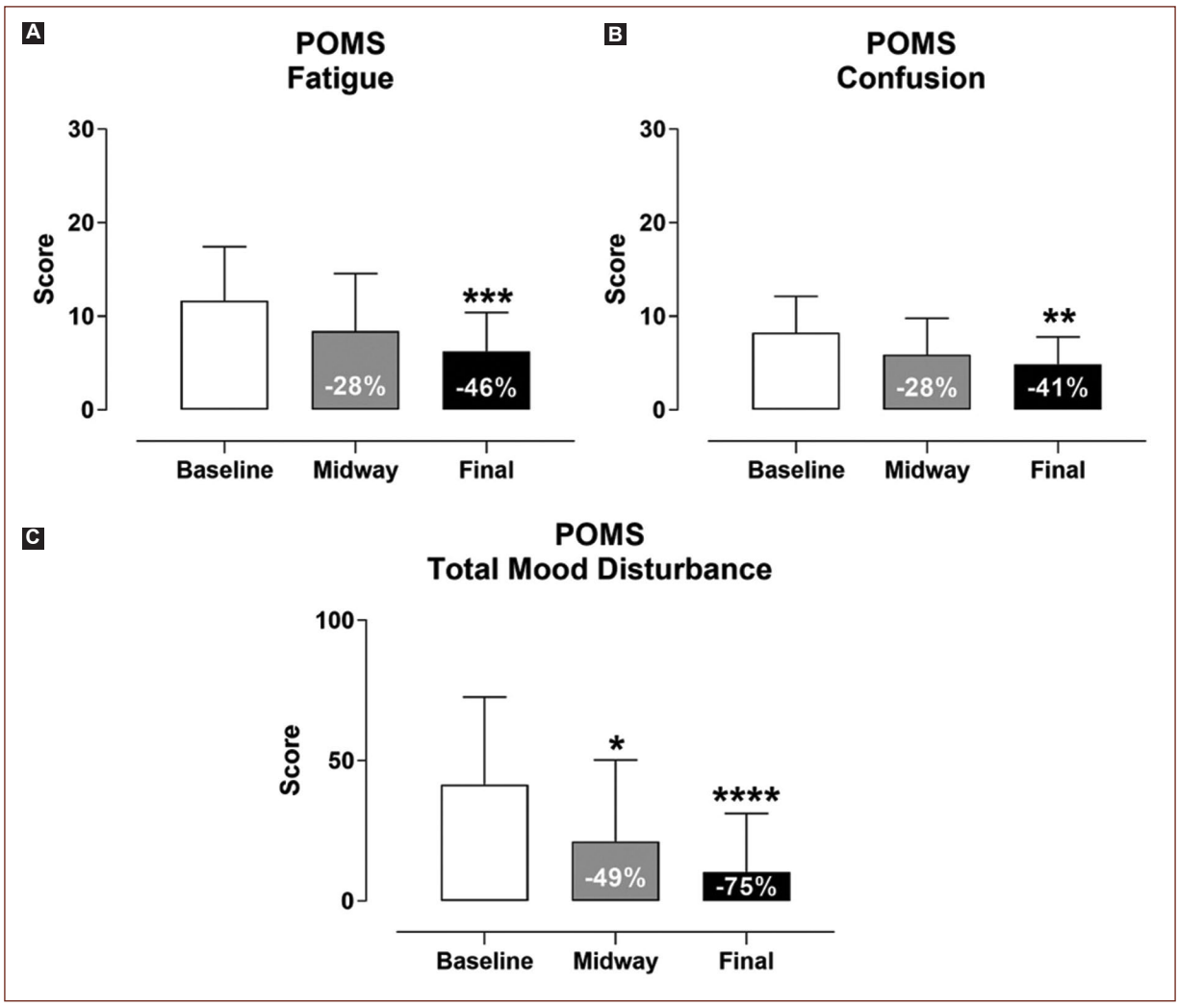

Figure 6. A-D: 6 and 12 weeks of Audio Brainwave Entrainment sessions significantly changes participants' mood states. Each point represents the mean of 29 participants and vertical lines show the mean with SD.
*Significant difference of $p < 0.05$ when compared baseline evaluations. The % value is in relation to the baseline. Statistical analysis was performed by Friedmans' test followed by Dunn's multiple comparison test. POMS: Profile of Mood States; RM: repeated measures; SD: standard deviation.

mood, quality of sleep, while also reducing anxiety and stress.

Our findings align with existing literature, such as Dabiri and colleagues[25] that demonstrated improvements in sleep parameters and mood with 90 min of exposure to Delta Binaural beats[25]. However, their study only observed improvements in anxiety and anger, while in ours there were also changes in other mood parameters such as tension and depression. Maybe these differences could be attributed to the fact that their treatment period was 1 week, while ours was 12 weeks, suggesting that more improvements are obtained with long-term exposure. Abeln and colleagues[26] showed in elite soccer players enhancements in sleep quality, wakefulness, and motivation by 6 weeks of α, Theta, and Delta binaural beats during sleep[26].

Further studies have also corroborated the efficacy of Audio Stimulation in reducing anxiety and improving mood across various frequency bands, with combinations of α-Theta-Gamma[27] or Theta alone[28]; also under different conditions, such as surgical procedures[10-13,29-31].

A meta-analysis by Garcia-Argibay et al.[31] concluded that Binaural-beat stimulation could impact cognition, anxiety, and pain perception without needing prior training, indicating a positive correlation between exposure time and effect sizes without leading to habituation. Despite

the heterogeneity and sometimes unclear frequency parameters in these studies, there is growing evidence supporting binaural beats' influence on psychophysiological states[31]. Aparecido-Kanzler et al.[32] explained that brainwave activity results from the bioelectric interactions among neuronal networks, suggesting that BWE can modulate mind states[32].

Another important observation of our study was that there were no adverse events reported by the participants during the entire study period. This shows that aBWE is not only a non-invasive intervention but also safe and feasible to perform for a longer period. Especially, because many improvements were achieved and it required only 20 min of practice, which is easy to integrate into an individual's routine, which is very important when it comes to students and health professionals who tend to have busy daily routines. As previously mentioned, poor sleep quality, anxiety, stress, and fatigue impose a high burden in health professionals and can negatively impact not only their quality of life but also their work performances, posing risks to patients[6]. Therefore, integrating 20 min of aBWE in work settings or in professionals' routines could be a great aid in mitigating these outcomes, since we also observed in our study a reduction in parameters such as fatigue, confusion, and an increase in vigor. Even though there could be a bias of these scales being self-reported, it is important to consider how the individual perceives itself.

Notably, our study predominantly involved female participants with an average age of approximately 39.41 years. This is a limitation because it restricts the generalizability of research findings and their applicability to clinical practice. However, it is also relevant because hormonal changes can increase the risk of sleep disturbances and disorders, with studies showing a decline in nocturnal melatonin secretion with age, accompanied by an increase in primary sleep disorders among post-menopausal women[33]. The observed improvements in sleep and mood among this demographic underscore the potential of aBWE as a therapeutic tool for enhancing women's health and quality of life across different life stages.

Our study faced several limitations, including a small sample size and the absence of a control or placebo group to definitively attribute the observed improvements to aBWE. Another issue was the high percentage of sample loss (75%, n = 87), which could be attributed to participants forgetting to complete the questionnaires on the indicated dates as they were answered online, which suggests the need for closer monitoring by researchers and more frequent individual reminders to prevent this from happening. In addition, the inability to verify the daily completion of sessions and the influence of sleep or mood medications taken by some participants, pose challenges to the study's conclusions. A randomized controlled trial, with a larger sample size and control of medications taken by participants, would be ideal to confirm the findings from our study.

Conclusion

Despite limitations presented in our study, the significant improvements noted –coupled with the lack of adverse events reported– suggest that daily sessions of aBWE represent a promising, non-invasive intervention for improving sleep, mood states, and reducing stress and anxiety among healthcare students. To solidify these findings, further research involving larger randomized controlled trials with placebo and control groups is recommended.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered 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 patients, and received approval from the Ethics

Committee. 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 was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Electroacupuncture therapy on non-motor symptoms of patients with Parkinson's disease: results of a pilot study

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Abstract

Objective: *This study aims to assess the effect of electroacupuncture (EA) on non-motor symptoms in Parkinson's disease (PD) patients as a primary goal and motor symptomatology as a secondary outcome.* **Methods:** *Twenty-five patients were enrolled in a non-controlled pilot study that involved a 10-session EA intervention in 16 acupoints, applied 3 times a week for 4 weeks. Motor, non-motor, cognitive, and quality of life evaluation were conducted before intervention and 7 days after concluding the last EA session through MDS-Unified PD rating scale (MDS-UPDRS), Non-motor Symptom Scale (NMSS), montreal cognitive assessment (MoCA), and PD questionnaire (PDQ-8), respectively.* **Results:** *Patients showed significantly lower scores in the MDS-UPDRS Part II (7.0 ± 5.7 vs. 10.5 ± 7.6, p = 0.046) and Part III (14.0 ± 8.6 vs. 23.1 ± 13.9, p = 0.002), and NMSS total score (35.2 ± 26.6 vs. 54.6 ± 32.5, p = 0.004) in the post-intervention evaluation, with mood/cognition domain of the NMSS being the only significantly affected by treatment. MoCA total score increased after the intervention (24.2 ± 4.5 vs. 21.6 ± 4.3, p = 0.020), while PDQ-8 scores were not significantly affected by the intervention.* **Conclusions:** *Non-motor and motor symptomatology were significantly improved after concluding a 10-session EA therapy. Mood and cognitive disorders were the most positively affected by the intervention. Evaluation of the long-term effects of EA in PD is further needed.*

Keywords: *Acupuncture. Parkinson's disease. Complementary therapy. Integrative medicine. Non-motor symptoms. Quality of life.*

Efecto de la electroacupuntura en los síntomas no-motores de pacientes con Enfermedad de Parkinson: resultados de un estudio piloto

Resumen

Objetivos: *Evaluar el efecto de la electroacupuntura (EA) sobre los síntomas no motores en pacientes con Enfermedad de Parkinson como objetivo principal y la sintomatología motora como resultado secundario.* **Métodos:** *Se incluyeron 25 pacientes en un estudio piloto no controlado cuya intervención implicó 10 sesiones de EA en 16 acupuntos, aplicada 3 veces por semana durante 4 semanas. Se realizó una evaluación motora, no motora, cognitiva y de calidad de vida antes de la intervención y siete días después de concluir la última sesión de EA mediante la escala unificada de la enfermedad de Parkinson modificada por la Sociedad de Trastornos del Movimiento (MDS-UPDRS), la escala de síntomas no motores (NMSS), Test Cognitivo de Montreal (MoCA) y cuestionario sobre la enfermedad de Parkinson 8 (PDQ-8), respectivamente.* **Resultados:** *En la evaluación posterior a la intervención, los pacientes mostraron scores significativamente menores en la*

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Parte II (7.0 ± 5.7 vs. 10.5 ± 7.6, p = 0.046) y la Parte III (14.0 ± 8.6 vs. 23.1 ± 13.9, p = 0.002) de la MDS-UPDRS y en el score total del NMSS (35.2 ± 26.6 vs. 54.6 ± 32.5, p = 0.004), siendo el dominio del estado de ánimo/cognición del NMSS el único afectado significativamente. El score total del MoCA aumentó después de la intervención (24.2 ± 4.5 vs. 21.6 ± 4.3, p = 0.020), mientras que los scores del PDQ-8 no se vieron afectados significativamente. **Conclusiones:** *La sintomatología motora y no motora mejoró significativamente después de concluir una terapia de EA de 10 sesiones.*

Palabras clave: *Acupuntura. Enfermedad de Parkinson. Terapia complementaria. Medicina integrativa. Síntomas no motores. Calidad de vida.*

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, with morbidity and mortality increasing in the last 25 years[1,2]. Regarding prognosis, it is expected that its incidence in the general population continues to grow[3], which has raised awareness toward an early and integrative diagnosis.

In the absence of a disease-modifying drug and the development of motor complications arising from standard pharmacological treatment with levodopa, patients with PD often seek complementary and alternative therapies. Acupuncture is the most commonly employed[4,5], with reports of up to 50% of patients using this modality.[6]

Several studies have been conducted assessing the effect of acupuncture in PD symptomatology, with a special focus on motor symptoms[7]. Two meta-analyses showed inconclusive results regarding acupuncture effectiveness in PD[7,8], with sample size being a major limitation in most included studies. Another limitation of these studies is their low quality, which limits the applicability of their results. A more recent meta-analysis demonstrated a positive effect of acupuncture in PD symptomatology, suggesting a potential role as a complementary therapy alongside symptomatic treatment[9]. Nonetheless, evaluation of PD symptomatology was focused on motor symptomatology, with no emphasis on acupuncture's effect on non-motor symptoms.

Scarce studies have evaluated electroacupuncture (EA) therapy on non-motor and motor symptoms in PD patients[10]. Specifically in Mexico, no studies were found that reported acupuncture or EA use in PD patients. We aimed to evaluate EA effect on non-motor symptomatology as a primary outcome and motor symptoms and quality of life as a secondary outcome in PD patients through a 10-session EA intervention.

Material and methods

Consecutive patients from the neurology outpatient clinic of our University with idiopathic PD diagnosis according to UK PD Society Brain Bank clinical criteria[11] were recruited between September 2019 and January 2020 for a 10-session EA therapy intervention.

This study was approved by the local Research Ethics Committee of our institution (NR 19-00004). All patients signed informed consent for inclusion in this study, all in compliance with the Declaration of Helsinki.

Inclusion and exclusion criteria

Inclusion criteria involved: patients > 18 years, any gender, and PD diagnosis according to UK PD Society Brain Bank clinical criteria. Exclusion criteria included: acupuncture exposure in the previous 4 months, receiving anticoagulant treatment or having blood dyscrasias, prolonged fasting (> 6 h), and having a cardiac pacemaker. Among the withdrawal criteria: patients who did not assist for ≥ 2 acupuncture sessions, without any clinical evaluation, or presented inflammatory reaction or infection in any acupunctural sites were withdrawn from the study.

Recruitment

During follow-up consultation, PD patients who fulfilled the inclusion criteria were invited to participate in the study, explaining EA therapy's objectives and possible side effects. Patients that accepted and signed informed consent were evaluated, where demographics and clinical assessments through Non-Motor Symptom Scale (NMSS), Movement Disorder Society-unified PD rating scale (MDS-UPRDS), Hoehn and Yahr (HY), Montreal Cognitive Assessment (MoCA), and PD questionnaire-8 (PDQ-8) were registered. After this, they were scheduled to attend their initial EA session.

Intervention

EA was conducted through 10 sessions, each lasting 30 min, three sessions per week. A total of 16 acupoints

were used for all patients according to Chinese Traditional Medicine[12,13] (see Supplementary Material for acupunctural sites used). Physicians with a master's degree in Chinese Traditional Medicine with at least 5 years of clinical experience performed the intervention.

With the patient in a prone position, asepsis was performed with alcohol 96% to later proceed with needle colocation. The sterile needles used (Natural E-M Medical Treatment and Electron (Suzhou) Co., Ltd., China) are made from surgical stainless steel with a silicon guide tube. Needle diameter and length were 0.22 mm and 40 mm, respectively. The depth and direction in which the needles were inserted varied based on the acupoint, the maximum depth was no > 25 mm. The effective depth of needling was determined when the DeQi response was obtained[14]. This is described by patients as aching or soreness, numbness, distention, or heaviness, and felt by acupuncturist as tense and tight needle grasp[14]. Electrical stimulation was applied with a KWD808-I electrostimulation device in a dense-dispersed mode in the EX-HN-1 Sishencong points, with a frequency of 2 Hz and intensity depending on the patient's tolerance. The needles remained inserted for 20 min and were later removed, ending the session. The study adhered to the revised standards for reporting interventions in clinical trials of acupuncture.

Post-intervention assessment

The patients were scheduled to attend the neurology outpatient clinic 7 days after concluding the last EA session (session 10). A neurologist expert in movement disorders evaluated non-motor, motor, cognitive function, and quality of life through the NMSS, MDS-UPDRS, MoCA, and PDQ-8, respectively. The estimated time for outcome evaluation was approximately 60 min, depending on the severity of the disease. Moreover, any changes in pharmacological treatment that occurred during sessions were documented.

Sample size calculation

We used a formula for estimating the mean in a population. No other studies have evaluated acupuncture's effect on non-motor symptoms through NMSS; however, two studies have shown a decrease of 21-50% in the UPDRS Part I score, which assesses non-motor symptoms, after acupuncture therapy[15,16]. Using the mean NMSS score (52.6 ± 47.0) of our registry of treated PD patients from the neurology outpatient clinic of our University Hospital (total n = 105), we set a 38% decrease in the baseline value of NMSS with EA therapy as effective, with a precision of ±13.3 points. Thus, a sample of 40 patients should provide approximately 80% test power at a confidence level of 95% and considering a dropout rate of 10%.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences computer program (SPSS version 22.0, SPSS Inc., Chicago, Illinois, USA). Data were tested for normality using the Shapiro–Wilk test, and continuous variables were thus expressed as mean ± standard deviation (SD) or as median (range), and categorical variables as percentages. A paired t-test was conducted to evaluate differences between parametric measures in the pre-and post-intervention evaluations, whereas the Wilcoxon test was conducted for non-parametric variables. A $p < 0.05$ was considered significant.

Results

Baseline characteristics

Forty patients were initially invited to participate in the study protocol, with only 30 accepting and 25 initiating the EA sessions. Three of these 25 patients were withdrawn from the protocol as they discontinued the therapy, stating lack of time. The rest (22 patients) concluded the therapy sessions and clinical evaluation. No more patients could be recruited due to COVID-19 pandemic contingency.

Regarding baseline characteristics, 11 (50%) patients were male; the mean age of the whole sample was 60.7 ± 11.7 years, with a mean age at diagnosis of 53.6 ± 12.2 years. Most patients corresponded to a tremor motor subtype at onset. Mean H and Y were 2.2 ± 0.8, the mean MDS-UPDRS score was 32.3 ± 11.7, the mean NMSS score was 54.6 ± 32.5, and the mean MoCA score was 21.6 ± 4.3. During the intervention period, no modifications to the pharmacological treatment were reported among patients. The rest of the baseline characteristics are shown in table 1.

Acupuncture effect on non-motor symptomatology

When comparing NMSS and MDS-UPDRS Part I scores between pre-and post-intervention evaluations,

Table 1. Baseline characteristics of the total population

Variable	n = 22
Gender (%)	
Male	11 (50.0)
Female	11 (50.0)
Age, mean ± SD (years)	60.7 ± 11.7
Comorbidities (%)	
Arterial hypertension	5 (22.7)
Dyslipidemia	9 (40.9)
Type 2 diabetes mellitus	6 (27.2)
Cardiovascular disease	10 (45.5)
Familiar history of PD (%)	17 (77.2)
Parkinson's disease features	
Years of evolution, mean ± SD	7.1 ± 5.1
Age at onset, mean ± SD	53.6 ± 12.2
Motor subtype at onset	
Tremor (%)	14 (63.6)
Rigidity-bradykinesia (%)	5 (22.7)
Levodopa equivalent daily dose, mean ± SD (mg)	781.7 ± 399.9
Hoehn and Yahr, mean ± SD	2.2 ± 0.8
MoCA, mean ± SD	21.6 ± 4.3
MDS-UPDRS total score, mean ± SD	32.3 ± 11.7
NMSS, mean ± SD	54.6 ± 32.5
PDQ-8, mean ± SD	8.0 ± 7.1

SD: standard deviation; PD: Parkinson's disease; MoCA: Montreal Cognitive Assessment; MDS-UPDRS: Movement Disorders Society-unified Parkinson's disease Rating Scale; NMSS: Non-motor Symptom Scale; PDQ-8: Parkinson's disease questionnaire-8.

a significant decrease in NMSS total score (p = 0.011) and MDS-UPDRS Part I (p = 0.004) was observed. When evaluating each domain from NMSS, only the mood/cognition domain showed a significant decrease in scores (p = 0.013). Other domains, except for the gastrointestinal tract domain, showed a reduction in scores that were, however, non-significant (Table 2).

Cognitive function by MoCA showed significantly higher scores in the post-intervention evaluation compared to the pre-intervention (p = 0.020) (Table 3). Among cognitive domains, only delayed recall showed a significant increase in score after the intervention (p = 0.038).

Acupuncture effect on motor-symptomatology and quality of life

Significant lower scores were observed in MDS-UPDRS Part II (p = 0.046), MDS-UPDRS Part III (p = 0.002), and total MDS-UPDRS score (p = 0.044) in the post-intervention evaluation. Regarding quality-of-life evaluation through PDQ-8, no differences were observed between both evaluations (Table 3).

Safety evaluation

Regarding potential side effects associated with EA therapy (nausea and vomiting, bleeding, infection at the puncture site, dizziness), no patient reported any of the previously mentioned.

Discussion

In the present study, a 10-session EA intervention improved non-motor symptomatology through NMSS. Mood/apathy domain of NMSS was the only that significantly decreased after concluding treatment. To the best of our knowledge, scarce literature has evaluated EA effect on non-motor symptoms[10], and no other study has conducted an overall evaluation of EA on non-motor symptoms through NMSS. Various studies have assessed acupuncture's effect on specific non-motor symptoms. For example, a recent study showed a greater improvement in depressive and sleep disorders after concluding an intervention that involved 18 weeks of twice-weekly acupuncture plus symptomatic treatment compared to symptomatic treatment alone[16]. Another study showed similar results regarding depressive symptoms[17], a finding shared by our study. Comparing methodological issues between studies, the former involved a small sample as ours (20 vs. 22 patients) but a longer treatment duration (36 vs. 10 sessions), whereas the latter was a multi-center randomized study with a higher sample size (76 patients) and longer treatment duration (32 sessions). Nonetheless, depressive symptoms improved in the latter from week 4 of treatment initiation, comparable to our study. Other symptoms ameliorated by acupuncture shown in other studies are constipation[18,19] and autonomic disorders such as bladder dysfunction[20], results not supported by our report.

In our study, cognitive function was improved after concluding the EA intervention. This finding has been observed in another study in a PD population[21], whereas evidence from patients with Alzheimer's disease shows upregulation of cognitive functions after acupuncture treatment[22]. This mechanism may be explained by the regulatory effect of neural activity within cognitive brain regions after acupuncture therapy in PD patients[23].

Regarding motor symptoms, EA treatment improved MDS-UPDRS Part II and Part III total scores, supporting other studies' findings[9]. In contrast, our study found no significant effect on the quality of life assessed by PDQ-8. This contrasts with other studies that have

Table 2. Electroacupuncture intervention effect on non-motor symptoms through MDS-UPDRS Part I and NMSS

Scale	Pre-intervention evaluation (n = 22)	Post-intervention evaluation (n = 22)	p
MDS-UPDRS Part I	7.7 ± 5.3	5.3 ± 4.5	0.004
NMSS total score	54.6 ± 32.5	35.2 ± 26.6	0.011
Cardiovascular domain	1.4 ± 3.4	1.1 ± 2.7	0.414
Sleep/fatigue domain	12.3 ± 10,1	7.1 ± 8.5	0.414
Mood/cognition domain	14.4 ± 14.9	4.0 ± 4.2	0.013
Perceptual problems/ hallucinations domain	1.3 ± 2.1	0.5 ± 1.0	0.109
Attention/memory domain	5.5 ± 5.1	4.2 ± 5.4	0.283
Gastrointestinal tract domain	4.7 ± 5.2	7.1 ± 11.4	0.899
Urinary domain	5.2 ± 6.5	5.1 ± 5.6	0.622
Sexual function domain	1.8 ± 5.8	0.1 ± 0.5	0.180
Miscellaneous domain	8.1 ± 8.7	6.0 ± 4.7	0.173

MDS-UPDRS: Movement Disorders Society-unified Parkinson's disease rating scale; NMSS: Non-Motor Symptom Scale. The value of bold numbers is p < 5.

Table 3. Electroacupuncture intervention effect on motor and cognitive symptoms through MDS-UPDRS and MoCA

Scale	Pre-intervention evaluation (n = 22)	Post-intervention evaluation (n = 22)	p
MDS-UPDRS Part II	10.5 ± 7.6	7.0 ± 5.7	0.046
MDS-UPDRS Part III	23.1 ± 13.9	14.0 ± 8.6	0.002
MDS-UPDRS total score	32.3 ± 11.7	25.9 ± 16.2	0.044
MoCA total score	21.6 ± 4.3	24.2 ± 4.5	0.020
Visuospatial ability	3.4 ± 1.2	3.5 ± 1.0	0.796
Identification	2.9 ± 0.2	3.0 ± 0.0	0.317
Attention	4.9 ± 1.4	4.9 ± 1.3	0.764
Language	2.3 ± 1.0	2.2 ± 1.1	0.776
Abstraction	1.8 ± 0.5	1.8 ± 0.6	0.998
Delayed recall	2.2 ± 1.9	3.1 ± 1.4	0.038
Orientation	5.7 ± 0.7	5.7 ± 0.8	0.705
PDQ-8 total score	8.0 ± 7.1	5.9 ± 5.5	0.751

MoCA: Montreal Cognitive Assessment; MDS-UPDRS: Movement Disorders Society-unified Parkinson's Disease Rating Scale; PDQ-8: Parkinson's disease questionnaire-8. The value of bold numbers is p < 5.

found a significant improvement in quality-of-life measures[24,25], with more (> 12) acupuncture sessions than the present study. The latter may be a reason explaining the non-significant change in our results, in addition to a lack of long-term evaluation.

The therapeutic mechanisms behind acupuncture's effect are still not completely elucidated, with studies arguing for a placebo effect, while others showing biological changes due to acupuncture treatment[26]. Animal models of PD using 6-hydroxydopamine have reported a reduction in the loss of dopaminergic neurons after 14 sessions of stimulation in an acupoint and an improvement in behavior patterns caused by the induced lesion[27,28]. Other studies in animal models have shown

antioxidant and anti-inflammatory effects, regulation of neurotransmitters in the striatum, and neurochemical modulation in the basal ganglia, which could explain acupuncture's therapeutic effect[29]. Despite not producing the De qi sensation of real acupuncture, sham acupuncture may have other elements that contribute to its efficacy in alleviating some PD symptoms shared by real acupuncture and placebo[30].

On the other side, as the outcome evaluation time lasted approximately 60 min, it is reasonable to consider its influence on the accuracy of patients' responses. Nonetheless, an expert in movement disorders and with clinical experience in applying the MDS-UPDRS, NMSS, MoCA, and PDQ-8 guided the interview, which could diminish the bias of an extended evaluation time. For instance, this helped shorten the interview in mild PD cases. However, the lack of blinding of the intervention could contribute to a bias in data recording, a limitation of this preliminary study.

This study has some limitations. Among the most important, the lack of a control group limits the interpretation and generalization of results, considering the placebo effect that has been attributed to sham acupuncture. In addition, among other related potential biases, the constant interaction with eager researchers might influence patients' responses to the clinical scales evaluated in favor of the intervention, a point that needs consideration. Another important limitation is its preliminary characteristic, as the small sample size limits the further generalization of results. Finally, another potential limitation is the lack of evaluation of any long-term effect attributed to EA intervention. However, we believe the results justify implementing a randomized controlled study with sham acupuncture as a placebo control group. Among the strengths of this study, an overall formal evaluation of non-motor symptoms through NMSS allowed identifying those that could benefit the most from EA therapy. Thus, a new randomized, placebo-controlled trial with increased sample size and assessment of long-term outcomes lies in future research plans.

Conclusion

A 10-session EA intervention has a protective and ameliorating effect on non-motor and motor symptomatology of PD patients with no treatment-related side effects presented. Among non-motor symptoms, mood, and cognitive function appear to be improved by acupuncture, which might thus represent a complementary therapy for PD patients with any mood or cognitive disorders. A future placebo-controlled randomized study with a comprehensive assessment of mood and cognitive function would better characterize the potential role of EA in these non-motor symptoms.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of 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 followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. 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 was used in the writing of this manuscript.

Supplementary data

Supplementary data are available at DOI: 10.24875/RMN.24000035. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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REVIEW ARTICLE

Managing atherosclerotic carotid disease: treatment essentials

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Abstract

Atherosclerotic carotid disease (ACD) is a common etiology of stroke, demanding a comprehensive understanding of effective intervention. This review explores the pathophysiology and treatment strategies for ACD, as well as the diagnostic imaging findings. ACDs can cause ischemic strokes by different mechanisms including plaque rupture, embolism, and stenosis-induced hypoperfusion. Early intervention is vital to avert adverse outcomes. Medical management remains the first line of treatment in the form of antiplatelets, antihypertensives, and statins. While carotid artery stenting (CAS) has gained traction in the last few years, carotid endarterectomy (CEA) remains favored for asymptomatic cases in international guidelines. Current evidence has revealed that both CAS and CEA are reasonable options for symptomatic cases. Doppler ultrasound, computed tomography angiography, and magnetic resonance imaging are pivotal in diagnosing and characterizing ACD plaques. Plaque features, such as lipid-rich necrotic core, fibrous cap thickness, or intraplaque hemorrhage are essential in guiding the treatment.

Keywords: *Atherosclerotic. Carotid. Stroke. Stenosis. Plaque.*

Manejo de la enfermedad carotídea aterosclerosa: puntos esenciales para el tratamiento

Resumen

La enfermedad carotídea aterosclerosa (ACD, por sus siglas en inglés) es una etiología común de infartos cerebrales, requiriendo de comprensión integral para una intervención efectiva. Esta revisión explora la fisiopatología y estrategias de tratamiento para la ACD, así como los hallazgos diagnósticos por imagen. La ACD puede causar infartos cerebrales por diferentes mecanismos, incluyendo la rotura de placa, embolismo e hipoperfusión inducida por la propia estenosis. La intervención temprana es crucial para evitar resultados adversos. El manejo médico continúa siendo la primera línea de tratamiento en forma de antiagregantes plaquetarios, antihipertensivos y estatinas. A pesar de que la angioplastía carotídea con stent (CAS, por sus siglas en inglés) ha ganado popularidad en los últimos años, la endarterectomía carotídea (CEA, por sus siglas en inglés) sigue siendo preferida para casos asintomáticos según las guías internacionales. La evidencia actual

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ha demostrado que tanto CAS como CEA son opciones razonables para casos sintomáticos. La ecografía Doppler, la angiotomografía computarizada y la resonancia magnética son fundamentales para diagnosticar y caracterizar las placas de ACD. Las características de la placa, como lo son el núcleo necrótico rico en lípidos, el grosor de la capa fibrosa o la hemorragia intraplaca son esenciales para guiar el tratamiento.

Palabras clave: *Aterosclerosis. Carótida. Infarto cerebral. Estenosis. Placa.*

Introduction, background, and epidemiology

In 1951, Miller-Fisher published a seminal paper that described the symptoms and physiopathological substrate of atherosclerotic carotid disease (ACD), using the radiological evidence of 45 published cases[1]. Dr. Miller-Fisher concluded that this disease was much more frequent than previously thought and pointed out that, because of its location in the neck, atheroma plaques in carotids stood in a "no man's land" situation between pathology and neuropathology, and thus were not receiving the attention they warranted[1].

Today we know that carotid stenosis is responsible for up to 25% of ischemic strokes (IS) in the US[2]. In addition, it has been reported that 10-15% of all IS happen in the setting of ≥ 50% stenosis of the internal carotid artery (ICA)[3].

This sort of information is scarce in Mexico, with the Brain Attack Surveillance in Durango (BASID)[4] study and *Primer Registro Mexicano de Isquemia Cerebral* (PREMIER)[5], a registry, providing the most recent data. PREMIER noted a funnel effect at the end of its median follow-up of 358 days, with a third of the patients with an excellent outcome (modified Rankin Score [mRS] 0-1), another third with mRS 2-5, whereas the other third dead[5]; only 8% of all strokes were classified as large-artery atherosclerosis, and 0.1% and 0.5% of patients underwent carotid endarterectomy (CEA) and carotid artery stenting (CAS), respectively[5]. In a subanalysis of strokes of undetermined cause, 40% of those had evidence of two or more risk factors for large-artery atherosclerosis[5]. The investigators noted a very low use of the complete diagnostic tools to determine etiology because of limited resources[5]. BASID reported a prevalence of 5.1-7.7 strokes/1,000 persons in the Durango municipality, which is within the range of other door-to-door surveys in Latin America[4].

Historically, ACD has been classified according to the degree of stenosis, using either the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[6] or European Carotid Surgery Trial (ECST)[7] criteria. Between the two, NASCET has seen a wider use. However, there are more biomarkers for stroke risk than just the degree of stenosis[8].

Treatment options include medical treatment, CEA, and CAS, with the latter now employing transcarotid artery revascularization as an option to mitigate the risk of artery-to-artery embolism due to dislodged atheroma during the passage of the catheter over the aortic arch and the supraaortic arteries[9]. The decision for revascularization is greatly influenced by whether the stenosis is symptomatic, and the treatment of choice is determined by the patient's status (unilateral or bilateral stenosis, location and morphology of the plaque, vessel anatomy, and degree of stenosis). Most of the available evidence is on symptomatic stenosis and medical and surgical management. No doubt the data regarding ACD management has exploded in the last few decades, with an ever-growing body of evidence for CAS.

This review aims to provide a simple, treatment-oriented guide to the different situations the physician may find in a patient with ACD. Sections are organized into symptomatic and asymptomatic disease, and each one of these refers to each of the current treatment modalities according to international guidelines.

A systematic search was conducted on MEDLINE (PubMed), using the following Medical Subject Headings terms: (ACD) + (neuroimaging findings) + (revascularization techniques [either CEA or CAS]). We selected original articles, as well as clinical trials and review articles. Each article was read to completion, to check for other useful references. This paper will focus on ACD at the ICA, both symptomatic and asymptomatic, and its treatment modalities: medical, surgical, and neurointerventional.

Plaque formation

Atherosclerosis is a systemic disease, chronic and progressive, characterized by a constant state of inflammation and cholesterol plaque formation with different degrees of hemodynamic repercussion in the affected arteries[10]. Carotid atherosclerosis has been identified as a surrogate for systemic atherosclerosis in a subclinical stage and a predictor of cardiovascular events, such as

coronary disease and IS[10]. Because of this, the current management of ACD is focused on detecting the plaque in a timely manner, early recognition of intimal thickening, and the degree of occlusion as markers of ACD[10]. In this line of thought, it is now known that ACD will cause IS by one of these two mechanisms: (1) plaque rupture and thrombosis with subsequent artery-to-artery embolism, and (2) flow-reducing stenosis.

Some risk factors such as being male, overweight, hypertension, diabetes, and smoking have been linked to ACD. Hypertension has the most remarkable correlation to the early stages of this disease[11].

The most common site for plaque formation in the cerebral circulation is the ICA, within 2 cm of the carotid bifurcation[12]. There are three molecular stages in the natural history of this disease[13]: (1) the fatty streak phase, in which macrophages are transformed into foam cells due to oxidative stress, (2) the formation of a fibrous cap (FC) by myocytes, and (3) the fibrous surface of the so-called complex plaque will rupture, causing ulceration, intraplaque hemorrhage (IPH), *in situ* thrombosis, or calcification. It is during this stage that the disease becomes symptomatic[13]. Furthermore, Glagov et al.[14] described how coronary arteries also change throughout the evolution of plaques. Initially, the artery will enlarge to maintain a proper or normal lumen due to the growing atheroma. With > 40% stenosis, the plaque's area will continuously increase up to the point where it will encircle all the arterial walls. Eventually, the artery will not be able to keep up with its enlargement to preserve patency. This report proposed that the plaque disrupts the widening of the artery because it covers up the endothelium that can react and remodel the vessel in response to the increased flow[14].

The current plaque classification established by the American Heart Association (AHA) comprises six types of lesions with their respective subtypes but does not include the correlation between plaque composition and size with the degree of occlusion[15]. One must remember that these studies pertain to coronary disease and have been extrapolated to ACD.

Symptomatic carotid stenosis

CEA is currently the gold standard for treating ACD, whether symptomatic or asymptomatic, whereas CAS is usually reserved for those with a high cardiovascular risk for surgery[16]. One of the more significant disadvantages of both procedures is the risk of restenosis due to neointimal hyperplasia or recurrent atherosclerotic plaque[17].

Medical treatment

When carotid atherosclerotic stenosis is associated with minor non-cardioembolic IS, such as a National Institutes of Health Stroke Scale < 4 or a high-risk transient ischemic attack (TIA) with $ABCD^2 \geq 4$, dual antiplatelet therapy (DAPT) becomes necessary[18]. This therapy has shown greater long-term results than monotherapy in reducing new heart attacks and death, especially if it is started within the first 7 days after the index event[18]. The first-line pharmacological therapy in these cases is a combination of aspirin and clopidogrel, recommended from 3 weeks to 3 months after infarction, as informed by two large trials[18]. Regarding ticagrelor, its addition (90 mg twice a day) to aspirin may be beneficial with a minor stroke or a high-risk TIA in the context of ipsilateral intracranial stenosis of > 30%, for up to 30 days[18].

Surgical treatment

CEA is a surgical procedure that aims to remove plaque from the carotid artery, reducing the risk of stroke in patients with carotid artery disease.

Some patients may particularly benefit from CEA:

- Older patients with highly calcified vessels
- Contraindications to double antiplatelets
- Those with no previous ipsilateral CEA
- Furthermore, the lesion should be surgically accessible.

In symptomatic patients, the NASCET[6] and the ECST[7] trials demonstrated that CEA is effective in reducing the risk of stroke in selected patients with high-grade (70-99%) carotid stenosis. NASCET found that CEA reduced the risk of ipsilateral stroke from 26% to 9% over 2 years, whereas ECST found a similar reduction in risk from 26% to 13% over 3 years. Both trials concluded that CEA was most beneficial for patients with high-grade stenosis and that the benefits of surgery decreased as the degree of stenosis decreased[6,7]. For patients with a moderate (50-69%) and a life expectancy of at least 3 years, revascularization should be considered if it can be done within 2 weeks from symptom onset, as with high-grade lesions[18].

Endovascular treatment

The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST), which included 2502 patients with symptomatic and asymptomatic carotid stenosis (ACS), was randomly assigned either to an endovascular

or surgical approach. There was no difference between the two groups for the primary outcome (which included death, stroke, and myocardial infarction), with similar results for asymptomatic patients[19].

The following is the current consensus in the American and European guidelines regarding CAS in asymptomatic ACD:

For an endovascular approach in patients with a symptomatic, intracranial ACD and optimal medical treatment, the AHA[18] has no definite answer for using stenting or angioplasty alone to prevent IS. As such, the class of recommendation is 2b (weak) with a level of evidence C (limited data)[18]. Overall, angioplasty and stenting are not recommended as the initial treatment for patients with a stroke or TIA attributable to ACD, except when the patient's anatomy and medical conditions would pose an increased risk for surgery, especially when the stenosis is moderate by non-invasive imaging or > 50% by catheter-based imaging[18].

The 2021 European Stroke Organisation's guidelines[16] make similar recommendations regarding the choice between CEA and CAS, with a preference for the former and the second being relegated to an option after careful consideration and a high risk for the surgical approach.

In addition, these guidelines suggest a risk of in-hospital stroke or death for symptomatic ACD following revascularization to be, ideally, below 4%[16].

ACS

While there is ample data on treating symptomatic carotid stenosis, ACS remains controversial, with advocacy for both an exclusive optimal medical treatment approach and revascularization for certain cases, with increasingly better results for each[20].

At present, the largest trial for intervention in ACS is the Second Asymptomatic Carotid Surgery Trial (ACST-2)[21], which reported that during a 5-year follow-up among 3625 patients, 1% had a procedure-related disabling stroke or death, and 2% had a non-disabling procedural stroke. ACST-2 concluded that serious complications were uncommon for both CEA and CAS, with the latter having a slightly higher incidence of non-disabling procedural stroke, although this difference was non-significant[21]. In addition, stroke risk for ACS was recently assessed in a meta-analysis that found that it was linearly associated with the degree of stenosis, with a greater risk found among those with 70-99% versus those with 50-69% (odds ratio [OR] 2.1), and an even higher risk for those with 80-99% stenosis compared to those with 50-79% (OR 2.5)[22]. It is worth noting that neither of these revascularization trials employed what is now considered to be the optimal medical management[23].

Medical treatment

Management of asymptomatic carotid atherosclerosis disease should be started with low doses of aspirin[24]. DAPT with aspirin/clopidogrel is discouraged as it has not shown greater benefits[25].

A double-blind trial from 2017 reported that the combination of aspirin and rivaroxaban was superior to monotherapy in terms of preventing stroke with better results in the long term, including bleeding risk[25]. In contrast, rivaroxaban monotherapy did not show superior results to aspirin in preventing infarction but was found to increase the risk of bleeding, and thus it is not recommended as monotherapy in carotid atherosclerosis disease[25].

Surgical treatment

The Asymptomatic Carotid Atherosclerosis Study (ACAS)[26] and the first Asymptomatic Carotid Surgery Trial (ACST-1)[27] showed that CEA is beneficial in reducing the risk of stroke in certain populations. ACAS found that CEA reduced the risk of stroke from 11% to 5.1% over 5 years in patients with high-grade (60-99%) carotid stenosis, whereas ACST-1 found a similar reduction in risk from 6.4% to 3.6% over 10 years. However, both trials noted that the absolute benefit of CEA was relatively small and that the risks associated with surgery (such as myocardial infarction, cranial nerve injury, and death) must be carefully weighed against the potential benefits[26,27]. It is worth noting that ACAS was published almost 30 years ago, and ACST-1 followed almost a decade later.

As mentioned before, ACST-2[21], which compared CEA versus CAS in ACS concluded that there was no significant difference in the rates of stroke, myocardial infarction, or death between patients who underwent CEA and those who underwent CAS. However, CEA (4.5%) was found to be slightly more effective than CAS (5.3%) in preventing any type of stroke in 5-year estimates. Overall, CEA is still considered the treatment of choice for patients with ACS[16].

Endovascular treatment

Evidence for the endovascular approach to ACS is scarce. Because of this, most current guidelines

recommend CEA over CAS. Published in 2016, ACT-1 (Randomized Trial of Stent vs. Surgery for ACS) randomly assigned 1452 patients for either carotid stenting or endarterectomy in a 3:1 proportion; there were no differences between groups regarding stroke, myocardial infarction, and death (3.3% for stenting and 2.6% for endarterectomy)[28].

A 2022 meta-analysis[29] published the results of different trials comparing CAE and CAS for ACS (the most recent being ACST-2[21]), concluding that both procedures have similar safety profiles for stroke, death, and myocardial infarction in the long term[29]. Nevertheless, CAS had a higher risk of any stroke during the perioperative period (OR, 1.62 [95% confidence interval (CI), 1.16-2.[24]; p = 0.004, I^2 = 0%) and an increased risk of non-disabling stroke (OR, 1.81 [95% CI, 1.23-2.65]; p = 0.003, I^2 = 0%)[29].

Imaging markers

Doppler ultrasound (DUS)

Carotid DUS is a popular and accessible tool for evaluating carotid plaques, given its widespread availability, ease of use, non-invasive nature, and cost. Still, it is a user-dependent technique, and thus its reliability will vary from center to center. It has a two-dimensional (2D) grayscale mode and a color Doppler mode to detect stenoses.

Color-Doppler US (CDUS) measures velocity on a grayscale image and codes it in color for an enhanced appreciation of blood flow in the segment, which in turn will help detect stenosis[30]. Waveform analysis is one of the three main components of CDUS, along with plaque characterization and grading of the stenosis with Doppler velocity criteria. A pulsed wave Doppler will also measure blood flow velocity which will be shown as a curve for each pulsation, with different morphologies depending on the flow's velocity[30]. Depending on the peak systolic velocity (PSV), each value will be used as a surrogate to determine stenosis percentage.

Severe stenosis will show two waveform changes: *pulsus tardus* (due to delayed upstroke) and *pulsus parvus* (diminished waveform), which in conjunction are usually referred to as *tardus parvus* waveform[31].

Intima-media thickness (IMT)

The 2D mode grayscale –or B-mode– has been used to measure the IMT, which has seen use as a biomarker for early-stage atherosclerosis[31]. IMT should be measured in a segment with no focal lesion[30].

The very definition of an abnormal IMT has not been standardized, with some studies defining it as greater than the 75th percentile, others as > 1 standard deviation from the mean, IMT at the upper quartile, IMT at the upper tercile, or an absolute value of ≥ 0.9 mm or ≥ 1 mm[32]. The American Society of Echocardiography recommends the 75th percentile definition for sex, age, and ethnicity as abnormal[33].

It is uncertain whether effects on IMT progression may reflect a decreased risk of cardiovascular disease (CVD) events. A 2020 meta-analysis by Willeit et al.[34] revealed that for each 10 μm/y reduction of IMT progression, there was a relative risk of 0.91 for CVD (95% CI, 0.87-0.94) and an additional relative risk for CVD of 0.92 (CI 0.87-0.97) achieved independent of IMT progression. It was concluded that the extent of the intervention would affect IMT progression and may be used to predict the degree of CVD risk reduction[34]. On the other hand, a 2007 meta-analysis by Lorenz et al. concluded that each interval increase in IMT over 0.9 mm was associated with a 13-18% higher risk of future stroke and a 10-15% increased risk of myocardial infarction[35]. As it stands, the current ACC/AHA guidelines do not recommend IMT measurement as a marker for risk assessment of a first CVD event (recommendation class III, level of evidence B)[36].

Plaque characterization

Both grayscale and CDUS must be used in conjunction to properly assess the plaque to describe plaque burden, echogenicity, and surface. During plaque screening, the carotid bulb warrants special attention because plaque typically develops earliest in this segment[33].

Echogenicity is described as hypoechoic versus echogenic and heterogeneous versus homogeneous[37]. Hemorrhagic and lipid-rich plaques are more likely to be hypoechoic, a plaque > 50% hypoechogenic is of particular concern, as they have been reported to have an increased likelihood of being symptomatic[38].

Plaque ulceration is another source of emboli, as thrombi are less likely to form on smoothly hyalinized, fibrous, or calcified plaque[37]. CDUS may prove unwieldy or insufficient when trying to characterize the plaque. Ulceration may register as a focal defect, either depression or indentation, or as an anechoic area that extends from within the plaque to the vessel's lumen with no echogenicity in between[31]. The definition of an

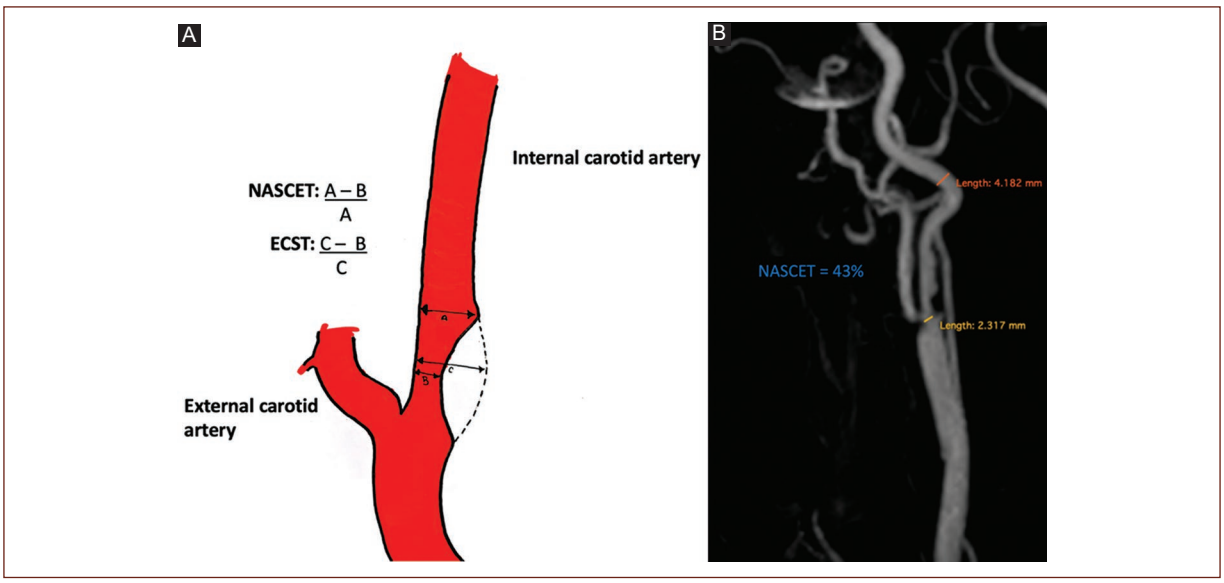

Figure 1. A: NASCET and ECST methods of carotid plaque stenosis. **B:** example of the NASCET method. ECST: European Carotid Stenosis Trial; NASCET: North American Symptomatic Carotid Endarterectomy Trial.

ulcer is a defect > 2 mm in 2 orthogonal planes[37]. All plaques should be assessed in grayscale, Color Doppler, and PSV, as an apparent large plaque with no associated increased velocities warrants further exploration or even new imaging studies.

Estimation of the stenosis

NASCET remains the most popular method to grade stenosis, even if the plaque burden may be underestimated. Spectral Doppler is considered a reliable tool to measure stenosis, with PSV recommended as the primary Doppler criterion for grading ICA stenosis – until the stenosis is > 95%[37], as PSV may register as either normal or even low.

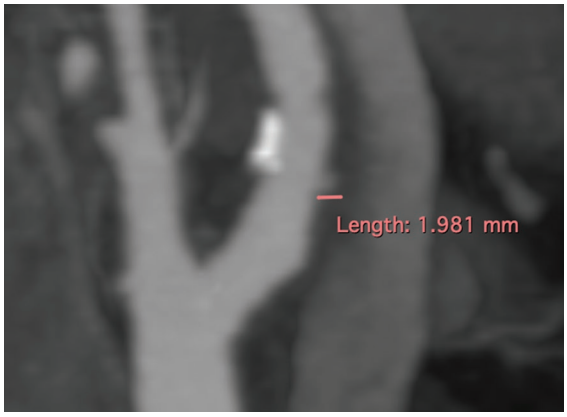

Figure 2. Ulcerated plaque with contrast entering the plaque, labeled with a length of 1.981 mm.

Computerized tomography

Multidetector computerized tomographic angiography (MDCTA) is a valuable tool for the evaluation of ACD. It identifies and classifies stenosis and ulcerated plaque with great accuracy[39]. The different techniques offered by MDCTA include maximum intensity projection, multiplanar reconstruction, shaded surface display, and volume rendering[40].

The degree of stenosis is classified according to the NASCET criteria, in which the measurements are made in a strictly perpendicular manner regarding the carotid axis. The value is calculated by comparing the stenotic segment's diameter with the most normal distal segment[39] (Fig. 1A and an example in Fig. 1B).

The plaque surface's morphology, especially the irregularity assessed with MDCTA, has been identified as an important risk factor for patients with a 30-69% stenosis, with an increased risk of developing symptoms[40].

Promising results with MDCTA have demonstrated the ability to assess plaque composition, compared to histology[39].

The plaque's surface may be classified as smooth, irregular, or ulcerated; an irregular plaque's surface may fluctuate between 0.3 and 0.9 mm, whereas an ulcerated

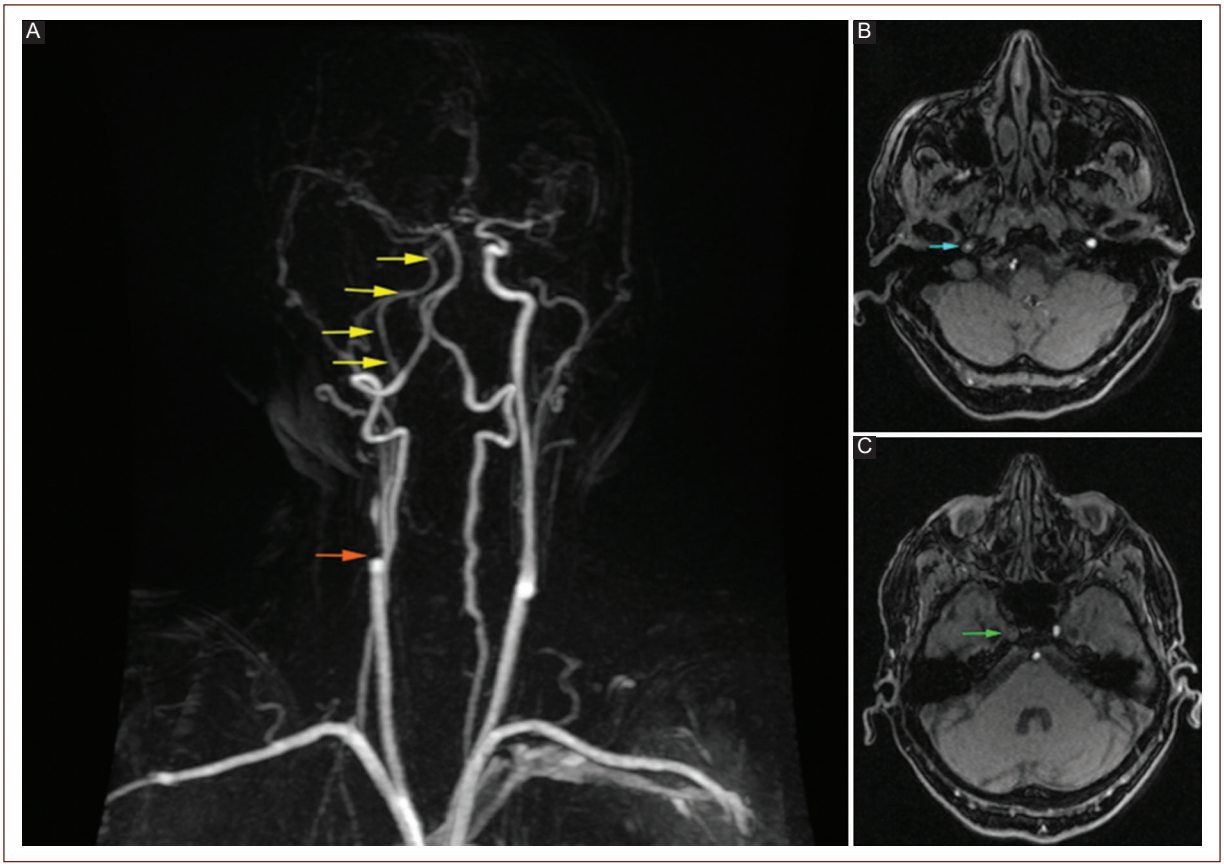

Figure 3. A: 3DTOF of the RICA (yellow arrows) with a decreased signal due to a critical stenosis at the carotid bulb (orange arrow). This image may be confused with hypoplastic vessels, and occlusion in extreme cases. **B:** this may affect distal segments, with a loss of signal of the RICA at the ophthalmic segment (cyan arrow) and **C:** apparent occlusion by the communicating segment (green arrow). 3DTOF: 3D time-of-flight; RICA: right internal carotid artery.

plaque will demonstrate cavities of > 1 mm[8] (Fig. 2). Logically, an irregular surface signals a higher risk for IS, especially when it is an ulceration; nevertheless, such findings may be the evidence of a previous IS, and thus its predictive value is yet not well defined[8].

Magnetic resonance imaging (MRI)

The MRI work-up for a patient with ACD necessitates, at the very minimum, a set of sequences to better identify any findings that might increase the risk for IS: pre- and post-contrast T1-W turbo-spin echo, magnetization-prepared rapid acquisition gradient-echo (MPRAGE), black-blood sequences, fat suppression, and time-of-flight (TOF)[41]. It should be noted that because TOF uses flow to construct a vessel's morphology, slow or turbulent flow may result in loss of signal[42], with an apparent occlusion, and thus should be carefully interpreted; likewise, signal intensity may be different between two vessels because of differences in flow speed, with seemingly hypoplastic or even occluded vessels (Fig. 3). Adding contrast to the study will allow for a better distinction between the FC and the lipid-rich necrotic core (LRNC), whereas black-blood sequences are beneficial to differentiate the lumen from the vessel wall[41]. MRI uses the same criteria as MDCTA for plaque morphology and thickness.

LRNC, FC, and plaque ulceration

LRNC is a compound made up of cholesterol crystals, apoptotic cellular detritus, and calcium particles[8]. Closely linked to the LRNC is the FC: once the cholesterol crystallizes, it will expand, which will also cause the FC to expand and become thinner, with the risk of rupture. These crystals' edges may cut through the neighboring fibrous tissue[43]. A plaque with > 40% of LRNC, along with a thin FC has an increased risk for stroke[8].

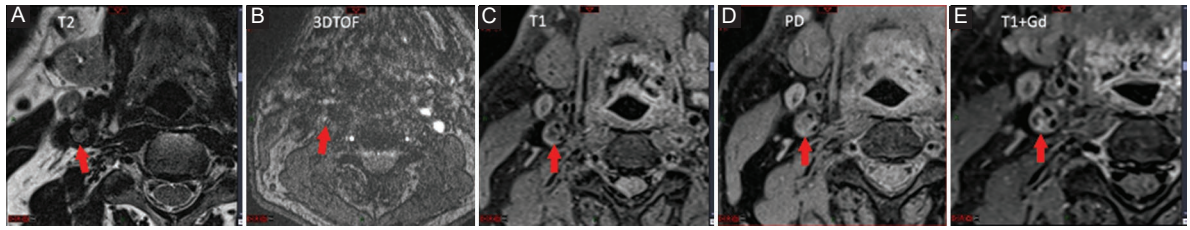

Figure 4. Severe left atherosclerotic carotid disease with a vulnerable plaque assessed with magnetic resonance imaging. Arrows in **A** and **C** point to the lipid-rich necrotic core. Arrow in **B** points to a severely decreased flow due to the stenosis. Arrow in **D** reveals intraplaque hemorrhage. The arrow in **E** shows enhancement after gadolinium. PD is hyperintense compared to T2. 3DTOF: 3D time-of-flight; PD: proton density; Gd: gadolinium.

While both CT and MRI may detect lipidic components, MRI has been found to be superior for the characterization of the LRNC, given that this technique can distinguish between IPH and LRCN (Fig. 4)[44]. Multi-contrast MRI for carotids with T1 and T2-weighted black-blood sequences, as well as the bright-blood TOF, have been histologically validated for detecting LRNC; gadolinium may help with the distinction between LRNC and hyperintense fibrous tissue[41].

The FC's status must be assessed: whether it is intact, thinned, or ruptured, as plaque thickness and integrity are associated with varying degrees of IS risk[41]. Multicontrast MRI (TOF, proton density, T1, and T2, Fig. 4) has proved to be a very useful tool to determine FC integrity[45].

A ruptured FC will expose the plaque's thrombogenic contents for platelets and coagulation factors, which may lead to clot formation and distal embolism[46]. A thin but intact FC will feature a smooth surface and will not enhance after contrast, whereas a ruptured FC will demonstrate an interrupted and hypointense band after contrast[41].

IPH

IPH is one of the key features in identifying an unstable plaque and contributes to the acceleration and growth of the LRNC[8]. A plaque with IPH is considered to be in a more advanced stage than the ones containing only LRNC and FC[41].

IPH may be better appreciated with common MRI sequences[8]. It will be hyperintense in all T1-weighted sequences, including MPRAGE, TOF, and fast spin-echo[41].

IPH has been reported with an adjusted HR of 11.0, independent of stenosis degree and with no difference for sex[47]. Furthermore, it is more prevalent in ipsilateral ICAs to embolic strokes of undetermined source[48], even if other causes are still possible[8].

Conclusion

Revascularization for ACD is an evolving field with an increasing body of evidence for different types of medical and surgical treatments. Treatment for ACS is less certain, although trials like CREST-2[49] are expected to shed light on the possibilities of both CEA and CAS, plus medical management.

Plaque analysis is now paramount to evaluation, as stenosis alone has often proved to be an unreliable marker of stroke risk.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of 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 study does not involve patient personal data nor requires ethical approval. The 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 of this manuscript.

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REVIEW ARTICLE

Cavernomas: a literature review

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Abstract

Cavernomas are slow-flow benign vascular lesions. Globally, they represent the second most common vascular malformation of the central nervous system. They primarily occur sporadically, with documented cases of de novo development, radiation-associated cases, or cases without identifiable risk factors. In their hereditary form, they are associated with the genes KRIT1, CCM2, and CCM3. The most frequent clinical manifestations include headache, seizures, focal deficits, and hemorrhagic events, with intracranial hemorrhage being the main cause of disability. Magnetic resonance imaging is the most precise diagnostic tool, allowing the classification of cavernomas based on the hemorrhage phase. Management varies from surveillance to surgical intervention, especially in symptomatic cases or drug-resistant epilepsy. Management during pregnancy should be individualized to avoid teratogenic effects. This article aims to review and update information on cavernomas, addressing their epidemiology, pathophysiology, predominant localization, and various clinical and imaging presentations despite their dynamic growth or association with underlying comorbidities in the context of a clinical case. The goal is to expedite accurate diagnosis and treatment, reducing associated disability in patients.

Keywords: *Cavernomas. Intracranial hemorrhage. Magnetic resonance imaging.*

Cavernomas: una revisión de la literatura

Resumen

Los cavernomas son lesiones vasculares benignas de flujo lento. A nivel global constituyen la segunda malformación vascular más común del sistema nervioso central. Se presentan principalmente de forma esporádica, asociados a radiación o sin factores de riesgo identificables. En su forma hereditaria están asociados a los genes KRIT1, CCM2 Y CCM3. Las manifestaciones clínicas más frecuentes incluyen cefalea, convulsiones, déficits focales y eventos hemorrágicos, siendo la hemorragia intracraneal la principal causa de discapacidad. La resonancia magnética es la herramienta diagnóstica más precisa, permitiendo clasificar los cavernomas según la fase de hemorragia. Su manejo varía desde la vigilancia hasta la intervención quirúrgica, especialmente en casos sintomáticos o de epilepsia refractaria a fármacos. Su manejo en el embarazo debe individualizarse para evitar efectos teratogénicos. Este artículo tiene como propósito revisar y actualizar la información sobre los cavernomas, abordando su epidemiología, fisiopatología, localización predominante y sus diferentes formas de presentación clínica e imagenológica a pesar de su crecimiento dinámico, o aparición asociada a comorbilidades a propósito de un caso clínico. El fin es agilizar su correcto diagnóstico y tratamiento, reduciendo la discapacidad asociada en los pacientes.

Palabras clave: *Cavernomas. Hemorragia intracraneal. Resonancia magnética.*

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Introduction

Intracranial or cerebral vascular malformations, including cavernomas, form a group of vascular lesions with variable hemodynamic or structural characteristics. Aneurysms, for example, are abnormal saccular dilatations of the cerebral arteries. Arteriovenous malformations are clusters of abnormal arteries and veins with an increased risk of intracranial hemorrhage. Capillary telangiectasia is characterized by dilated thin-walled capillaries due to the absence of smooth muscle or elastic fibers. Developmental venous anomalies (DVA), the most common intracranial venous malformation, are also known as venous angiomas or cerebral venous malformations. Cavernomas in contrast, consist of vascular spaces of varying sizes lined by a single layer of endothelial cells, without specific arterial or venous characteristics[1].

Cavernomas, also known as cavernous angiomas or cerebral cavernous malformations (CCM), are benign, slow-flow vascular lesions[2,3]. Until 1960, they were considered rare lesions; with the arrival of cerebral magnetic resonance imaging (MRI)[4,5], their prevalence has increased, ranging from 0.3% to 0.9%[6-9], constituting between 9% and 15% of cerebral vascular malformations[6,10].

Traditionally, cavernomas were thought to be congenital lesions, existing de novo only in the hereditary form. Nevertheless, an increasing number of cases have been reported where lesions develop de novo, either secondary to radiation or without any other identifiable risk factor[2,8].

Cavernomas are angiographically hidden malformations lined with endothelium and filled with blood products at various stages of evolution[4,10,11]. They are dynamic lesions that can grow or downsize over time and rarely remain stable. The diameter of these lesions can vary significantly, ranging from millimeter-scale abnormalities to being considered giant when exceeding 6 cm in at least one dimension[3].

Epidemiology

Cavernomas are considered the second most common vascular malformation of the central nervous system after DVA[3]. They do not exhibit a gender predilection and are typically presented between the ages of 20 and 50 years (with a mean range of 35-40 years)[6]. Cavernomas can exist in two forms: the hereditary form, characterized by a familial pattern (autosomal dominant with incomplete clinical penetrance), and the isolated form (sporadic)[2,12].

Approximately 75% of cases present as a solitary lesion, while in familial cases, 62% are associated with multiple lesions[13].

Topographically, most lesions are located in the supratentorial region (80-92%), followed by the infratentorial compartment (15%), and the spinal cord (5%). Less frequently, they appear in the retina, cranial nerves, meningeal layers, and intraventricular spaces[3].

Associated genes

Cavernomas occur sporadically in 80% of cases, while their appearance in familiar forms is associated with three main genes that affect endothelial structure. One gene, KRIT1, also known as CCM1, is mapped to the long arm of chromosome 7, and two other genes, CCM2 (MGC4607) and CCM3 (PDCD10) have been found on the short arm of chromosome 3 (3q25.2-27), respectively[12,14]. Sporadic lesions show somatic mutations in three genes, although they lack germline inherited mutations. This indicates a molecular mechanism similar to that associated with the loss of gene function[3].

Peyre et al., demonstrated in a study that sporadic cavernomas also originate from activating mutations in the PIK3K-AKT-mTOR pathway, primarily in PIK3CA, and these exceed the number of activating mutations in genes causing familial forms[14].

The de novo formation of cavernomas with hereditary patterns has been documented at a frequency of 0.2 to 0.4 new lesions per patient per year[15]. In sporadic cases, they have only been described following radiation[5] or radio neurosurgery[2,7].

Etiopathogenesis

Cavernomas are vascular spaces that manage low pressure and slow blood flow within the lesion, which allows the formation of a clot, followed by its organization, and this process occurs repetitively. There is a deficiency in the tight and adherent junctions of endothelial cells, leading to leaks and impaired function of the blood-brain barrier[2].

The occurrence of de novo cavernoma has been associated with exposure to radiotherapy, traumatic brain injury, previous surgery, or coexisting vascular lesions[11].

Their relationship with DVA has been reported up to 33%[15,16], such as capillary telangiectasia and moyamoya disease[17].

In a study by Ha et al., they specifically investigated the connection between cavernomas and arteriovenous dural fistulas. Notably, in 83% of these cases, the cavernoma located adjacent to or within the venous drainage territory of the involved sinus associated with the arteriovenous dural fistula, this may be linked to the venous hypertension generated by these fistulas[11,15].

The theories regarding the appearance of these lesions are 1) new lesions with rapid growth that makes them symptomatic, and 2) small lesions undetectable by imaging, remaining quiescent for an extended period with subsequent rapid growth. Cavernomas, in general, tend to decrease in size once they reach a predetermined size and stage of development, their growth potential undergoes some form of involution with concurrent stagnation or even contraction. In other words, their progression is parabolic and non-linear[6].

The evolution of cavernomas can be classified into 1) quiescent, 2) variations in volume and signal in relation to hemorrhagic phenomena, and 3) luminal thrombosis and repermeabilization[6].

Regarding radio-induced cavernomas, which are predominantly described in individuals under 15 years old undergoing radiation[6,18], two explanations can be offered: First, while the cavernoma was present at the time of irradiation but undetectable, radiation may have favored its development or second, radiation resulted in the appearance of the cavernoma by inducing the proliferation and dilatation of vascular endothelium through hyalinization and fibrinoid necrosis of vascular walls[6].

Evidence suggests that radiation-induced cavernomas develop from a cavitary lesion rather than a vascular malformation. Following tissue destruction, a new cavity forms and fills with blood, while fibrin inhibits the spread of hemorrhage, leading to the formation of a consolidated hematoma. Support for this hypothesis comes from the locations of radiation–induced cavernous hemangiomas (RICH), which turn out to be identical to the sites of stereotactic radiosurgery (SRS) treatment, where previous tumors or vascular malformations existed[9].

Some authors have postulated the role of angiogenic factors in the occurrence of lesions in aggressive familial and sporadic forms[6]. In aggressive cases, Ki67 and bcl-2 are evident in cavernoma tissue, similar to proliferative lesions, platelet-derived growth factor, tenascin, and transforming growth factor beta are expressed in perilesional brain tissue, suggesting possible neoangiogenesis that initiates lesion growth[6]. Recent immunohistochemical studies have also demonstrated the expression of biological markers in cerebral cavernomas, such as nuclear antigen of cell proliferation, MIB-1, Flk-1, vascular endothelial growth factor, hypoxia-inducible factor-1α, and matrix metalloproteinase-9, indicating that cavernomas exhibit proliferative and neoangiogenic characteristics[15].

The appearance or growth of cavernomas during pregnancy has been a longstanding controversy. Some researchers suggest that anemia and increased blood flow during pregnancy raise circulating blood volume and create turbulent flow within thin-walled sinusoids, which worsens the behavior of CCMs and raises the risk of rupture[19]. Others speculate that increased estrogen and progesterone levels lead to higher expression of growth factors and cause endothelial cell degeneration in the arterial walls. However, more recent studies have found no solid evidence supporting the presence of estrogen and progesterone receptors in CCMs[20].

Tang et al.[21], conducted a study highlighting the role of the gut-brain axis in the development of cerebral cavernomas. They demonstrated, through fecal sample analysis, that patients diagnosed with cavernous malformation (75 patients) have an intestinal microbiome rich in gram-negative bacteria compared to the healthy control group (29 patients). They proved that lipopolysaccharide (LPS) derived from gram-negative bacteria in the gut microbiota triggers Toll-like receptor 4 and mitogen-activated protein kinase kinase 3 signaling in cerebral endothelial cells, promoting the development of cavernomas. However, according to this study, cavernoma formation is not limited to its association with intestinal dysbiosis; they also found an association between the presence of cavernomas and the loss of function of the PDCD10 (CCM3) gene, which is involved in mucus secretion by goblet cells and its presence in the intestinal lining preventing the passage of millions of bacteria into the bloodstream[21].

Histopathology

A cavernoma is composed of ectasic proliferation, a single layer of smooth muscle-lacking endothelium, a thin fibrous adventitia, and an absence of intermediate brain parenchyma within the lesion. Old hemorrhage and reactive gliosis are frequently found at the periphery of the lesion[9,22].

Macroscopically, cavernous malformations appear as a well-defined, lobulated mass with a dark blue color, resembling a “raspberry” or “popcorn” appearance[9].

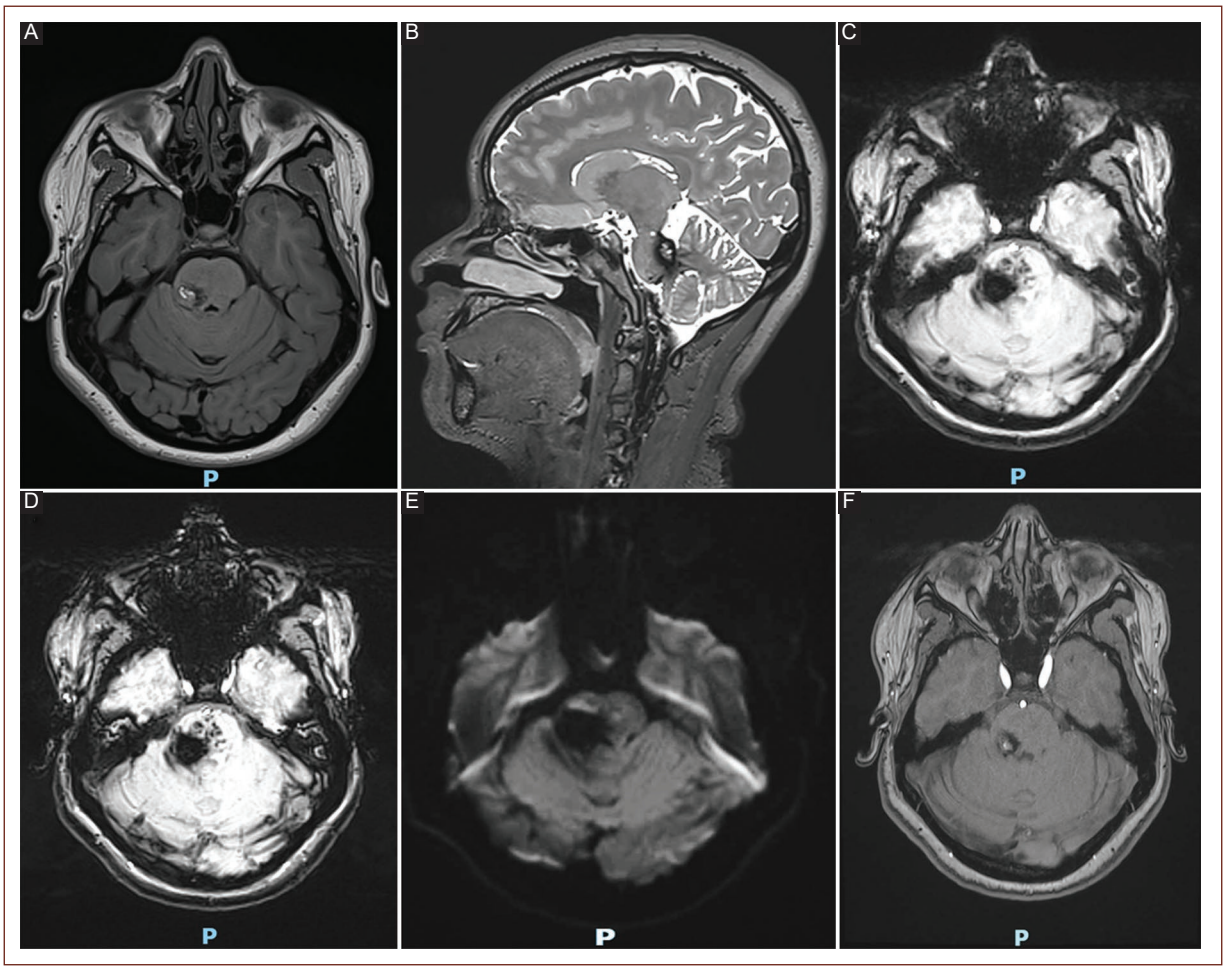

Figure 1. Magnetic resonance imaging sequences of a right posterolateral pontine cavernoma. **A:** axial T1-WI. **B:** sagittal T2-weighted imaging (T2-WI). **C** and **D:** axial gradient echo/susceptibility-weighted imaging sequences. **E:** diffusion-weighted imaging. **F:** axial contrast-enhanced T1-WI. **G:** axial 3D time-of-flight technique. T1-WI: T1-weighted imaging.

Microscopically, Cha et al.[9], described histological differences in patients with de novo cavernomas without any pre-disposing factors versus those with a history of stereotactic radiosurgery. RICH showed capillary-sized irregular vascular channels, partially compressed, with capillary proliferation in the center of the lesion, thin walls, less hyalinization, and infiltration of foamy macrophages compared to de novo cavernomas. In contrast, de novo cavernomas were composed of thick, well-formed vessels with well-defined endothelial cell-lined lumens, hyalinized walls with scattered macrophages located in old hemorrhages, and outside the vascular walls[9].

Clinical manifestations

The natural history of cavernomas involves five clinically relevant scenarios: 1) lesion stabilization, 2) lesion regression, 3) increased lesion density, 4) symptomatic hemorrhage, and 5) lesion growth[23].

The most frequent clinical manifestations in all patient groups include headaches, seizures, focal deficits, and hemorrhagic events[6,9]. Intracranial hemorrhage stands as the primary cause of disability in patients. It is believed that all cavernomas harbor hidden bleeding, as studies have documented hemosiderin halo signals in all existing classifications[24]. However, defining a cavernoma hemorrhage is a clinical event that involves both characteristics[25]:

– Acute or subacute onset symptoms (headache, seizures, altered consciousness, or new/worsened focal neurological deficit related to the anatomical location of the cavernoma)[25].
– Radiological, pathological, surgical evidence, or, rarely, cerebrospinal fluid evidence of recent extra or intralesional bleeding. The presence of hemosiderin

Table 1. Diagnostic imaging

Lesion	T1 Sequence	T2 Sequence	Gradient echo sequence	Cause	Histopathology
Type I	Hyperintensity[17]		-	Subacute hemorrhage[17]	Principal component: methemoglobin, surrounded by macrophages and gliotic brain tissue[12]
Type II	Classic appearance of "popcorn" Mixed signal intensity attributed to localized areas of hemorrhage[25]		-	Thrombosis at various stages of maturation[11]	Lesions with localized hemorrhage, enveloped by gliotic tissue, and hemosiderin staining within the lesion. In the brain, larger lesions may exhibit calcifications[29]
Type III	Isointensity or hypointensity[17]	Hypointensity with a hypotensive rim amplifying the lesion size[17]	Magnified hypointensity compared to T2[29]	Chronic hemorrhages[11]	Chronic blood products and hemosiderin rim[2]
Type IV	Limited or no visualization[25]		Small, punctate, hypointense foci, often multiple[17]	Likely a pre-cursor lesion of the cavernoma or corresponding to telangiectasias[12,25]	Multiple punctate microhemorrhage[2]

Table 2. $BLED_2$ risk score

Letter	Risk factor	Points
B	Bleeding at diagnosis	1
L	Large axial diameter (> 12 mm)	1
E	Eloquent area or brainstem location	1
D	Duration < 1 year since the previous symptomatic event	2

halo or an increase in cavernoma size without other evidence of recent bleeding is not enough[25].

The risk of bleeding varies based on age and gender. Women under 40 years had a higher risk of bleeding (34% per lesion per year) compared to men of the same age (22%). However, the authors did not establish a direct correlation between the risk of bleeding and pregnancy[5].

Clatterbuck and colleagues did not find a significant relationship between cavernoma size and the risk of hemorrhage. The annual risk of hemorrhage in their study was determined to be 3.1%[26]. In general, the estimated risk of developing symptomatic hemorrhage is 0.1 to 1.3% per person-year in patients who have not experienced previous hemorrhages[22,27-29]. On the other hand, the clinical risk of hemorrhage increases to 4.5% in patients who had experienced a previous symptomatic hemorrhage[28]. The risk of hemorrhage is notably higher in cavernomas located in the brainstem (10.9%) compared to those in supratentorial regions (1.7%)[4,30].

The location of cavernous malformations can significantly impact their clinical presentation. In one study, 53% of patients with supratentorial lesions presented with seizures, while 64% of patients with infratentorial cavernomas presented with focal deficits. The risk for developing epilepsy in parenchymal cavernomas is 1.51% per person-year (1.35% for a single lesion and 2.48% for multiple lesions)[27].

In a series of 137 patients with brainstem cavernomas, 77% presented with cranial neuropathies, and 53% had limb paresis, for cases located in the midbrain, symptoms included diplopia (69%), hemiparesis (48%), hydrocephalus, and ataxia (each in 38%). Uncommon symptoms found in this series included rubral tremor, involuntary laughter, paroxysmal coma, and vertical gaze palsy. Parkinsonism, hemichorea, and extrapyramidal symptoms have been attributed to cavernomas located in basal nuclei or thalamus[31].

Diagnostic imaging

MRI stands as the most sensitive and specific diagnostic tool for evaluating cavernomas. The MRI protocol should include conventional T1 and T2-weighted

images, Gradient Echo/susceptibility-weighted imaging (SWI) in the axial plane, and diffusion-weighted images[3].

Typically, magnetic resonance imaging reveals enhanced multiloculated cystic lesions with a "popcorn" or "mulberry" appearance on T1 and T2 sequences due to continuous bleeding from capillaries and venules[9]. On the susceptibility – weighted imaging sequence, they appear as hypointense cavities that can be observed from a few millimeters in diameter[5], proving highly sensitive in detecting the presence of small, cavernous malformations[7] (Fig. 1).

Based on the MRI appearance, Zabramski et al.[29], classify cavernomas into 4 types: Type I, subacute bleeding dominated by methemoglobin, showing hyperintensity on T1 and T2. Type II presents mixed signal intensity on T1 and T2 with a hypointense hemosiderin ring on T2, representing evolving hemorrhage with varying ages (thrombosis of different durations). Type III exhibits hypo- or isointensity on T1 and T2 due to chronic bleeding, commonly asymptomatic lesions often seen in familial forms[2]. Type IV, poorly visualized, appears normal on T1WI and T2WI except on susceptibility-weighted imaging (T1* and T2* sequences), and with contrast administration, it can be differentially diagnosed from capillary telangiectasias, which enhance with contrast. Among these, Type II is the most frequent and typical (50-67%)[3,12,26,29]. In the case of a large hemorrhage, a Type II or III lesion may revert to the appearance of a Type I lesion[26]. The classification serves to predict which cavernomas are at risk of bleeding[6].

Following an acute hemorrhage, the only possible imaging manifestation of a cavernous malformation may be a parenchymal hematoma. Yun et al. reported T1 hyperintensity in perilesional edema surrounding an acute or subacute hematoma in 62% of cavernomas with recent bleeding. This finding was highly specific (98%) and predictive (95%) for a cavernoma, considered a useful sign to discriminate hemorrhagic cavernomas from other bleeding lesions[3] (Table 1).

BLED$_2$ risk score

The BLED$_2$ scale is a tool created to assist physicians to evaluate the risk of recurrent hemorrhage in case of not following treatment (Table 2). Survival without events was significantly higher in patients with lower score values ($p < 0.001$). The score and percent risk at 1, 2, and 5 years can be calculated at: https://bled2-score.shinyapps.io/BLED2_Score/[32].

Treatment

The recommendations for the treatment of patients with cavernomas vary, ranging from operating on lesions as soon as they are discovered to opting for surveillance[11]. Consensus generally recommends surgery when cavernomas are symptomatic[4].

Treatment should be individualized by comparing it with the natural history of cavernomas in specific clinical scenarios and the region where they are located[33].

Neurological considerations

In clinical practice, for patients with epilepsy related to cavernomas, it is recommended to start antiepileptic treatment to achieve seizure freedom in 50-60% of cases after diagnosis. Conservative treatment should be offered to patients with incidental diagnoses due to their low risk of seizures (< 1%/year). Standard migraine therapy is suggested for patients with recurrent migraines and cavernous malformations. Although some studies show that non-steroidal anti-inflammatory drugs are safe, more research is needed to confirm this evidence[33].

Surgical treatment

For asymptomatic patients, surgical resection is not recommended, regardless of whether there is a single lesion or multiple cavernous malformations. Surgery should be considered for symptomatic cavernomas in easily accessible areas (supratentorial regions), where the risks of mortality and morbidity are comparable to living with the cavernous angioma for approximately 2 years. In contrast, surgery in more eloquent locations is associated with higher risks; and is generally recommended only for symptomatic cases or after a hemorrhage, where the risks of mortality and morbidity are comparable to living with the cavernous malformation for 5-10 years. Surgical resection has shown success rates ranging from 70% to 90% in patients with seizures refractory to medical treatment and sporadic seizures. Some authors advocate for early surgery, even if the criteria for medically refractory epilepsy are not met, to reduce the risk of hemorrhage[33].

Indications for surgery in brainstem cavernomas

General indications for operating on brainstem cavernomas include any of the following scenarios: first or second clinically symptomatic hemorrhage, aggressive lesions with multiple hemorrhages,

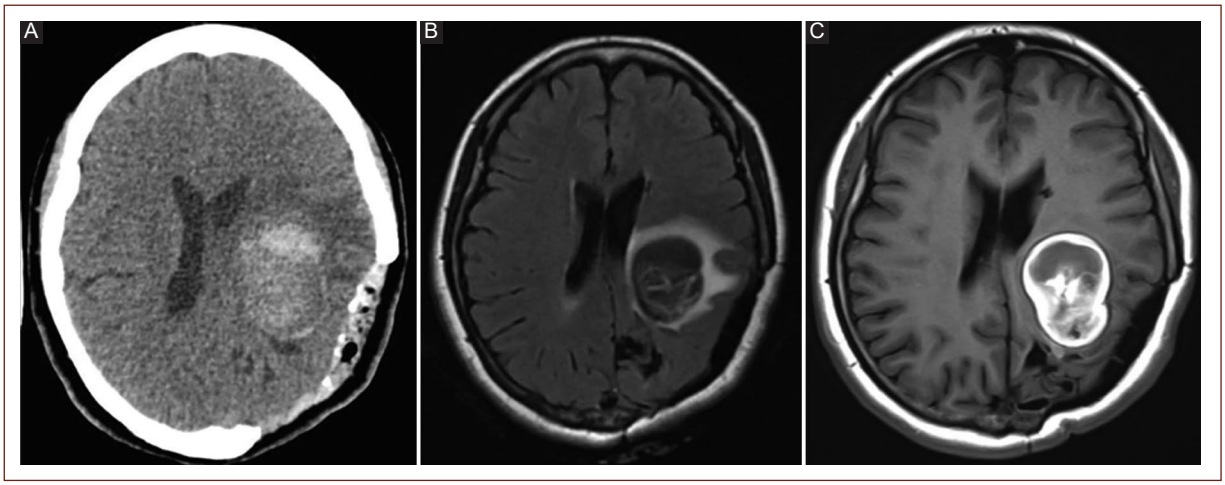

Figure 2. CT and MRI Images**. A:** a simple head CT scan shows a rounded heterogeneous left parietal lesion with a hyperdense border, surrounded by an area of hypodensity. **B** and **C:** axial T1 - weighted FLAIR MRI, left parietal lesion with heterogeneous content and perilesional edema. MRI: magnetic resonance imaging; CT: computed tomography.

superficial or exophytic lesions, lesions located near the pial membrane, mass effect on the brainstem causing altered consciousness or requiring life support, lesions ≥ 20 mm in size and severe or progressive neurological dysfunction[34].

Currently, it is recommended to delay surgery for a period of 4-6 weeks after a symptomatic hemorrhage, unless the patient exhibits altered consciousness, cardiorespiratory instability, or progressive neurological deficits. This time frame corresponds to a subacute phase. Surgical intervention within the initial 2 weeks is discouraged because the hematoma remains solid, and perilesional edema reaches its peak, heightening the risk of post-operative complications. During the recommended period, the hematoma liquefies, and edema decreases, facilitating dissection. Evacuating the hematoma typically creates an ideal space for cavernoma removal without the need to retract the brainstem. In contrast, surgery after 8 weeks involves hematoma retraction and organization, accompanied by gliosis, hyaline degeneration, and calcifications. This leads to adhesion between the cavernoma and brain parenchyma, escalating the risk of mechanical trauma during the procedure[34].

Management during pregnancy

In pregnancy, when dealing with seizure disorders secondary to cavernomas, the appropriate antiepileptic medication should be carefully chosen to minimize teratogenic effects[33].

Neurosurgery during pregnancy is rarely required but must be performed immediately in life-threatening and rapidly progressing clinical situations. It may be considered in cases of previous hemorrhage, family history of cavernomatosis, high-risk genes, or uncontrolled seizures. If such symptoms arise after the 30th week of gestation, surgery should be performed during the postpartum period[19,20].

It is important to highlight the challenges encountered when performing neurosurgery during pregnancy. The first challenge is pre-operative evaluation. Since the use of gadolinium is contraindicated, some authors recommend its use based on the risk-benefit ratio for the patient. Alternatively, they suggest considering the possibility of a subsequent surgery during the postpartum period after an MRI with gadolinium to complete the intervention performed during pregnancy. The second issue is the use of general anesthesia, primarily due to the difficulty in securing the airway, which is the most common cause of fatal adverse events associated with general anesthesia in pregnant women[19,20].

Currently, there is no consensus on the optimal delivery method for pregnant women with CCM. Some specialists prefer cesarean delivery, reasoning that it may prevent elevated blood pressure and lower the risk of hemorrhage. However, vaginal delivery is not contraindicated[19,20].

A multidisciplinary team should be involved to determine the most appropriate delivery method and assess

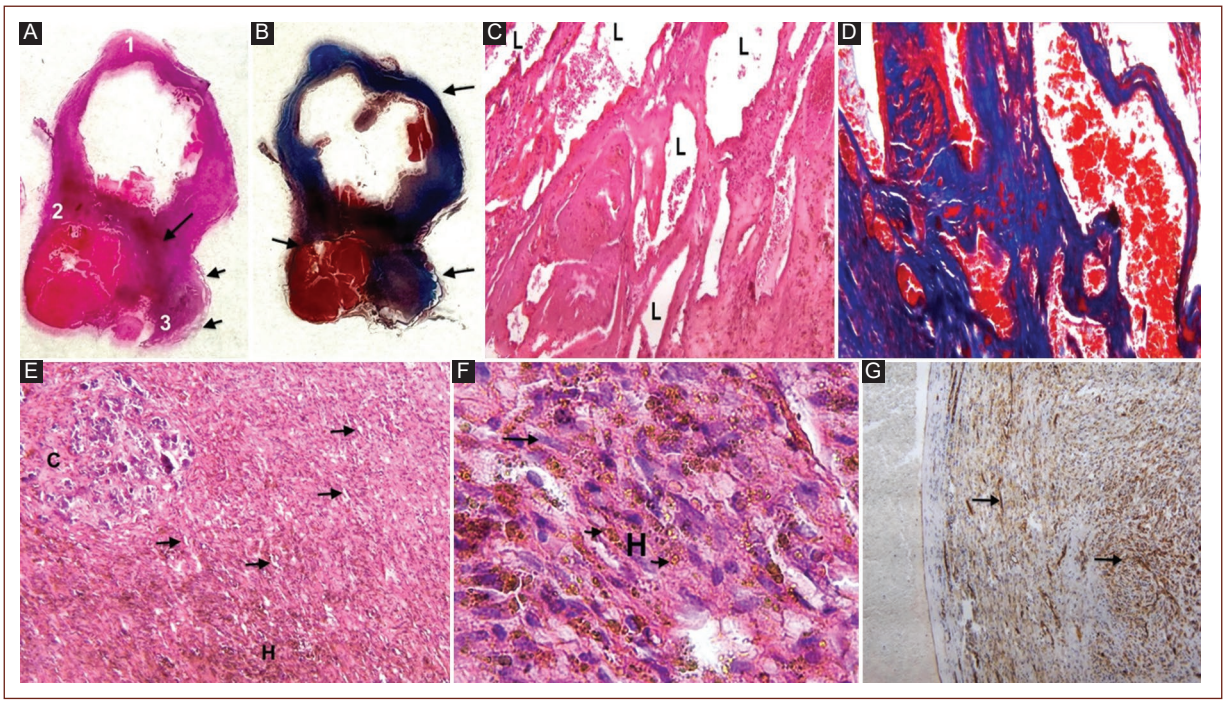

Figure 3. Histopathology. **A:** a complete section of the lesion is observed showing at least three very dilated venous vessels (1-3) and the periphery, numerous dilated vessels with smaller diameters (short arrows). A more hyperchromatic irregularly nodular area is also observed (long arrow), which corresponds to part of a thrombus in the process of recanalization and endothelial proliferation without atypia, as well as numerous hemosiderin deposits. **B:** Masson's trichrome stain shows that the vascular walls are made of collagen. **C:** at higher magnification, the vessels in the periphery show dilated lumen (L) and fibrous, irregular walls. The vessels are in close contact with each other. **D:** the walls of these vessels are made up of collagenous tissue (blue staining). Masson's trichrome. ×50. **E:** the thrombus in the process of recanalization shows calcifications (C), and moderate cellularity, with a proliferation of small vascular channels, lined with endothelial cells (arrows), and numerous hemosiderin deposits (H), H&E, ×50. **F:** at higher magnification in the area of the thrombus, the proliferation of small vessels is observed, with prominent endothelium, with elongated nuclei, slightly hyperchromatic, but without atypia (long arrow), as well as numerous hemosiderin deposits (short arrows). **G:** immunohistochemistry for CD34 shows vascular proliferation (arrows).

the need for neurosurgical intervention to ensure the safety of both the mother and the fetus[19,20].

Similarly, it is important to reach a consensus on the risks, or lack thereof, regarding hemorrhage during pregnancy, as a study by Witiw and colleagues found that patient's reproductive decisions were influenced by counseling from neurosurgeons and obstetricians. On the other hand, some patients reported not receiving any information on this matter[35].

Prognosis and follow-up

Due to the unpredictable evolution of CCM, there are no guidelines to guide follow-up in asymptomatic patients. In these cases, the use of serial imaging remains controversial. The emergence of new neurological symptoms suggestive of bleeding justifies a repeat imaging as soon as possible. Follow-up imaging is suggested when cavernoma growth of 5 mm or more has been demonstrated or in patients with risk factors for mimicking these malformations (e.g., advanced age or a history of systemic cancer)[3].

Alafi et al. conducted a 10-year prospective study on 75 patients newly diagnosed with cavernoma. Twenty-one percent had the familial form, while 72% did not have a confirmed genotype. Initially, 36% were asymptomatic, and 64% exhibited symptoms. The most common included cerebral hemorrhage, seizures unrelated to hemorrhage, spinal cord hemorrhage, and focal neurological deficits. Regardless of the treatment provided (pharmacological, surgical, or SRS) and the number of surgeries, the study results indicate that at the last follow-up, 83% of the patients were independent, with a modified Rankin Scale (mRS) score of ≤ 2, and patients with multiple hemorrhages (> 1)

were more likely to have an mRS score of 3 or higher[36]. However, data on short- and long-term functional prognosis remains limited.

Clinical report

A 37-year-old woman with a medical history of well-controlled epilepsy and no family history of cavernomas, presented with an obstetric history of three pregnancies, three vaginal deliveries, and tubal ligation.

At age 28, during her third pregnancy (at 23 weeks of gestation), she suffered a left parietal intracerebral hemorrhage with ventricular rupture, requiring surgical intervention. This hemorrhage was not associated with pregnancy-induced hypertension, and diagnostic evaluation did not reveal any vascular malformations.

Eight years later, she had a recurrence manifesting as a left frontoparietal hemorrhage, which did not require surgical intervention. Subsequent brain imaging and angiography did not show any vascular malformations. Several months later, she experienced another bleeding episode, and MRI identified a circumscribed, heterogeneous, hyperintense lesion with a hemosiderin halo. She was discharged without complications for further outpatient evaluation.

One year later, during a follow-up visit, a left frontoparietal lesion was noted, showing contrast enhancement and perilesional edema, although it was neurologically asymptomatic. The imaging findings suggested a cerebral abscess (Fig. 2), prompting surgical resection. One month post-discharge, she was evaluated with a mRS score of 3, which improved to 1 after 3 months. During surgery, a 32×30×30 mm smooth, shiny, reddish-brown tissue fragment was excised. Histopathological examination revealed multiple cavities with identifiable vascular walls. Several sections confirmed the presence of a cavernous malformation, with three markedly dilated vessels, one of which contained a thrombus. The vessel walls were thin and irregular, primarily composed of collagenous tissue, as demonstrated by Masson's trichrome staining. The thrombus demonstrated active recanalization, with numerous vessels lined by prominent endothelium, without atypia, and extensive hemosiderin deposits that extended into the vessel walls. The final diagnosis was cavernoma, with areas of calcification, hemosiderin deposition, and a large thrombus undergoing recanalization (Fig. 3). Currently, at 44 years of age, she has a mRS score of 0 and maintains good control of her epileptic seizures on carbamazepine 200 mg 3 times daily.

Conclusion

Cavernomas present a challenge in treatment selection due to their clinical variability. Medical attention should focus on evaluating risk factors and cavernoma characteristics, considering that the risk of seizures and bleeding is directly proportional to the number of cavernomas. In addition, the risk of bleeding increases after a previous hemorrhage. However, there is no causality between bleeding and pregnancy. MRI and risk scales, such as $BLED_2$ score are crucial for diagnosis, patient guidance, prognosis assessment, treatment, and personalized follow-up based on symptoms, location, and short/long-term morbidity.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of 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 study does not involve patient personal data nor requires ethical approval. The 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 of this manuscript.

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