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EDITORIAL

Meet the editor: Ulises R. Coffeen-Medina

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Ulises R. Coffeen-Medina

Integrative Neurophysiology Laboratory, Neuroscience Research Unit, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Mexico City, Mexico

Dr. Coffeen was born in Mexico City. He received his degree in biology from the Metropolitan Autonomous University. Under the supervision of Dr. Rafael Villalobos Molina, he conducted research on cell membrane phospholipids during aging as part of his social service at the National Polytechnic Institute's Department of Pharmacobiology of the Center for Research and Advanced Studies (CINVESTAV) (Fig. 1).

He completed his Master of Science degree in the postgraduate course Neuropharmacology and Experimental Therapeutics at CINVESTAV, under the co-tutorship of Dr. Francisco J. López Muñoz and Dr. Francisco Pellicer Graham. The study carried out addressed the mechanisms of central neurotransmission during the development of neuropathic pain. During this period, she joined as a research assistant in the Integrative Neurophysiology Laboratory in the Neuroscience Research Unit of the Ramón de la Fuente Muñiz National Institute of Psychiatry (INPRFM).

He continued his research on pain mechanisms at the level of the central cortical nuclei associated with pain perception to get his PhD in the aforementioned postgraduate program at CINVESTAV. At the same time, he did a research stay at the Neurobiology Unit of Trigeminal Pain, belonging to the INSERM in Clermont-Ferrand, France, then under the direction of Dr. Luis Villanueva, carrying out anatomical and electrophysiological studies on the corticothalamic and corticotrigeminal pain mechanisms.

Throughout his career, he has been part of different collegiate bodies and scientific committees, highlighting his current participation as a member of the INPRFM Research Ethics Committee. He has been an evaluator of research projects at the Secretariat of Science, Technology, and Innovation of Mexico City and in the Research Summer of the Mexican Academy of Sciences. He has also received funding from the National Council of Humanities, Science, and Technology (CONAHCYT) for research projects. He has taught various courses related to the neurophysiology of pain and is an accredited tutor in the Biological Sciences Postgraduate Program at the National Autonomous University of Mexico (UNAM).

He has published 28 peer-reviewed scientific papers in indexed international journals, mostly focus on pain and neurosciences. He has attended 25 national conferences and 38 international ones. It should be emphasized that in 2021, the UNAM, the Ramón de la Fuente National Institute of Psychiatry, and the Ramón de la Fuente A.C. Foundation presented him with the distinction of First Place as a Neuroscience Researcher.

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Figure 1. Ulises Coffeen-Medina.

He is currently employed by the Ministry of Health as a Researcher in Medical Sciences “C” and is Level 1 of the National System of Researchers by CONAHCYT. He is conducting research on the neurophysiopathological mechanisms underlying neuropathic pain and alternative therapies in addition to branching out into translational biomedicine to directly connect neurobiological bases with clinical practice.

Regarding his experience in editorial work, he served as the Guest Lead Editor for the special issue “Chemotherapy-Induced Neuropathic Pain: From Bench to Bedside” of the journal Pain Research and Management. He is also a reviewing editor in the Headache and Neurogenic Pain section of the journal Frontiers in Neurology. Recently, he has started a new phase as editor of the Translational Neurosciences section of the journal Archivos de Neurociencias.

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ORIGINAL ARTICLE

Conditions of equality between doctors in 2021 at the National Institute of Neurology and Neurosurgery

Condiciones de igualdad entre médicas y médicos en 2021 en el Instituto Nacional de Neurología y Neurocirugía

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Abstract

Background: *Despite efforts to achieve equality in education and professionalization, gender biases persist and affect the professional development of women in neuroscience.* **Objective:** *To provide an overview of the conditions of equality in the professional and academic environment of the National Institute of Neurology and Neurosurgery (INNN) during 2021, aiming to document the extent of inequality between female and male physicians.* **Method:** *An observational, retrospective, cross-sectional, and analytical study was conducted. Information on the number and gender of residents, researchers, staff, and administrators at INNN in 2021 was collected. The records of research protocols submitted in 2021, and their outcomes were analyzed.* **Results:** *In 2021, there were a total of 320 physicians at INNN (122 women [38.1%] and 198 men [61.9%]). The breakdown by groups was 186 residents (58.2%; 73 women [39.35%] and 113 men [60.75%]), 82 specialists (25.6%; 34 women [41.46%] and 48 men [58.54%]), 12 researchers (3.8%; 6 women [50%] and 6 men [50%]), and 40 administrators (12.5%; 9 women [22.5%] and 31 men [77.5%]).* **Conclusions:** *Despite some progress, female physicians continue to face gender gaps. Policy changes towards gender parity in medicine are necessary to create equal opportunities in academic and professional settings, ensuring fair and comprehensive development for women.*

Keywords: *Sexism. Female physicians. Neuroscience.*

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Resumen

Antecedentes: *A pesar de los esfuerzos por alcanzar la igualdad en el acceso a la educación y la profesionalización, persisten sesgos de género que inciden en el desarrollo profesional de las mujeres en las neurociencias.* **Objetivo:** *Presentar un panorama general de las condiciones de igualdad en el ámbito profesional y académico del Instituto Nacional de Neurología y Neurocirugía (INNN) durante 2021, con la finalidad de documentar la magnitud de desigualdad entre médicas y médicos.* **Método:** *Se realizó un estudio observacional, retrospectivo, transversal y analítico. Se recolectó información sobre el número y el sexo de residentes, investigadores, adscritos y administrativos del INNN en 2021. Se analizó el registro de los protocolos de investigación sometidos en 2021, así como sus productos.* **Resultados:** *En 2021, en el INNN hubo un total de 320 médicas y médicos (122 mujeres [38.1%] y 198 hombres [61.9%]). Las proporciones correspondientes por grupo fueron 186 residentes (58.2%; 73 mujeres [39.35%] y 113 hombres [60.75%]), 82 especialistas (25.6%; 34 mujeres [41.46%] y 48 hombres [58.54%]), 12 investigadores (3.8%; 6 mujeres [50%] y 6 hombres [50%]) y 40 administrativos (12.5%; 9 mujeres [22.5%] y 31 hombres [77.5%]).* **Conclusiones:** *A pesar de los avances, actualmente las médicas siguen luchando contra las brechas de género. Es necesario un cambio de políticas a favor de la paridad en la medicina, para crear igualdad de oportunidades en los ámbitos académico y profesional, y así garantizar un desarrollo justo e integral de las mujeres.*

Palabras clave: *Sexismo. Médicas. Neurociencias.*

Introduction

In 2021, the United Nations Educational, Scientific and Cultural Organization (UNESCO) published the Report on Higher Education in Latin America and the Caribbean from 1995 to 2018, highlighting that in terms of enrollment in higher education, women were overrepresented in 74% of countries with available data (including Mexico). In the field of medicine, approximately 50% of all undergraduate entrants are women[1]. Do these percentages result in equality in access to specialization levels and, especially, in professional development? This question is the main focus of this study, which aims to understand and describe the distribution of men and women at *Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez (INNN)*.

Although since the 1970s, women have entered various academic and professional spaces in large numbers, this has not necessarily translated into true equality. For instance, between 2017 and the first quarter of 2020, the mean wage gap was 15%, which means that for every 100 pesos men earned monthly, women only earned 85 pesos[2]. In medicine, studies indicate that horizontal segregation persists, both academically at the specialization level and in access to professional spaces. A 2015 study conducted by *Universidad Nacional Autónoma de México* found that female doctors tend to cluster in certain specialties (public health, ophthalmology, pathology, pediatrics, rehabilitation, anesthesiology, and family medicine) and are underrepresented in surgical specialties, such as traumatology and orthopedics, general surgery[3].

According to the *National Survey of Occupation and Employment*, in 2021, Mexico had 305,418 people employed as doctors, 54% of whom were men and 46%, women. Among residents, specialists, researchers, and administrative staff in the medical field, there is an unequal professional trajectory: women experience less promotion and professional recognition than men do. In some cases, they are asked to be twice as productive to gain access to research funding or obtain a position of the same rank as their male colleagues[4]. Furthermore, a male-focused perspective[5] prevails in the workplace, based on gender roles and duties assigned to men and women. Women's work is also precarious, as they still occupy low-paying positions with limited decision-making power and few, if any, labor rights.

Neurology is one of the medical fields where underrepresentation of women has been recognized. Although specific data on the presence of men and women in Mexico is lacking, it is known that in 2017, the estimated number of male and female neurologists was 906 and 351, respectively, and the ratio of men to women training as neurosurgeons in Mexico was 18:1[6].

Research in other locations provides a more detailed view of the discipline. For example, a study conducted in the United States found that, in 2013, women made up 32.6% of the general physician workforce and only 26.9% of the 13,142 practicing neurologists. This study clearly demonstrates a pattern showing a near-identical gender gap in academic medicine, including neurology, with disparities increasing with academic rank[7,8].

Another measure of how gender inequality manifests is scientific output[9]. Among authorships in neuroscience research[10-13], only between 23.8 up to 39.6% are women. Similarly, women are less likely to gain prominence on multi-author reports[10].

A cross-sectional study in the United States that included a total of 1712 academic neurologists found that only 31% were women. Men outnumbered women across all academic faculty ranks, with the discrepancy growing at higher ranks. This contrasts with the fact that 44.9% of neurology residents were women, suggesting that although a significant number of women train as neurologists, few reach high-ranking professional and academic positions[13].

Theoretical framework

The analytical tools used in this study derive from a gender perspective. Gender is an analytical category that helps us understand how the relationships between men and women function both in practice and symbolically within a given society. Gender is defined as "the articulated set of customs, values, rules, norms, and laws with which societies regulate the formation of subjectivities; the definition of roles, functions, and lifestyles permitted and accepted for women and men"[14].

Gender relations permeate the cultural and social lives of human beings through education, work, health, and access to opportunities. Even legal life is shaped by agreements defining the masculine and feminine in social interaction spaces. Thus, gender is expressed on individual, cultural, and structural levels.

Applying a gender perspective to the analysis of social reality allows us to visualize different phenomena (scientific, academic, social, or political) that consider the implications and effects of social power relations between genders, male and female, on one level, and between men and women, on another[15].

According to United Nations Women, gender equality refers to equal rights, responsibilities, and opportunities for men and women alike, as well as girls and boys. It recognizes the diversity among different groups of women and men[16]. Gender inequality arises from numerous interactions and feedback loops across individual, family, work, and social spheres[17]. Historically, women and other groups have been excluded from fully enjoying and exercising their rights. This practice is known as structural violence and has certain characteristics: 1) it is based on a social order that transcends individual will; 2) it accumulates disadvantages over a lifetime and across generations; and 3) it has broad social implications, affecting the enjoyment of fundamental rights and perpetuating inequality[18].

Gender disparities are varied and context dependent. Specifically, in the workplace, the International Labour Organization has identified multiple forms of these disparities, which can manifest in hiring and recruitment processes, in setting salaries and promotions, and in participation in decision-making spaces within organizations[19].

The goal is that recognizing these inequalities and discriminatory conditions will enable changes to achieve an equitable distribution of activities and fair valuation, and above all, to rebuild the social and cultural structures that reproduce these asymmetries.

Objective

The objective of this study is to describe the differences in the presence of men and women in the areas of training, clinical care, and academic development within the field of neurosciences at the INNN.

Method

We conducted an observational, retrospective, cross-sectional, quantitative, and analytical study. Information was collected on the number and sex of all licensed doctors and those in training (i.e., those undergoing residency) at the INNN during 2021. Data collection was conducted through information provided by the Teaching Directorate, the Research Directorate, and the website of the Public Service Secretariat of the Mexican Government. For practical purposes of this study and based on their main institutional role (academic or professional), individuals were categorized into: doctors in residency for specialty, sub-specialty, and high specialty were categorized into group #1; doctors with medical specialist appointments were included in group #2; doctors with research appointments were categorized into group #3; and doctors with administrative appointments were categorized into group #4.

The sociodemographic data collected are described below on a per group basis. For group #1, data collected included sex, number of residents by year, and postgraduate course (specialty, sub-specialty, and high specialty). For groups #2, #3, and #4, data on sex, highest level of education, specialty title, membership in the National System of Researchers, and participation as a principal or adjunct professor in postgraduate courses were gathered. Additionally, for group #2, the type of medical appointment (A or C) was recorded; for group #3, the type of research appointment (A to F, or emeritus); and for group #4, the administrative level was categorized based on net monthly salary (Level 1: $12,731.9 up to $17,869.63;

Table 1. Proportion of male and female doctors by groups (residents, specialists, researchers, and administrative staff), relative to the total, at *Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez*, in 2021

Groups	Men	Women	Total
	n (%)	n (%)	n (%)
Group #1: Total of male and female residents (specialty, subspecialty, and high specialty courses)	113 (60.8%)	73 (39.3%)	186 (58.2%)
Group #2: Total of male and female doctors with medical appointment	48 (58.5%)	34 (41.5%)	82 (25.6%)
Group #3: Total of male and female doctors with research appointment	6 (50%)	6 (50%)	12 (3.8%)
Group #4: Total of male and female doctors with administrative appointment	31 (77.5%)	9 (22.5%)	40 (12.5%)
Total	198 (61.9%)	122 (38.1%)	320 (100%)

Level 2: $31,327.12; Level 3: $43,119.19; Level 4: $95,037.77).

For purposes of this research, scientific productivity was quantitatively defined through the total accumulated for the year 2021 of the following indicators: the number of research protocols submitted by doctors to the Clinical Research Department from January 1st, 2021 through December 31st, 2021; the number of theses published in 2021 in the academic thesis catalog in the electronic database of the General Directorate of Libraries and Digital Information Services of Universidad Nacional Autónoma de México (tesiunam.dgb.unam.mx), and those for which they served as tutors; the number of citations; and the H-index (the last 2 obtained through www.scopus.com).

Results

In 2021, there was a total of 320 doctors at INNN (122 women [38.1%] and 198 men [61.9%]). The corresponding proportions of groups #1, #2, #3, and #4 are shown in table 1. In group #1, a total of 5 residents (1.6%) held the distinction of chief resident, 4 of whom were men (80%) and only 1, a woman (20%).

The distribution of male and female residents by specialty, sub-specialty, and high specialty is shown in table 2. Fisher's exact test was used to determine whether there was a significant association between gender and postgraduate course, finding a significant difference between men and women ($p = 0.012$). The predominance of men was evident in neurosurgery and neurology, as well as in high-surgical specialties, including skull base surgery, endoneurosurgery, spine surgery, vascular neurosurgery, neuro-oncology, and radiosurgery, among others.

In groups #2, #3, and #4, 14 female doctors (28.6%) and 22 male doctors (25.9%) had a specialty in neurology, 13 women (26.5%) had a master's degree, and 3 (6.1%) had a PhD, while 13 men (15.3%) had a master's degree and 4 (4.7%) had a PhD.

Regarding membership in the National System of Researchers, most women (77.6%) were not members; however, those who were members, were concentrated in levels 2 and 3, with 4 in each (8.2%). Similarly, most men (88.2%) were not members, but those who were members, were more concentrated in level 1 (5.9%).

Regarding their participation in postgraduate courses, women did not hold any specialty courses as principal or adjunct professors. Only 3 women (6.1%) were principal professors in sub-specialty courses, and 4 women (8.2%) were adjunct professors in sub-specialty courses. Regarding high-specialty courses, 5 women (10.2%) were principal professors and 10 (20.4%) were adjunct professors. On the other hand, 3 men (3.5%) were principal professors in specialty courses, and 4 (4.7%) were adjunct professors in specialty courses; 3 (3.5%) were principal professors in sub-specialty courses and 2 (2.4%) were adjunct professors; and 15 (17.6%) were principal professors and 11 (12.9%) were adjunct professors in high-specialty courses.

In group #2, 27 women (79.4%) and 38 men (79.2%) had a medical appointment type C.

In group #3, most women (33.3%) fell in the group with a research appointment in medical sciences type E. In the case of men, 33.3% fell in the group with a medical appointment type D. However, it is important to note that the only emeritus researcher was in the male group.

Regarding group #4, most women (77.8%) and men (74.2%) fell in the first administrative level based on their net monthly salary.

Table 2. Distribution of residents by sex and specialty, subspecialty, and high specialty courses, at *Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez*, in 2021

Course	Men, n (%)	Women, n (%)	Total, n (%)
Specialties			
Neurology	24 (66.7)	12 (33.3)	36 (19.4)
Neurosurgery	29 (93.6)	2 (6.5)	31 (16.7)
Psychiatry	12 (46.2)	14 (53.9)	26 (14.0)
Subspecialties			
Neuroradiology	4 (40)	6 (60)	10 (5.4)
Neurotology	3 (75)	1 (25)	4 (2.2)
Neuroanesthesiology	6 (37.5)	10 (62.5)	16 (8.6)
Clinical neurophysiology	5 (83.3)	1 (16.7)	6 (3.2)
Neurological ophthalmology	0 (0)	2 (100)	2 (1.1)
Endovascular therapy	5 (55.6)	4 (44.5)	9 (4.8)
High specialty postgraduate courses in medicine			
Skull base surgery and endoneurosurgery	1 (100)	0 (0)	1 (0.5)
Spinal surgery	2 (100)	1 (33.3)	3 (1.6)
Epilepsy surgery	0 (0)	2 (66.7)	2 (1.1)
Cerebrovascular disease	2 (66.7)	2 (66.7)	4 (2.2)
Autoimmune and demyelinating diseases of the central nervous system	0 (0)	0 (0)	0 (0)
Neurodegenerative diseases and movement disorders	2 (66.7)	1 (33.3)	3 (1.6)
Neuromuscular diseases	2 (66.7)	1 (33.3)	3 (1.6)
Cognitive aging and dementias	1 (50)	1 (50)	2 (1.1)
Clinical epileptology	0 (0)	1 (100)	1 (0.5)
Schizophrenia neurobiology	2 (66.7)	0 (0)	2 (1.1)
Nuclear neurosciences	0 (0)	2 (100)	2 (1.1)
Functional and stereotactic neurosurgery	1 (33.3)	1 (100)	2 (1.1)
Vascular neurosurgery	1 (33.3)	1 (100)	2 (1.1)
Neuroendocrinology	1 (100)	1 (50)	2 (100)
Neurogenetics	1 (50)	1 (33.3)	2 (100)
Neuro-oncology	1 (33.3)	1 (50)	2 (100)
Neuropsychiatry	3 (60)	3 (100)	6 (3.2)
Radioneurosurgery	0 (0)	3 (42.9)	3 (1.6)
Neurological rehabilitation	1 (33.3)	1 (100)	2 (100)
Magnetic resonance	0 (0)	2 (100)	2 (100)
Neurological intensive therapy	3 (60)	2 (40)	5 (2.7)
Neurological emergencies	0 (0)	2 (100)	2 (100)
Total	113 (60.75)	73 (39.25)	186 (100)

Table 3. Mean productivity of groups #2, #3, and #4 in published theses, H-index, and citations at *Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez*, in 2021

	Men	Women
Theses	0.65 ± 1.17	0.55 ± 1.20
H-index	4.89 ± 7.19	4.24 ± 6.50
Citations in 2021	26.65 ± 60.71	34.55 ± 102.95

In terms of productivity, 78 (53.4%) out the 146 protocols submitted to the Clinical Research Department in 2021 had male principal investigators, and only 68 (46.6%), female principal investigators. During the first half of 2021, 59 high-impact publications were made at INNN in the main lines of research on neurological problems, of which female researchers at INNN were involved in 33 (55%); however, only in 2 of these publications (6%) were women listed as first authors[20].

Table 3 shows the differences between men and women regarding published thesis data in the electronic database of the General Directorate of Libraries and Digital Information Services of Universidad Nacional Autónoma de México, as well as the H-index and number of citations during 2021.

Discussion

It has been observed that women face invisible barriers that hinder their progress and negatively affect efforts to achieve gender parity in science, medicine, and scientific research, understood as balanced participation and representation of women and men in decision-making and positions of power[21,22].

Among these obstacles are "sticky floors," a metaphor representing the historical, social, and cultural difficulties and conditions that women must overcome to access the initial levels of the academic career; "concrete walls," lateral barriers that limit their potential; and "glass ceilings," hard-to-identify obstacles that keep women from reaching the highest positions in the hierarchy[23,24].

Our results are consistent with national and international data: there is a difference in the presence of men and women. In most areas of training, clinical care, and administration, there is a higher proportion of men. This indicates a formative, technical, and administrative organization with a significant imbalance, negatively affecting gender parity in medicine, scientific research, and neuroscience.

An important gap can be observed in the figures once medical school is completed and when entering a postgraduate course or specialty, particularly in surgical fields such as neurosurgery. Thus, women are at a clear disadvantage in these cases. Even though women may initially be the majority, at some point, the situation reverses, making the gender gap evident, which is known as the "leaky pipeline theory"[25].

The number of female and male doctors in the workforce, in general, is not significantly different. However, the difference is significant in those holding administrative positions, 77.5% of whom are men. This is important because administrative positions involve power and access to decision-making. Due to the underrepresentation of women, there is a lack of recognition of policies favoring the comprehensive development of women. This difference highlights the existence of "sticky floors" and a significant "glass ceiling" in the organization[23].

Furthermore, there is an underrepresentation of women in research. Few women appear as first authors of articles published in high-impact journals, which reflects the poor recognition of their contribution. Moreover, men occupy more principal positions in postgraduate courses, while women are more concentrated in adjunct professor positions. This could largely be attributed to the fact that women tend to engage more in work associated with public services and domestic tasks compared to men, who can dedicate more time to curricular activities that contribute more to their professional development, such as research or teaching. This, in the long term, places them at a clear advantage over their female colleagues in the professional field[1,26].

As previously mentioned, this disparity is also expressed in horizontal and vertical segregation. At first, differences between sexes across various fields, disciplines, or work areas are observed longitudinally. In the second, discrimination within hierarchical organizations is noted transversally, such as the inability to access certain positions or differentiated salaries for the same work[27].

This analytical perspective uncovers both direct and indirect conditions of inequality and discrimination, that is, those expressed through rules or regulations, and those observed in practice through the division between femininity and masculinity by less visible mechanisms[28].

Conclusions

In light of these results, the key question we must address is the following: do the gender differences found in this study represent a manifestation of gender inequality, or are they simply a matter of chance, either due to women's lack of interest in participating or to a supposed lack of qualifications to do so?

To answer this question, it is important to highlight that there is a systematic tendency to attribute the gender gap to the alleged scarcity of qualified or interested women. This bias in the analysis of gender inequality is known as one of the "critical thinking errors related to gender equity." This approach, in addition to blaming women for the disparities, fosters deliberate ignorance among leaders and decision-makers, preventing the addressing of outdated practices and traditional criteria for evaluation, hiring, or promotion, to name a few[29].

The literature has identified various factors that contribute to inequities in income, retention, and advancement in the field of neurology. These include low levels of acceptance and integration into organizations, aggressive and male-dominated work environments, lack of policies that facilitate work-life balance, family responsibility overload, conscious or unconscious biases, lack of female role models in leadership positions, direct or indirect discrimination, and lack of gender parity in ranks and leadership[30-32].

Therefore, the answer to the initial question in this section is not found solely in the data of this study, but within a historical and global context regarding the representation and participation of women in the medical field, and particularly in neurology. There is compelling evidence that women practicing medicine have received lesser recognition despite their growing participation in medical education[30,33,34]. Data found intertwines with a broader picture that provides clear answers about how differences in access to certain positions, participation in research or publications, and other aspects, are fundamental to understanding that there is an environment

that does not favor equity between men and women. As numerous studies have pointed out, the problem of gender inequality in medical leadership is not due to a lack of qualified female candidates for leadership positions, nor can it be simply explained by suggesting that different genders do not have the same aspirations as men[35,36]. The problem is much deeper and more complex. We have systematic evidence of disparities against women in medicine (as students, clinicians, or leaders), which is reflected in differences in compensation, promotion, research funding, recognition, awards, and representation on the editorial boards of medical journals[35]. Additionally, hostile work environments persist, where violence such as harassment and sexual abuse occurs, supported by social norms and discourses that not only affect the medical field but society as a whole[37].

Various strategies have been proposed to address these gender inequities. Some authors suggest the use of unique and customizable metrics, as well as longitudinal data analysis that addresses plans for each institution, first evaluating the specific characteristics of organizations that contribute to disparities and then implementing concrete measures and assessing their effectiveness[34]. Furthermore, it is proposed to foster supportive communities, as well as the personal and professional development of women, and to make changes in policies at the systemic level that promote gender equity[38]. However, the need for policies that address the structural conditions supporting these inequalities is emphasized, leveraging collaboration with civil society, private organizations, and the state[33].

Despite advances, female doctors today continue to face significant social gaps. It is essential that, at INNN, being a center of great importance for training and research in our country, a diagnosis and changes of policies be made to promote gender parity. This will create equal opportunities both academically and professionally, ensuring a fair and comprehensive development of women.

Authors' contribution

AJ Hernández-Medrano and MA Sánchez-Guzmán: research project: a) conception; b) organization; c) execution. Analysis: a) design; b) execution; c) review and critique. Manuscript preparation: a) drafting of the first version; b) review and critique. GI Cerda-Hernández and A Domínguez-García: analysis: a) design; b) execution; c) review and critique. Manuscript preparation: a) drafting of the first version; b) review and critique. M Rodríguez-Violante, A Cervantes-Arriaga, and T Corona-Vázquez: analysis: a) design; b) execution; c) review and critique.

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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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ORIGINAL ARTICLE

Gender and functional status influence on emotional well-being in Parkinson's disease: insights from a cross-sectional study

Influencia del sexo y del estado funcional en el bienestar emocional en la enfermedad de Parkinson: conocimientos de un estudio transversal

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Abstract

Background: *Emotional well-being is a critical yet often overlooked component in the management of Parkinson's disease (PD), despite its profound impact on perception, decision-making, and social interactions. Previous studies have highlighted factors such as music therapy, social support, and motor symptom severity that influence emotions in PD. Gender, in particular, has been shown to affect emotional expression, with women generally displaying greater emotional expressiveness than men. However, the interaction between gender and emotional well-being in PD remains underexplored, warranting further investigation.* **Objective:** *To investigate the relationship between gender and emotional states in PD patients, exploring potential predictors of positive affect within this population.* **Method:** *An observational, cross-sectional study was conducted among 80 individuals with PD, assessing positive and negative affect using the Positive and Negative Affect Schedule (PANAS). Sociodemographic and clinical variables were collected, and statistical analyses were performed to identify associations and predictive factors.* **Results:** *Overall, no significant differences in affect were observed between male and female PD patients. However, male patients with higher functional status were predicted to exhibit greater positive affect. PANAS scores in our cohort were higher compared to previous studies, suggesting potential cultural or environmental influences on emotional outcomes.* **Conclusions:** *Our findings underscore the importance of considering functional status in understanding emotional well-being in PD patients. Tailored interventions targeting functional improvement may positively impact emotional health in this population. Further research is warranted to elucidate the complex interplay between gender, functional status, and emotional states in PD.*

Keywords: *Parkinson's disease. Emotional well-being. Gender differences. Positive affect. Functional status.*

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Resumen

Antecedentes: *El bienestar emocional es un componente crítico, pero a menudo pasado por alto en el manejo de la enfermedad de Parkinson (EP), a pesar de su profundo impacto en la percepción, la toma de decisiones y las interacciones sociales. Estudios previos han destacado factores como la musicoterapia, el apoyo social y la gravedad de los síntomas motores que influyen en las emociones en la EP. En particular, se ha demostrado que el género afecta la expresión emocional, con las mujeres generalmente mostrando una mayor expresividad emocional que los hombres. Sin embargo, la interacción entre el género y el bienestar emocional en la EP sigue estando poco explorada, lo que justifica una mayor investigación.* **Objetivo:** *Investigar la relación entre el sexo y los estados emocionales en pacientes con EP, explorando posibles predictores de afecto positivo dentro de esta población.* **Método:** *Estudio observacional, transversal, en 80 individuos con EP, evaluando el afecto positivo y negativo utilizando el Positive and Negative Affect Schedule (PANAS). Se recopilaron variables sociodemográficas y clínicas, y se realizaron análisis estadísticos para identificar asociaciones y factores predictores.* **Resultados:** *En general, no se observaron diferencias significativas en el afecto entre pacientes con EP de sexo masculino y femenino. Sin embargo, se predijo que los pacientes varones con un mayor estado funcional exhibirían un mayor afecto positivo. Los puntajes de PANAS en nuestra cohorte fueron más altos en comparación con estudios previos, lo que sugiere posibles influencias culturales o ambientales en los resultados emocionales.* **Conclusiones:** *Nuestros hallazgos destacan la importancia de considerar el estado funcional en la comprensión del bienestar emocional en pacientes con EP. Las intervenciones adaptadas que apuntan a mejorar la funcionalidad pueden impactar positivamente la salud emocional en esta población. Se requiere más investigación para elucidar la compleja interacción del sexo, el estado funcional y los estados emocionales en la EP.*

Palabras clave: *Enfermedad de Parkinson. Bienestar emocional. Sexo. Afecto positivo. Estado funcional.*

Introduction

The assessment of emotional well-being is often overlooked in the comprehensive management of individuals with Parkinson's disease (PD). Emotions play a pivotal role in human experience, influencing perception, decision-making, and social interactions, and hold significant predictive value for future outcomes[1-3]. While researchers have proposed various classifications of emotions, Ekman's model, initially comprising six universal basic emotions, remains widely accepted[4,5]. However, recent additions have expanded this spectrum, highlighting the complexity of human emotional experience. Despite the recognized importance of emotions, limited attention has been directed toward understanding their impact in PD.

Emotions and affect are vital to psychological experiences, but they differ in complexity and scope. Emotions are intense, triggered states characterized by specific responses such as feelings, physiology, and behavior (e.g., happiness, anger)[6]. Affect, in contrast, refers to general feelings or moods, not necessarily tied to a cause, influencing our perception and behavior more broadly[7]. Affect serves as the backdrop against which emotions unfold, reflecting underlying valence and arousal. Previous studies have explored the affect in PD, revealing associations with various factors such as music therapy, social support, and motor symptom severity[8,9]. Notably, gender has emerged as a significant factor influencing emotional expression and perception in adulthood. Research indicates that women tend to exhibit greater expressiveness across both positive and negative emotions compared to men, suggesting potential differences in emotional processing[10,11]. However, these distinctions are not necessarily indicative of women experiencing more positive affect; rather, they may reflect gender-related differences in emotional expression and reporting tendencies.

Considering these findings, investigating the interplay between gender and affect in PD is crucial for developing tailored interventions and enhancing the overall well-being of individuals living with this neurodegenerative disorder. However, there is a paucity of literature examining the influence of gender on affect in individuals with PD. Thus, our study sought to elucidate the relationship between gender and positive affect within a PD cohort. Furthermore, we aimed to construct a predictive model for positive affect scores in this population, contributing to a deeper understanding of emotional dynamics in PD.

Materials and methods

An observational, cross-sectional, comparative, and analytical study was conducted to explore the association between gender and positive and negative affect in individuals with PD (n = 80). Written informed consent was obtained from all participants, and the study received approval from our institutional review board. Subjects

were recruited from two movement disorders clinics: the National Institute of Neurology and Neurosurgery in Mexico City and Tecnológico de Monterrey in Monterrey. Participants were selected using convenience and consecutive sampling methods from May to August 2019. Diagnosis of PD was established by movement disorders neurologists based on clinical criteria[12]. Sociodemographic variables including gender, age, education, marital status, employment status, geographic location, physical activity, recreational/social activities, and physical therapy were recorded. In addition, PD clinical variables such as age at symptom onset, age at diagnosis, disease duration, initial symptom presentation, side of symptom onset, PD motor subtype as previously defined[11], Parkinsonian medications, antidepressants, deep brain stimulation, Hoehn and Yahr scale score, Schwab and England (S&E) scale score, and movement disorders society-unified PD rating scale score were documented. Outcome variables: gender, our primary independent variable, was categorized into female and male. Positive and negative feelings, our dependent variables, were assessed using the Spanish version of the Positive and Negative Affect Schedule (PANAS). PANAS is a self-report questionnaire consisting of 20 items aimed at measuring global affective judgments, representing a dimension of subjective well-being. Among these items, 10 evaluate negative feelings, while the remaining items examine positive feelings. Responses are rated on a 5-point Likert scale, with higher scores indicating a greater degree of positive or negative affect[13,14].

Statistical analysis

Descriptive analysis employed measures of central tendency and dispersion. Continuous variables were summarized using means and standard deviations (SD), while categorical variables were presented as frequencies and percentages. Normality assumptions were assessed using the Kolmogorov–Smirnov test. Pearson correlation was utilized to examine relationships between independent continuous variables (e.g., age, age at onset, and education) and dependent continuous variables (PANAS scores). Student's t-test was employed to assess associations between independent categorical variables (e.g., gender and marital status) and our dependent continuous variables. A multiple linear regression model was constructed to identify the optimal combination of variables predicting our outcome variables. Backward elimination regression was employed to derive a reduced model, considering multicollinearity assessed using the variance inflation factor. Model validation was performed using 80% of the data, with the remaining data used for validation. The goodness of fit was assessed using the Hosmer–Lemeshow test. IBM SPSS version 25 was utilized for all analyses.

Results

Table 1 displays the sociodemographic and clinical characteristics of the study participants. Overall, no significant differences were noted between study groups, except for the prevalence of recreational or social activities. Female patients reported engaging in these activities more frequently compared to male patients ($p = 0.016$).

Regarding PANAS scores, female patients exhibited a positive affect score of 34.2 (SD 8.6) and a negative affect score of 23.1 (SD 8.9). In contrast, male patients demonstrated a positive affect score of 37.6 (SD 7.8) and a negative affect score of 23.4 (SD 10.1). The bivariate analysis showed no significant differences between study groups, with positive scores yielding a $p = 0.071$ and negative scores yielding a $p = 0.892$.

We developed a model to predict positive affect scores. Male gender and the S&E scale were found as independent variables to predict the positive affect score (Table 2). The final model had an R^2 of 0.182 ($p = 0.025$). Our results suggest that male PD patients with high functionality were more likely to report higher positive affect scores.

Discussion

In our observational cross-sectional study conducted within a Mexican cohort of individuals with PD, our aim was to investigate the association between gender and the presence of positive or negative affect. Interestingly, we found that our cohort exhibited elevated levels of both positive and negative affect. Our analysis did not uncover a significant difference in affect between male and female PD patients. Notably, we observed that male patients with higher functional status were predicted to have higher scores on positive affect.

Our study revealed higher positive and negative affect scores across the entire cohort compared to previous research on individuals with PD. Specifically, our cohort exhibited a mean positive affect score of 36.1 (SD 8.3) and a percentile of 72, whereas previous studies reported lower scores ranging from 25.2 (SD 8.8) with a percentile of 21-34.1 (SD 11.3) with a percentile of 62[8,15]. In contrast, the mean negative affect score for

Table 1. Gender-based associations with sociodemographic and clinical characteristics in our Parkinson's disease population

Variables	Total	Female (n = 37)	Male (n = 43)	p
Age in years, mean (SD)	65.1 (12.4)	62.9 (12.9)	67.1 (11.7)	0.139
Education in years, mean (SD)	12.0 (4.6)	12.5 (3.8)	11.7 (5.3)	0.443
Marital status (single), n (%)	27 (33.8)	12 (32.4)	15 (34.9)	0.817
Employment status (retired/unemployed), n (%)	54 (67.5)	24 (64.9)	30 (69.8)	0.641
Geographic location (capital city), n (%)	24 (30.0)	10 (27.0)	14 (32.6)	0.590
Comorbidities, n (%)	38 (47.5)	16 (43.2)	22 (51.2)	0.479
Family history of tremors or Parkinsonism, n (%)	26 (32.5)	11 (29.7)	15 (34.9)	0.624
Physical activity, n (%)	45 (56.3)	23 (62.2)	22 (51.2)	0.323
Physical therapy, n (%)*	10 (12.5)	4 (10.8)	6 (14.0)	0.745
Recreational/Social activities, n (%)	24 (30)	16 (43.2)	8 (18.6)	0.016
Tremor-dominant subtype, n (%)	54 (67.5)	23 (62.2)	31 (72.1)	0.572
Levodopa/carbidopa, n (%)	61 (76.3)	30 (81.1)	31 (72.1)	0.346
Dopamine agonists, n (%)	44 (55.0)	21 (56.8)	23 (53.5)	0.770
Use of MAOBI, n (%)	13 (16.3)	6 (16.2)	7 (16.3)	0.994
Use of amantadine, n (%)	17 (21.3)	6 (16.2)	11 (25.6)	0.307
Use of antidepressants, n (%)	23 (28.7)	13 (35.1)	10 (23.3)	0.242
DBS therapy, n (%)	10 (12.5)	7 (18.9)	3 (7.0)	0.174
Disease duration in years, mean (SD)	6.3 (5.4)	6.1 (4.1)	6.5 (6.4)	0.776
MDS-UPDRS I score, mean (SD)	11.8 (6.2)	13.2 (6.2)	11.0 (6.1)	0.213
MDS-UPDRS II score, mean (SD)	13.6 (7.3)	12.3 (9.1)	14 (6.3)	0.577
MDS-UPDRS III score, mean (SD)	34.2 (13.3)	32.0 (15.0)	35.4 (12.4)	0.387
MDS-UPDRS IV score, mean (SD)	2.0 (3.3)	1.1 (3.0)	2.5 (3.4)	0.141
Hoehn–Yahr scale score, mean (SD)	2.6 (0.6)	2.5 (1.0)	2.6 (1.0)	0.626
Schwab and England score, mean (SD)	4.3 (1.2)	4 (1.2)	4.4 (1.2)	0.251

*Fisher exact test. MAOBI: monoamine oxidase inhibitors type B; DBS: deep brain stimulation; MDS-UPDRS: movement disorders society-unified Parkinson's disease rating scale.

our cohort was 23.2 (SD 9.4), with a percentile of 88, exceeding the scores reported in prior studies, which ranged from 11.8 (SD 3.6) with a percentile of 28-14.1 (SD 5.4) with a percentile of 47[15]. These findings suggest that patients with PD in our cohort reported higher levels of positive and negative affect compared to previous studies, potentially reflecting cultural or environmental differences among populations. Further investigation is warranted to elucidate the underlying factors contributing to these discrepancies.

Our analysis revealed no significant difference in affect between male and female PD patients. Female patients exhibited a positive affect score of 34.2 (SD 8.6) with a percentile of 62 and a negative affect score of 23.1 (SD 8.9) with a percentile of 88, while male patients demonstrated a higher positive affect score of 37.6 (SD 7.8) with a percentile of 77 and a similar negative affect score of 23.4 (SD 10.1) with a percentile of 88. The previous research has indicated that individuals with PD often experience elevated levels of negative emotions and reduced enjoyment compared to elderly control subjects[16]. Similarly, studies focusing on affect in PD patients have consistently reported diminished positive affect compared to

Table 2. Multiple linear regression model used to predict the positive affect schedule score

Variables	Coefficient (beta)	SE	Standardized coefficient (beta)	t-test	p	95% CI
Constant	41.16	4.12	-	9.96	> 0.001	32.84-49.47
Gender (Male)	5.85	2.31	0.35	2.53	0.015	1.19-10.50
Recreational/Social activities	5.12	3.65	0.19	1.40	0.168	–2.24-12.47
Schwab and England Scale	–2.00	0.93	–0.29	–2.16	0.036	–3.87–-0.13

This regression model had a R^2 of 0.182 (p = 0.025).

controls[9]. Notably, our findings align with initial observations in non-PD individuals, where males tended to score higher on the positive affect scale[13]. These findings could potentially be explained by various factors such as cultural differences, social norms, coping mechanisms, or individual differences in disease progression and symptom severity[17,18]. Further research exploring these factors in depth could provide valuable insights into the observed differences in affect scores among individuals with PD.

Indeed, our observation that male patients with higher functional status were predicted to have higher scores on positive affect suggests a potential association between functionality and emotional well-being in individuals with PD. This finding underscores the importance of considering functional status as a factor influencing positive affect and overall quality of life in PD patients. It implies that maintaining or improving functional abilities through appropriate interventions may positively impact emotional health and subjective well-being in this population[19-22]. Further research exploring the mechanisms underlying this relationship and the effectiveness of interventions targeting functional improvement in enhancing positive affect in PD patients could provide valuable insights for optimizing comprehensive care strategies.

While our study provides valuable insights into the association between gender and emotional states in PD patients, several limitations warrant consideration. First, the cross-sectional design of the study restricts our ability to establish causality between gender, functional status, and affective outcomes. In addition, our study sample was limited to a specific geographic region, potentially limiting the generalizability of our findings to broader populations of PD patients. Furthermore, the reliance on self-reported measures of emotional states may introduce bias, as individuals may underreport or overreport their experiences. Finally, the exclusion of certain demographic or clinical variables, such as socioeconomic status or medication history, may have overlooked potential confounding factors influencing emotional outcomes in PD. These limitations underscore the need for future longitudinal studies with larger and more diverse cohorts to further elucidate the complex interplay between gender, functional status, and emotional well-being in PD.

Conclusion

Our study contributes to the growing body of literature examining the relationship between gender and emotional states in PD patients. While no significant difference in affect was observed between male and female patients, our findings highlight the importance of considering functional status in understanding emotional outcomes. Specifically, male patients with higher functional status were predicted to exhibit greater positive affect. These findings underscore the need for tailored interventions aimed at promoting emotional well-being in PD patients, with particular attention to the influence of gender and functional status. Future research endeavors should prioritize longitudinal designs and incorporate a broader range of demographic and clinical variables to provide a more comprehensive understanding of emotional dynamics in PD. Such insights are crucial for optimizing patient care and enhancing the overall quality of life in individuals living with PD.

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Contribution of each of the authors

All authors participated in conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, visualization, writing–original draft, writing–review and editing of the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

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ORIGINAL ARTICLE

Reference values of motor evoked potentials with magnetic stimulation of upper limbs at a health center in Colombia

Valores de referencia de potenciales evocados motores con estimulación magnética de miembros superiores en un centro de salud en Colombia

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Abstract

Background: *Motor-evoked potentials (MEPs) with magnetic stimulation (MEP-MS) are a valuable non-invasive neurophysiological method for evaluating corticospinal and corticobulbar pathways in neurological pathologies. Despite the existence of reference values in other contexts, literature is scarce.* **Objective:** *To establish reference values for MEP-MS of the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles in healthy subjects at a health center in Colombia in 2023.* **Method:** *Cross-sectional descriptive observational study including 45 participants evaluating 90 APB and 90 ADM muscles. Sociodemographic characteristics, latency, amplitude, and central motor conduction time (CMCT) were measured. Descriptive, bivariate, and multivariate statistical analyses were performed comparing subgroups.* **Results:** *Reference values for MEP-MS were obtained for the Colombian population; CMCT had a mean of 6.62 ms (SD: 1.30 ms) and 7.15 ms (SD: 1.13ms) for the ADM and APB, respectively. Statistically significant differences were found between height and sex and cortical and medullary latency of MEP. Also, some differences were found when analyzing by age and body mass index. Variability in MEP amplitude was evident with demographic variables.* **Conclusion:** *This is the first study in Colombia that determines reference values for the characteristics of motor-evoked potentials (latency, amplitude, CMCT) of the APB and ADM muscles. Statistically significant differences were found between demographic and anthropometric variables and characteristics of MEP.*

Keywords: *Transcranial magnetic stimulation. Motor evoked potentials. Reference values.*

Resumen

Antecedentes: *Los potenciales evocados motores (pEM) con estimulación magnética (pEM-EM) son un método neurofisiológico no invasivo útil que evalúa las vías corticoespinales y corticobulbares en patologías neurológicas. A pesar de la existencia de valores de referencia en otros contextos, la literatura es limitada.* **Objetivo:** *Establecer los valores de referencia de los pEM-EM del músculo abductor pollicis brevis (APB) y músculo abductor digiti minimi (ADM) en sujetos sanos en un centro de salud de Colombia en 2023.* **Método:** *Estudio observacional descriptivo transversal que incluyó a 45 participantes y evaluó 90 músculos APB y 90 músculos ADM. Se midieron características sociodemográficas, latencia, amplitud y tiempo de conducción motora central (TCMC). Se realizó un análisis estadístico descriptivo, bivariante y multivariante comparando por subgrupos.*

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Resultados: *Se obtuvieron los valores de referencia de pEM-EM para un centro de salud en Colombia, el TCMC tuvo una media de 6.62 ms (DE: 1.30 ms) y 7.15 ms (DE: 1.13 ms) para el ADM y el APB, respectivamente. Se encontraron diferencias estadísticamente significativas entre subgrupos de talla y sexo, para la latencia cortical y foraminal del pEM. También algunas diferencias al analizar por subgrupos de edad e índice de masa corporal. Se evidenció variabilidad en la amplitud de los pEM en relación con variables demográficas.* **Conclusión:** *Este es el primer estudio en Colombia que determina los valores de referencia de las características propias de los pEM (latencia, amplitud, TCMC) del músculo APB y del ADM. Se encontraron diferencias estadísticamente significativas entre subgrupos por variables demográficas y antropométricas, y características propias del pEM.*

Palabras clave: *Estimulación magnética transcraneal. Potenciales evocados motores. Valores de referencia.*

Introduction

Motor evoked potentials (MEPs) are a type of non-invasive electrophysiological study, useful for evaluating the integrity and functional suitability of motor pathways by identifying amplitude and latency parameters specific to MEPs[1,2]. However, multiple factors could influence the measurement of the stimulus. For example, coil orientation, muscle contraction states[3,4], the magnetic field induced by the coil[3], coil shape[3,5], pulse waveform[3,4], the presence of metallic objects[3], and visual attention[6]. Additionally, a low rate of adverse effects due to their performance has been described[7].

Although these values have been standardized in Japan, Germany, U.S.A., and other countries[8-10], these parameters do not meet the ethnic and phenotypic characteristics of the Colombian population, while in Mexico there are reference values of latency and amplitude that could be comparable to our population[11]. However, the information available in Colombia is scarce. There is only one study from 1992 conducted in Medellín, evaluating the MEPs of 42 healthy subjects, in this case with an electrical stimulator[12]. Currently in our country, this process is carried out based on the presence of MEPs, asymmetry of more than 50% in their amplitude, or changes in their morphology, limiting their adequate interpretation for clinical use in neurological conditions[5].

MEPs with magnetic stimulation (MEP-MS) are a recommended method for the study of neurological conditions (Supplementary table 1)[13,14]. For example, in stroke, there is prolongation of latencies or absence of MEPs, the latter indicating a worse prognosis[3]. In multiple sclerosis, delays in central motor conduction time[15]. Similar data have been evidenced in cervical myelopathy[16]. Conversely, MEPs in Parkinson's disease show greater amplitude, possibly related to hyperexcitation of spinal or cortical motor neurons[17]. They also provide valuable information in the study of dementia, neurodegenerative disorders, schizophrenia, autism, and coma[18,19].

For an adequate interpretation of the study, each electrodiagnostic laboratory must standardize the reference values, identified in its population and with its equipment[20]. Similarly, applications of MEPs have been established according to clinical correlations, such as:

- Stroke. Different investigations have demonstrated the importance of MEPs as a tool to predict prognosis, including a study by Macdonell et al. in 1989, who, when comparing MEPs vs. somatosensory evoked potentials (SSEPs) concluded that the presence or absence of these potentials was related to the degree of functional recovery, with MEPs having a slightly better predictive value than SSEPs[21].
- Multiple sclerosis. In patients diagnosed with this disease, low amplitude and/or prolonged latency MEPs have been found, in addition to delays in central motor conduction time (CMCT)[22]. In a study published in 2013[23], they recommend the use of MEPs in patients with relapsing-remitting multiple sclerosis phenotype and inconclusive brain magnetic resonance imaging (MRI). On the other hand, in patients with primary-progressive multiple sclerosis phenotype, they recommend its use in search for excluding processes that may cause a picture of progressive disability and confirming the presence of demyelinating lesions. The most typical abnormality in multiple sclerosis is the prolongation of CMCT.
- Extrapyramidal disorders. Studies have shown that the mean CMCT is normal in relation to the normality that exists in the descending motor pathways[24].
- Compressive myelopathy. Prolongation in CMCT has been evidenced, possibly related to slow conduction in demyelinated corticospinal fibers[16].

For all the above, this research aims to establish reference values, allowing their clinical use in a more accurate way and enabling the development of clinical protocols. The objective is to evaluate the MEP-MS of the APB and ADM in healthy subjects in a health

service provider specialized in physical medicine and rehabilitation in Bogotá, Colombia. Sociodemographic variables are identified, as well as latency, amplitude, and CMCT of MEPs.

Finally, there are some factors that can interfere with the performance and interpretation of this neurophysiological method, among which the following stand out: the difficulty of determining the motor cortical threshold, given its intraindividual variability (technical configuration, patient position, drugs, age, and target muscle) and interindividual variability, the discomfort it entails, the increase in intensity required by transcranial magnetic stimulation (TMS) to evoke a maximum amplitude MEP, and the relative contraindications that may prevent its performance such as seizures, syncope, brain diseases, and pregnancy[25].

Method

Design and population

We conducted a descriptive, cross-sectional observational study that evaluates physiological values. Healthy adult subjects who attended IPS Rangel in Bogotá, Colombia, were included. They were relatives or companions of patients who agreed to participate in the study during 2023 by non-probabilistic convenience sampling. A physical examination and checklist were performed, ruling out pathological conditions, evaluating clinical signs or symptoms that suggested neurological alteration and possible confounding variables. Among the inclusion criteria, it was considered that they were healthy people between 18 and 65 years of Colombian nationality. The exclusion criteria were pregnancy, cardiac pacemaker, diseases or interventions of the central or peripheral nervous system, cervical spine, peripheral nerve injury of the upper limbs, neurocognitive or psychiatric disorder, use of sodium and calcium channel blockers or antidepressants.

Data collection

The reference values of MEP-MS of the abductor digiti minimi muscle (ADM) and abductor pollicis brevis muscle (APB) were evaluated. Compound muscle action potentials (CMAPs) and MEPs were recorded with Cadwell Laboratories cup-type surface electrodes, model 302694-200 (2017) on the APB and ADM, bilaterally. The 12 mm x 15 mm (area) active electrode was placed on the muscle belly, next to the motor point: for the APB, at the midpoint between the distal wrist crease and the first metacarpophalangeal joint (MCP). For the ADM, it was placed on the hypothenar eminence, halfway between the pisiform bone and the 5th MCP. The reference electrodes, for both the APB and ADM, were located slightly distal to the 1st and 5th MCP joints, respectively. Finally, the ground electrode (25 mm in diameter) for both measurements was fixed on the back of the hand.

Each stimulus was recorded individually, starting with the APB muscle and then the ADM, first right and then contralateral. The TMS protocol was configured with a gain of 5 mV per division and a sweep speed of 5 ms per division.

The Sierra Summit Cadwell laboratories equipment, 19027205AC027053 model 2017 USA was used to record the MEPs and CMAPs. Electrical stimulation on the peripheral nerve was performed orthodromically by means of a stimulator (part of the above-mentioned equipment) to obtain the CMAPs. On the other hand, magnetic stimulation was performed by means of a MagPro R20-Magventure 9016E0861 Company, Georgia, USA machine, using monophasic waves applied with a simple circular MCF-B65 coil of 14 cm with a maximum magnetic field of 2 teslas.

The motor cortical threshold was determined by performing a first stimulus with low intensity on the cortex, which was increased until it induced a muscle contraction of the target muscle that corresponded to the generation of an MEP in 5 out of 10 different trials. This value was increased by 20% to initiate magnetic stimulation.

Three to 5 different stimulus trials (depending on participant tolerance) were performed for each muscle, and the MEP with the highest amplitude and lowest latency was chosen.

Distal peripheral nerve stimulation

For the APB muscle, electrical stimulation was performed on the median nerve pathway, placing the cathode 8 cm proximal to the active electrode in a line measured first to the midpoint of the distal wrist crease and then to a point slightly ulnar to the flexor carpi radialis tendon. The anode was located proximal to perform orthodromic stimulation. With respect to the ADM muscle, electrical stimulation was performed, positioning the cathode 8 cm proximal to the active electrode, in a line measured slightly radial to the flexor carpi ulnaris tendon. The anode was positioned proximal. For both nerves, an electrical pulse duration of 200 ms and a current intensity that started at 0 mA with increments

of 10 mA until the CMAP of greater amplitude was obtained were used. Once the CMAP reached maximum amplitude, the current was increased by 20% to ensure supramaximal stimulation. Data obtained on amplitude measured in millivolts and latency measured in milliseconds were saved.

Foraminal stimulation

Spinal root stimulation was performed in muscle activity. For this, the participant was instructed to perform a movement to contact the fingertips of the thumb and little finger lightly and without applying pressure to activate approximately 10% of the pyramidal neurons. The coil was placed on the spinous process of the C7 cervical vertebral body (placing the center of the coil just on the relief generated by the spinous process) in the direction of the exit of the cervical root.

Cortical stimulation

Cerebral cortex stimulation was also performed in muscle activity. The coil was placed on the scalp at the vertex level Cz point according to the international 10/20 system. The coil was rotated clockwise and counterclockwise until the best quality MEP was obtained. For both the foraminal and cortical stimulus, the measurement of the MEPs of the first evoked wave was performed. The total duration of the test was approximately 25 minutes.

Statistical analysis

Normality was evaluated using the Shapiro-Wilk test and histogram. Normal values were expressed as absolute or relative values; applying means, standard deviations, and ranges. The sample was evaluated by subgroups with the chi-square and Fisher's exact test, and an ANOVA was applied for multivariate analysis. The Stata 18.0 statistical program was used, with a statistical significance level of $p < 0.05$.

Ethical aspects

This study had authorization from *Universidad El Bosque* Research or Ethics Committee in full compliance with national and international regulations, while guaranteeing the subjects' free participation and informed consent.

Table 1. Sociodemographic variables by sex of healthy subjects in a health care institution in Bogotá, Colombia

Variable	Women Total (n = 26)	Men Total (n = 19)
Age (years), mean (SD)	33.11 (9.79)	31.63 (9.42)
Age (years), n (%)		
18-40	22 (84.6)	17 (89.47)
41-52	3 (11.5)	1 (5.26)
53-65	1 (3.8)	1 (5.26)
Weight (kg), mean (SD)	60.88 (10.14)	71.76 (8.46)
Height (cm), mean (SD)	159.96 (5.37)	173.42 (5.49)
BMI (kg/m²), mean (SD)	23.78 (4.18)	23.91 (2.94)
BMI (kg/m²), n (%)		
< 18.5	1 (3.8)	-
18.5-24.9	18 (69.2)	15 (78.95)
25-29.9	5 (19.2)	4 (21.05)
> 30	2 (7.7)	-

BMI: body mass index; SD: standard deviation.

Results

Sociodemographic characterization

A total of 45 participants were included, most whom were women (57.70%), with a mean age of 32.5 (± 9.56) years, which corresponded to an analysis of 90 APB muscles and 90 ADM muscles included. Only two participants presented mild headache after the study, resolving immediately (< 5%).

Mean weight was 65.48 kg, and mean height, 165.64 cm. By body mass index (BMI), the mean was 23.84 kg/m². Similarly, we found that most population was categorized as normal BMI (73.33%). Most participants were in the 18-40 age range. When comparing between men and women, the mean age was similar, while weight and height were slightly higher in men (Table 1).

Reference values for the study population

The values obtained from the stimuli performed are shown in table 2: peripheral with electrical stimulation, foraminal and cortical with magnetic stimulation. Latencies and amplitudes of MEPs were obtained, the side-to-side amplitude difference, the MEP/CMAP ratio, and the CMCT were calculated. The side-to-side difference is presented as a percentage. The MEP/CMAP ratio corresponds to the amplitude ratio of the MEP in millivolts divided by the amplitude of the CMAP, also, in millivolts. Central motor conduction time was calculated by subtracting the latency of the foraminal

Table 2. Reference values for the APB and ADM of healthy subjects in the motor evoked potentials study with magnetic stimulation in a health care center in Bogotá, Colombia

Total reference values	Mean	SD	Minimum	Maximum
APB				
Cortical				
Latency (ms)	19.71	4.76	8.98	34.11
Amplitude (mV)	4.76	1.56	1.30	9.30
Side-to-side amplitude difference (%)	17.27	1.76	0.00	59.38
Foraminal				
Latency (ms)	12.56	1.14	10.20	15.20
Amplitude (mV)	5.23	3.54	1.00	14.70
Side-to-side amplitude difference (%)	15.87	11.82	0.00	54.72
CMCT	7.15	1.13	4.40	10.30
Peripheral				
Latency (ms)	3.04	0.42	2.20	4.10
Amplitude (mV)	10.96	2.66	0.00	18.40
Side-to-side amplitude difference (%)	12.77	8.98	0.00	34.11
MEP/CMAP ratio*	45.59	18.21	8.39	90.91
ADM				
Cortical				
Latency (ms)	19.24	4.63	6.79	28.30
Amplitude (mV)	4.63	1.65	1.60	7.70
Side-to-side amplitude difference (%)	14.34	1.47	2.04	34.72
Foraminal				
Latency (ms)	12.62	1.29	10.10	15.60
Amplitude (mV)	3.32	2.17	1.00	11.20
Side-to-side amplitude difference (%)	18.56	11.41	0.00	37.93
CMCT	6.62	1.30	3.00	11.40
Peripheral				
Latency (ms)	2.53	0.30	2.00	3.40
Amplitude (mV)	9.52	1.69	0.93	13.30
Side-to-side amplitude difference (%)	11.00	6.79	0.93	28.30
MEP/CMAP ratio*	49.29	15.18	17.02	98.67

*The MEP/CMAP ratio corresponds to the amplitude of the MEP evoked by cortical magnetic stimulation divided by the amplitude of the CMAP obtained through electrical stimulation of peripheral nerve.
APB: abductor pollicis brevis; ADM: abductor digiti minimi; SD: standard deviation; MEP: motor evoked potential; CMAP: compound muscle action potential; CMCT: central motor conduction time

stimulus in milliseconds (corresponding to peripheral motor conduction time) from the latency of the cortical stimulus in milliseconds (corresponding to total motor conduction time). Similar values were found according to laterality with respect to latencies, amplitudes, and CMCT for the APB and ADM muscles (Supplementary tables 2 and 3).

A difference > 50% between side-to-side amplitudes was found in 2 participants. The first for the cortical and foraminal stimulus of the APB (56.67 and 54.72%) and the second for the cortical stimulus of the APB (59.38%). For the ADM, the side-to-side amplitude difference range for the cortical stimulus was between 2.04 and 32.72%, and for the foraminal between 0 and 37.93%. The MEP/CMAP amplitude ratio showed a mean for the APB of 45.29% and 49.29% for the ADM. Regarding the APB, 2 participants presented a difference of < 15% (with values of 8.39 and 14.86%). While for the ADM, a range between 17.02 and 98.67% was found. In general, the amplitude of the cortical stimulus MEP was lower vs the foraminal.

Statistically significant comparisons by subgroups

Only the cortical latency of the ADM had differences between stimuli according to different age groups ($p < 0.001$). Therefore, the other stimuli did not differ by age. When comparing by sex, differences were found for cortical and foraminal latency of the APB ($p < 0.001$) and ADM ($p = 0.000$), as well as foraminal amplitude of the ADM MEP ($p = 0.0097$). Table 3 illustrates the reference values by sex subgroups. Similarly, the foraminal amplitude of the ulnar also showed

differences (p = 0.0018). Table 4 describes reference values by height subgroups > and < 165 cm. Regarding CMCT, differences were identified for height in the APB (p = 0.0365). Comparing by BMI, only differences in cortical amplitude of the APB were found (p = 0.0399). With respect to height, differences were found in the latency of the cortical and foraminal MEP for both muscles (p < 0.0001) (Table 5).

Multivariate analysis of reference values by subgroups

A multivariate analysis was performed to compare by sex and height, finding statistically significant differences for the foraminal and cortical latency of the APB (p = 0.000) and ADM (p = 0). Even the amplitude of the foraminal stimulus of the ADM showed statistically significant differences (p = 0.0065).

Table 3. Reference values of latency by sex for the APB and ADM muscles of healthy subjects in the motor evoked potentials study with magnetic stimulation in a health care center in Bogotá, Colombia

Latencies (ms)	Mean	SD	Minimum	Maximum
APB				
Women				
Cortical	19.04	1.35	16.00	22.10
Foraminal	11.98	0.94	10.20	14.60
Men				
Cortical	20.61	1.35	18.20	23.60
Foraminal	13.36	0.88	11.80	15.20
ADM				
Women				
Cortical	18.59	1.45	15.50	21.90
Foraminal	11.92	1.02	10.10	14.10
Men				
Cortical	20.13	1.49	15.70	22.60
Foraminal	13.58	0.95	11.30	15.60

APB: abductor pollicis brevis; ADM: abductor digiti minimi; SD: standard deviation.

Discussion

This is the first study in Colombia that determines the reference values of the MEP parameters (latency, amplitude, CMCT) of the APB and ADM muscles. In comparison, the results of the current study are consistent with previous investigations[9,11,25-31] (Supplementary table 1)[25,32]. For example, the CMCT had a mean of 6.62 ms (standard deviation [SD], 1.30 ms) and 7.15 ms (1.13 ms) for the ADM and APB, respectively. Additionally, an analysis by subgroups was performed with the evaluated variables, finding that latencies show statistically significant differences between sex and height groups (p < 0.01). A side-to-side amplitude difference > 50% has been reported as abnormal[4,28]. However, in this study, 2 participants presented this difference, which would lead to a false positive rate of 4.4%, so it is prudent to consider the possibility of a higher cut-off point in our population. Therefore, it is striking that one participant presented a side-to-side difference value > 50% of the cortical MEP.

In principle, the mean age of this study was 32 years, similar to what is reported in the previous literature[9,11,26,27,30,31]. This is justified by the inclusion of healthy participants, as well as the direct relationship between age and diseases of the nervous system such as motor neuron diseases, Alzheimer's or Parkinson's disease[33-35]. Similarly, the mean height in men was higher vs women (173.42 cm vs 159.96 cm). Therefore, this is a result consistent with former studies and with population characteristics[29,30].

Table 4. Reference values of latencies by height for the APB and ADM muscles of healthy adult subjects in the motor evoked potentials study with magnetic stimulation in a health care center in Bogotá, Colombia

Latencies (ms)	Mean	SD	Minimum	Maximum
APB				
≤ 165 cm				
Cortical	18.74	1.15	16.00	20.90
Foraminal	11.82	0.86	10.20	13.90
> 165 cm				
Cortical	20.71	1.27	18.20	23.60
Foraminal	13.33	0.85	11.80	15.20
ADM				
≤ 165 cm				
Cortical	18.35	1.37	15.50	21.90
Foraminal	11.70	0.86	10.10	14.10
> 165 cm				
Cortical	20.17	1.38	15.70	22.60
Foraminal	13.58	0.89	11.30	15.60

APB: abductor pollicis brevis; ADM: abductor digiti Minimi; SD: standard deviation.

Regarding side effects, only 2 participants presented mild headache after magnetic stimulation. Similarly, this phenomenon has been reported in other studies[8,11,30]. Moreover, some analyses suggest that the use of magnetic stimulation seems to be safe in patients with epilepsy or previous head trauma[4,5]. However, literature recommends excluding these conditions due to the risk of isolated focal seizures during or after the study, in patients who used drugs with a decreased seizure threshold[7]. On the other hand, there were no differences when comparing between the lateralities of the

Table 5. Differences by sex, height, BMI, and age in Motor Evoked Potentials for APB and ADM muscles

Variable differences	By sex value (p)	By height value (p)	By BMI value (p)	By age value (p)
APB				
Cortical				
Latency (ms)	–1.571 (< 0.001)	–1.961 (< 0.001)	–0.1917 (0.2996)	0.28 (0.393)
Amplitude (mV)	–0.362 (0.279)	0.026 (0.4719)	–0.7180 (0.0399)	–0.309 (0.408)
Foraminal				
Latency (ms)	–1.383 (< 0.001)	–1.463 (< 0.001)	0.030 (0.5457)	0.070 (0.771)
Amplitude (mV)	(0.997)	(–0.735)	(–0.7317)	(0.9967)
CMCT	–0.188 (0.438)	–0.498 (0.0365)	–0.2224 (0.2005)	0.2113 (0.3788)
MEP/CMAP amplitude ratio (%)	–1.465 (0.354)	0.439 (0.9099)	–5.493.574 (0.0981)	0.6110 (0.8747)
ADM				
Cortical				
Latency (ms)	1.542 (< 0.000)	–71.276 (< 0.001)	–11.433 (0.256)	–0.3351 (< 0.001)
Amplitude (mV)	0.207 (0.512)	0.8927 (0.3745)	–0.5537 (0.5812)	–0.2613 (0.4034)
Foraminal				
Latency (m.s)	1.666 (< 0.000)	–97.626 (< 0.001)	–0.0242 (0.9358)	–0.1543 (0.286)
Amplitude (mV)	(0.0097)	(0.0018)	(0.9645)	(0.7806)
CMCT (ms)	0.1244 (0.656)	–0.5015 (0.6173)	–13.718 (0.1736)	–0.1808 (0.5127)
MEP/CMAP amplitude ratio* (%)	2.249 (0.490)	–0.6473 (0.5191)	–10.332 (0.3044)	–1.673.527 (0.3019)

*MEP/CMAP ratio corresponds to the amplitude of the MEP evoked by cortical magnetic stimulation divided by the amplitude of the CMAP obtained by electrical stimulation of the peripheral nerve. APB: abductor pollicis brevis; ADM: abductor digiti minimi; BMI: body mass index; CMAP: compound muscle action potential; MEP: motor evoked potential; CMCT: central motor conduction time.

study subjects. Studies in Germany, France, and Mexico had similar results in healthy participants[9,11,30].

Additionally, the MEP/CMAP ratio was analyzed, obtaining a mean for the APB of 45.29% and 49.29% for the ADM, without any finding differences being reported, which is consistent with previous literature[28]. Additionally, 2 participants with a difference < 15% were observed. International literature[25] indicates that in hand muscles, if ratio is < 15% or values are 2.5 or 3 SD below the mean of the normative data, it could be considered abnormal, representing a loss of cortico-motor neuronal cells.

In general, the amplitude of the cortical stimulus MEP was lower vs the foraminal, which is consistent with a 1980 Taiwan study[29]. Furthermore, no differences were observed in the amplitude of the APB MEP between men and women, which is consistent with a 2010 Mexico study[11]. On the other hand, the mean amplitude of the cortical and foraminal ADM MEP was slightly higher in women, with a significant difference for the foraminal MEP. In contrast, a study in France did not report differences by sex[30].

Furthermore, statistically significant differences were found in the latency of the cortical and foraminal MEP between sexes for both muscles, with a directly proportional relationship between height and latency. Similarly, it was estimated that the mean height in men was higher, obtaining longer latencies. This phenomenon has been previously described in studies with different contexts[26,29,31]. One hypothesis indicates that wingspan has a direct relationship with height[29]. Therefore, if a person is taller, their wingspan will be greater. Then, the time from the cortical or foraminal stimulus to the hand recording site will be longer due to a longer conduction path. Similarly, the correlation between arm length and thenar eminence MEP latency has been reported[13].

Of note, a 1991 Italian study explains that transcranial MEPs correlate better with body height than with arm length[31]. Therefore, it is recommended to consider this variable in clinical practice. On the other hand, a 1991 French study indicated that despite the existence of the relationship between height and cortical and foraminal conduction time, these were not due to a correlation

between the cortex, cervical conduction time and height but to the relationship between the cortex and lumbar conduction time[30], which suggests that MEP latencies are length-dependent. In the multivariate analysis by sex and height, both are significantly associated with the foraminal and cortical latency of both muscles, and with the amplitude of the foraminal stimulus of the ADM. In contrast, other studies found no differences[29].

Regarding age, there was a tendency for lower amplitude and longer latency in older participants. Only statistically significant differences were found for the cortical latency of the ulnar nerve. Different authors have described a similar finding[11,28,31]. This is attributed to the gradual loss of cortical neurons (36-60%) and anterior horn cells (approximately 25%) with physiological aging.

The mean CMCT of the evaluated muscles was similar among the sex, age, height, and BMI subgroups. Only statistical differences were observed in the APB when comparing by height, consistent with the literature[31]. Conversely, different authors found no differences[9,14,29] probably because the length from head to neck is not related to height[29].

Regarding BMI, only statistically significant differences were found in the cortical MEP amplitude of the APB. Literature does not evaluate BMI, identifying a gap in the evidence. Finally, variability in amplitude was described in relation to demographic variables; it has even been established that amplitude may not be very reliable for MEP-MS analysis[5]. For this reason, the importance of obtaining the MEP/CMAP ratio is highlighted.

Strengths and limitations

As limitations, selection bias is considered, taking into account that most participants were in the age range between 18 and 40 years and a BMI between 18.5 and 24.9 kg/m², which may lead to an inaccurate representation of the sample; as well as confounding, information, and response bias, given that unexpected results arose regarding the side-to-side amplitude difference and the MEP/CMAP ratio that suggested abnormality in healthy patients, who could modify the information during initial data capture. Local factors, lifestyles, and temporary changes can bias the results, affecting their applicability to broader populations. The first study was conducted to determine reference values for MEP-MS in Colombia. We also obtained a larger sample than theoretically calculated. Studies were conducted by trained personnel (physiatrist and residents). Complementarily, quality control and risk of adverse effects were carried out with the checklist and a physical examination prior to the study that served to rule out antecedents, reducing biases in this study. All participants tolerated the study, presenting adverse effects without clinical relevance. As an innovative factor, reference values were disclosed for the characteristics of MEPs with respect to height, BMI, and sex; in addition, a multivariate analysis was performed for sex and height.

Conclusions and recommendations

The first study in Colombia was conducted, determining reference values of MEP-MS for the APB and ADM muscles. Data similar to those reported in the international literature were obtained. A significant relationship was found between the demographic variables of height and sex, and the cortical and foraminal latency of MEP, which allowed describing additional reference values for these subgroups. Age and BMI seem to influence MEPs. Given the variability of the amplitudes of the MEPs obtained, it is important to analyze the MEP/CMAP ratio. However, more studies are needed that evaluate other muscles of the upper and lower limbs, and research including the pediatric population.

Authors' contributions

Conceptualization: K.J. Garzón-Ortega, C. Montaño-Rodríguez, and C.E. Rangel-Galvis. Data curation: K.J. Garzón-Ortega, C. Montaño-Rodríguez, and S.A. Gaitán-Caicedo. Formal analysis: K.J. Garzón-Ortega, C. Montaño-Rodríguez, and S.A. Gaitán-Caicedo. Funding acquisition: K.J. Garzón-Ortega, C. Montaño-Rodríguez, E. Méndez, and C.E. Rangel-Galvis. Research: K.J. Garzón-Ortega, C. Montaño-Rodríguez, E. Méndez, S.A. Gaitán-Caicedo, and C.E. Rangel-Galvis. Methodology: K.J. Garzón-Ortega, C. Montaño-Rodríguez, E. Méndez, S.A. Gaitán-Caicedo, and C.E. Rangel-Galvis. Project administration: K.J. Garzón-Ortega, C. Montaño-Rodríguez, E. Méndez, S.A. Gaitán-Caicedo, and C.E. Rangel-Galvis. Resources: K.J. Garzón-Ortega, C. Montaño-Rodríguez, E. Méndez, S.A. Gaitán-Caicedo, and C.E. Rangel-Galvis. Software: E. Méndez, and C.E. Rangel-Galvis. Supervision: E. Méndez, and C.E. Rangel-Galvis. Validation: K.J. Garzón-Ortega, C. Montaño-Rodríguez, E. Méndez, S.A. Gaitán-Caicedo, and C.E. Rangel-Galvis. Visualization: K.J. Garzón-Ortega, C. Montaño-Rodríguez, E. Méndez, S.A. Gaitán-Caicedo, and C.E. Rangel-Galvis. Writing-original draft: K.J. Garzón-Ortega, C. Montaño-Rodríguez, and S.A. Gaitán-Caicedo. Writing-review and editing: K.J. Garzón-Ortega, C. Montaño-Rodríguez, E. Méndez, S.A. Gaitán-Caicedo, and C.E. Rangel-Galvis.

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Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

Protection of people and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and in full compliance with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the center Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed the confidentiality protocols of their institution, have obtained informed consent from the patients, and have the approval of the Ethics Committee. The recommendations of the SAGER guidelines have been followed, according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for the writing of this manuscript.

Supplementary data

Supplementary data associated with this article can be found in the online version available at DOI: 10.24875/ANC.M24000020.

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ORIGINAL ARTICLE

Clinical profile of frontotemporal dementia: case series from a national reference neurological care center in Peru

Perfil clínico de la demencia frontotemporal: serie de casos de un centro neurológico de referencia nacional en el Perú

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Abstract

Background: *Frontotemporal dementia (FTD) is a clinical syndrome characterized by progressive deterioration of behavior, language, executive function and, occasionally, motor dysfunction. In Latin America, many FTD patients are underrecognized or are diagnosed late in their disease course. There is limited information on clinical aspects of FTD in the Peruvian population.* **Objective:** *To describe the clinical characteristics of patients with frontotemporal dementia (FTD) evaluated at a national neurology referral center in Peru.* **Method:** *Retrospective study. We reviewed 161 clinical records, of which 24 met the diagnosis of probable FTD, and descriptive analysis was performed for each of the variants of FTD.* **Results:** *Twelve cases of behavioral variant FTD, nine of primary progressive aphasia non-fluent variant, and three of the semantic variants were included. The most frequent symptom in behavioral variant FTD was executive dysfunction (92%), while forced speech and impaired naming (100%) were more frequent in primary progressive aphasia non-fluent variant and primary progressive aphasia semantic variant, respectively. Depression and parkinsonism were present in 45 and 38%, respectively.* **Conclusions:** *Behavioral variant FTD was the most frequent clinical syndrome, and lack of empathy was the least reported nuclear symptom in this variant.*

Keywords: *Frontotemporal dementia. Frontotemporal lobar degeneration. Behavioral variant. Primary progressive aphasia. Peru.*

Resumen

Antecedentes: *La demencia frontotemporal (DFT) es un síndrome clínico caracterizado por el deterioro progresivo del comportamiento, el lenguaje, la función ejecutiva y, ocasionalmente, de la función motora. En América Latina, muchos pacientes con DFT no son reconocidos o son diagnosticados tardíamente en el curso de la enfermedad. Existe información limitada sobre los aspectos clínicos de la DFT en la población peruana.* **Objetivo:** *Describir las características clínicas de los pacientes con DFT evaluados en un centro de referencia nacional de neurología en el Perú.* **Método:** *Estudio retrospectivo. Se revisaron 161 registros clínicos, de los cuales 24 cumplieron diagnóstico de DFT probable, se realizó el análisis descriptivo por cada una de las variantes de la DFT.* **Resultados:** *Se incluyeron 12 casos (50%) de demencia frontotemporal variante conductual (DFTvc), nueve de afasia progresiva primaria variante no fluente (APPvnf) y tres de la variante semántica (APPvs).*

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El síntoma inicial más frecuente en la DFTvc fue la desinhibición temprana (50%), mientras el habla forzada (77.8%) y el deterioro en la denominación (100%) fueron más frecuentes en la APPvnf y APPvs respectivamente. La depresión y el parkinsonismo estaban presentes en el 45 y 38% respectivamente. **Conclusiones:** *La DFTvc fue el síndrome clínico más frecuente, la falta de empatía fue el síntoma nuclear menos reportado.*

Palabras clave: *Demencia frontotemporal. Degeneración lobar frontotemporal. Variante conductual. Afasia progresiva primaria. Perú.*

Introduction

Frontotemporal dementia (FTD) is the second most common cause of early-onset dementia. It is a clinical syndrome characterized by progressive deterioration of behavior, language, executive function, and occasionally motor dysfunction[1]. It presents with atrophy of the frontal and anterior temporal lobes. Three main clinical syndromes are recognized, of which behavioral variant FTD (bvFTD) is the most frequent, followed by primary progressive aphasias (PPA) with their non-fluent (nfvPPA) and semantic (svPPA) variants[2].

The prevalence of FTD varies across region. In North America, Asia, and Europe, prevalence ranges from 2-31/100,000 inhabitants, while in Latin America, figures between 1.2 and 1.7/1,000 inhabitants have been reported[3,4]. Heritability in FTD is variable and complex, considering clinical phenotypes. Based on scoring systems, a family history was found in 26-31%; a strong family history has been found in bvFTD (48%), while only 12% in people with PPA[5]. It is estimated that autosomal dominant cases associated with parkinsonism represent more than 13% of the total number of FTD cases, mainly attributable to mutations in 3 genes (*C9orf72, MAPT, and GRN*)[5,6].

The diagnosis of FTD is based on the diagnostic criteria established in 2011 for each of the clinical syndromes. The core clinical features of bvFTD are apathy or inertia, disinhibition, lack of empathy or sympathy, stereotyped or ritualistic behavior, hyperorality or changes in diet, and executive dysfunction; three of these six characteristics are necessary, plus evidence of structural or functional changes in the frontal, insular, or temporal lobe in neuroimaging to establish the diagnosis of probable bvFTD (Table 1)[7]. For the diagnosis of PPA, it is necessary that patients present a predominant and isolated language deficit for at least two years[8] and then meet the criteria for each variant of PPA (Table 2). nfvPPA mainly presents with agrammatism and non-fluent language, omitting articles, prepositions, and verbs, with laborious speech, with interruptions and errors, inconsistencies, and distortions; there may also be alterations in prosody. In svPPA, the main impairment lies in an alteration in naming by confrontation and in the comprehension of isolated words rather than in the comprehension of sentences[9].

Table 1. Diagnostic criteria for bvFTD

Possible frontotemporal dementia	Symptoms have a gradual onset, not sudden. Three of the following must be present: 1. Early disinhibition 2. Early apathy or inertia 3. Early lack of empathy or sympathy 4. Stereotyped behaviors, compulsions, perseverative, or ritualistic behaviors 5. Dietary changes or hyperorality 6. Neuropsychological profile: executive dysfunction. Episodic memory and visuospatial skills relatively preserved Exclusion of other disorders
Probable frontotemporal dementia	Meets criteria for possible bvFTD Significant functional impairment is present Neuroimaging shows: – Frontal and/or anterior temporal atrophy on MRI or CT – Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

bvFTD: behavioral variant frontotemporal dementia; PET: positron emission tomography; MRI: magnetic resonance imaging; SPECT: single-photon emission computed tomography; CT: computed tomography.

In FTD, neuropsychiatric, amnestic, and motor component presentations have been reported. Neuropsychiatric presentation phenotypes characterized by hallucinations or delusional ideas are recognized; phenotypes with amnestic symptoms and mild behavioral alterations at the onset of the disease[2]. The two most common four-repeat tauopathies, progressive supranuclear palsy (PSP) and corticobasal degeneration, are associated with phenotypes such as nfvPPA and bvFTD[10]. Another entity related to motor impairment is the phenotype associated with amyotrophic lateral sclerosis[11].

FTD is an underdiagnosed clinical syndrome. The diagnosis of FTD can be difficult, not only because the clinical presentation is varied, but also because it does not always follow the strict pattern indicated in the diagnostic criteria. On the other hand, the limited

Table 2. Diagnostic criteria for PPA

Clinical diagnosis with neuroimaging support for non-fluent/agrammatic variant PPA	At least one of the following core features must be present: 1. Agrammatism in language production 2. Effortful, halting speech with inconsistent sound errors and distortions (speech apraxia) At least two of the following three features must be present: 1. Impairment in understanding syntactically complex sentences 2. Preserved comprehension of individual words 3. Preserved object knowledge Neuroimaging must show one or more of the following findings: a) predominant atrophy in the left posterior frontoinsular region on MRI; b) predominant hypoperfusion or hypometabolism in the left posterior frontoinsular region on SPECT or PET
Clinical diagnosis with neuroimaging support for semantic variant PPA	Both of the following core features must be present: 1. Impairment in confrontation naming 2. Impairment in understanding individual words At least three of the following additional diagnostic features must be present: 1. Impairment in object knowledge, particularly for low-frequency or unfamiliar items 2. Surface dyslexia or dysgraphia 3. Preserved repetition 4. Preserved speech production (grammar and motor speech) Neuroimaging must show one or more of the following findings: a) predominant atrophy in the anterior temporal lobe; b) predominant hypoperfusion or hypometabolism in the anterior temporal lobe on SPECT or PET

PPA: primary progressive aphasia; PET: positron emission tomography; MRI: magnetic resonance imaging; SPECT: single-photon emission computed tomography.

knowledge about FTD among health professionals does not allow a timely and accurate diagnosis of this entity, which can significantly affect the quality of life of patients and their caregivers, and hinder the development of effective comprehensive therapies that modify the course of the disease[12,13].

The objective of this study was to describe the clinical characteristics of patients with FTD evaluated in a specialized neurological institute of the public system in Peru in the years 2010-2020.

Method

Design and patients

We conducted a descriptive and retrospective study, including the health records of adult patients with a probable diagnosis of bvFTD, nfvPPA, and svPPA according to the 2011 diagnostic criteria (all cases with an MRI showing the characteristic pattern of atrophy corresponding to bvFTD, nfvPPA, and svPPA; no case corresponded to svPPA with atrophy of the right temporal pole)[7,9]. All health histories of patients registered with the International Classification of Diseases 10 (ICD-10) codes G31, F80.0, F80.2, and R47.0 who were evaluated between 2010 and 2020 at a national reference neurological center in Lima, Peru, were reviewed. It is a tertiary referral center, administered by the government, which serves around 30,000 people with neurological disorders (2020) referred from a wide geographical and sociodemographic area of Peru[14]. The study was reviewed and approved by *Instituto Nacional de Ciencias Neurológicas* Institutional Research Ethics Committee.

Variables

Patients were classified according to the three main clinical syndromes of FTD as follows: bvFTD, nfvPPA, and svPPA, according to the clinical criteria for each of the FTD subtypes[7,8]. This classification was carried out by expert neurologists[2] from the Behavioral Neurology Department of *Instituto Nacional de Ciencias Neurológicas*. The reviewed clinical and demographic data were age, sex, place of birth, place of residence, years of study, marital status, first clinical symptoms, and core clinical criteria for each of the FTD variants. The symptoms and criteria were based on what was recorded by neurologists in clinical histories; only 54% of cases had a neuropsychological evaluation that included the following tests: Wechsler Adult Intelligence Scale or WAIS-IV test, Trail Making Test forms A and B, Rey figure copy test, Rey Auditory Verbal Learning and Memory, Wechsler Memory Scale, Luria

Table 3. Demographic characteristics of FTD

Characteristics	FTD				p
	Total (n = 24)	bvFTD (n = 12)	nfvPPA (n = 9)	svPPA (n = 3)	
Age at first symptom	55.7 ± 11.5*	50.8 ± 9.7*	63 ± 12.4*	52 (52-64)†	0.07‡
Age at diagnosis	61.7 ± 10.1*	57.5 ± 8.1*	67.6 ± 11.1*	60.3 ± 6.7*	0.063§
Years of education	10.0 ± 4.9*	9.3 ± 5*	9.9 ± 4.2*	13.3 ± 6.4*	0.710§
Marital status					0.03¶
Married/partnered, n (%)	15 (62.5)	8 (66.7)	6 (66.7)	1 (33.3)	
Single, n (%)	4 (16.7)	0	3 (33.3)	1 (33.3)	
Widowed, n (%)	1 (4.2)	0	0	1 (33.3)	
Divorced/separated, n (%)	3 (12.5)	3 (25)	0	0	
Sex					0.049¶
Female, n (%)	11 (45.8)	3 (25)	5 (55.5)	3 (100)	
Male, n (%)	13 (54.2)	9 (75)	4 (44.4)	0 (0)	
CDR (0.5: mild cognitive impairment/1: mild dementia/ 2: moderate dementia/3: severe dementia)					
CDR: 2, n (%)	18 (75)	8 (33.3)	7 (29.2)	3 (12.5)	
CDR: 3, n (%)	6 (25)	4 (16.7)	2 (8.3)	0	

*Mean ± standard deviation.
†Median and quartiles.
‡Kruskal-Wallis.
§ANOVA.
¶Fisher's exact test.
bvFTD: behavioral variant frontotemporal dementia; nfvPPA: non-fluent/agrammatic variant primary progressive aphasia; svPPA: semantic variant primary progressive aphasia; CDR: Clinical Dementia Rating; FTD: frontotemporal dementia.

gnosia-praxis exploration, and a geriatric depression scale; on the other hand, 45% underwent a screening test (Mini-Mental State Examination/INECO frontal screening) to ensure that all participants could be validly considered "probable" (bvFTD, nfvPPA, and svPPA) based on the above-mentioned criteria, time from illness to diagnosis, and treatment.

Statistical analysis

For quantitative variables, measures of central tendency and dispersion were used. The distribution of data was evaluated using the Shapiro-Wilk test. Variables with normal distribution are expressed as means and standard deviation, and the others as medians and interquartile range. Statistical analysis was performed with Stata v.16.

Results

A total of 161 health records were reviewed, 137 of which were excluded because they corresponded to other diagnoses such as aphasia of vascular or traumatic etiology, diagnosis of aphasia in children, or because no health records that met the inclusion criteria were found. A total of 24 cases of probable FTD were identified, 12 cases (50%) corresponded to bvFTD, 9 cases (37.5%) to nfvPPA, and 3 cases (12.5%) to svPPA. A total of 17 patients (70%) resided in Lima (Peru). Table 3 illustrates the demographic characteristics of FTD by the different phenotypes, as well as the degree of dementia severity.

Clinical signs of FTD were evaluated taking into account the core characteristics for each of the FTD phenotypes. The most common early symptom in bvFTD was early disinhibition in 50%, followed by apathy in 41.7%; while forced speech (77.8%) and deterioration in naming (100%) were the most common initial symptoms in nfvPPA and svPPA, respectively. The core characteristics for each of the FTD variants can vary in frequency throughout the disease, as shown in figure 1.

Although episodic memory impairment in FTD is not part of the core characteristics, its involvement is currently clearly established. In this study, 33.3% of nfvPPA cases and 25% of bvFTD cases were found. On the other hand, among the psychological and behavioral symptoms, depression was found in a frequency of 55.6% in nfvPPA and 41.7% in bvFTD. Regarding

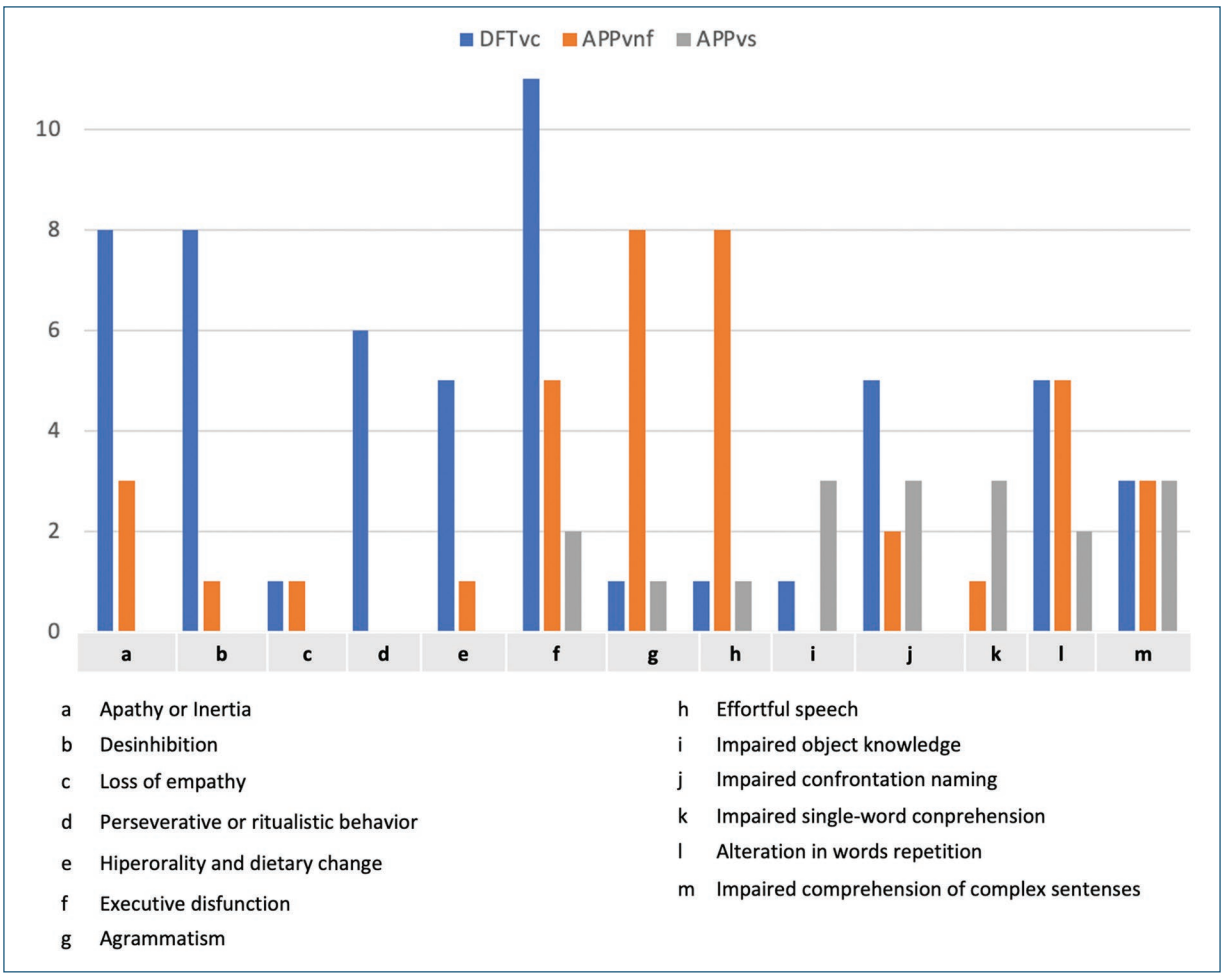

Figure 1. Core characteristics of the different FTD phenotypes throughout the disease. nfvPPA: non-fluent variant primary progressive aphasia; svPPA: semantic variant primary progressive aphasia; FTD: frontotemporal dementia; bvFTD: behavioral variant frontotemporal dementia.

psychotic symptoms (visual hallucinations and delusional ideas of grandeur and jealousy), they were reported in one case of bvFTD and one case of nfvPPA.

Motor involvement in FTD was present in the reviewed cases. Parkinsonian symptoms were found in 6 (66.7%) cases of nfvPPA, 2 cases (17%) of bvFTD, and one case of svPPA. On the other hand, only one case of mutism was found in a patient with bvFTD, while motor neuron disease symptoms were found associated with one case of bvFTD and one in nfvPPA.

Among personal history, four cases (16.7%) with hypothyroidism, three cases (12.5%) with diabetes, and three with traumatic brain injury were found. Regarding family history, parkinsonism was diagnosed in six cases (25%) and dementia in two cases (8.3%).

Discussion

A total of 50% out of a total of 24 patients with a diagnosis of FTD corresponded to probable bvFTD, as has been reported in other studies[15]. In this study, patients diagnosed with bvFTD had a mean age of 57.5, similar to that reported by Johnson et al., who evaluated 353 patients[15], but somewhat lower than that reported by researchers in Colombia (59.3 years)[16]. In the case of nfvPPA, the mean age was the same (63 years) as reported in a North American cohort[15]. In our study, a slight predominance of FTD in the male sex was observed (54.2%), similar to that found in a systematic review (52.5%)[17]; however, all patients in the svPPA group were women.

bvFTD has 6 core clinical features, 3 of which are required for the diagnosis of possible bvFTD[7]. In this

study, all 6 main features were found, with executive dysfunction (91.7%), early disinhibition (66.7%), and apathy or inertia (66.7%) being the most frequent; while the least frequent was lack of empathy or sympathy (8.3%). These findings vary partially from those found in the study of the diagnostic criteria for bvFTD by Rascovsky et al.[7], in which apathy and disinhibition, followed by lack of empathy and perseverative behavior were the most frequent symptoms, which was similar to that reported in the Colombian study (2021), in which 100% of their cases presented apathy, followed by executive dysfunction and disinhibition (96.4%) and 85.7% presented lack of empathy or sympathy[16]. The low percentage of lack of empathy found in the present series might not represent a real figure, which may be due to underreporting (in the observed evaluations, the evaluation of social cognition was not focused) or because both the patients' relatives and health professionals did not recognize these clinical features that form the necessary core for the diagnosis of possible bvFTD[1].

Among the core clinical features of PPA, the cases included in nfvPPA met 100% of both core characteristics of the diagnostic criteria (agrammatism and laborious speech), it was striking not to find cases of speech apraxia, perhaps because this sign was not recognized or was found at a stage where it had not yet presented, since apraxia is part of a clinical continuum of nfvPPA[17].

Neuropsychiatric symptoms are frequent in FTD. According to the systematic review by Hall et al., the prevalence of depression is present in 70% of cases (unspecified variant), it is more frequent in svPPA (78%), followed by nfvPPA (57%)[18]. In the present study, the frequency of depression in nfvPPA was found in more than 50%, similar to that found in the systematic review. The frequency of depression in svPPA could not be defined due to the small number of cases in this variant. Hallucinations and delusional ideas were infrequent; clinical series of FTD report prevalences of hallucinations of 0-50%, while delusional ideas in 25%[19]. In Colombia, a retrospective series of 28 patients with bvFTD found that delusional ideas had a frequency of 61% and hallucinations of 39%, much more than found in our findings[16]. Psychotic symptoms of FTD can be present from the onset of the disease; the importance of their identification lies in the fact that they correlate with the C9orf72 mutation (carrier families), where cases of FTD are also associated with amyotrophic lateral sclerosis (FTD-ALS)[19].

FTD occasionally overlaps with a motor component within its symptomatology and as part of the same neurodegenerative spectrum. In the present series, we only found 2 cases (8%) with this association, which is much lower than the figures reported in the literature, as shown by a study that included the entire clinical spectrum of FTD (bvFTD n = 123, nfvPPA n = 21, svPPA n = 72, PSP n = 50, corticobasal syndrome n = 53, and FTD-ALS n = 35) and found 11 patients with FTD-ALS carrying the C9orf72 mutation[20]. It is possible that these 2 cases found in the study have some important genetic component to study. On the other hand, parkinsonian symptoms were present in 37.5% of cases with FTD in this study. The parkinsonism observed in patients with FTD is usually characterized by a rigid-akinetic plus syndrome, initially only linked to the mutation of the MAPT gene, which encodes the tau protein, but mutations in the GNR genes and the C9orf72 gene have now been identified within the FTD and parkinsonism spectrum[21]. This genetic component could explain why 25% of parkinsonism was found within the family history of patients with FTD in this study.

The main limitations of the study are its retrospective design and the number of patients per subgroup. The information collected from clinical records was not systematized; only 13 had complete neuropsychological evaluations, and the rest had screening tests. A prospective study is currently being conducted to systematize the information of this group of patients with a condition considered a rare disease.

In conclusion, this work allows us to know the clinical profile of patients with FTD in a Latin American population, where similar publications are scarce, and reaffirms the predominance of the bvFTD subgroup; in this group, lack of empathy was the least reported core symptom. However, the predominance of sex may differ in some cases from the literature, and associated symptoms (psychosis, parkinsonism, depression) are less frequent than reported in other latitudes. Prospective studies are needed to better characterize our population, as well as greater dissemination of the characteristics of this disease to be recognized and treated comprehensively and in a timely manner.

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Authors' contributions

All authors declare that they meet the authorship criteria recommended by the International Commite of Medical Journal Editors (ICMJE).

Roles according to CRediT IA

S. Castro-Suárez: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, writing-original draft, writing-review and editing. E. Guevara-Silva, C. Caparó-Zamalloa, K.H. Álvarez-Toledo, and M. Meza-Vega: conceptualization, investigation, methodology, validation, writing-original draft, writing-review and editing.

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Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was deemed unnecessary. The relevant recommendations have been followed.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for the writing of this manuscript.

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Seizures in chronic kidney disease: etiology and approach

Crisis epilépticas en enfermedad renal crónica: etiología y abordaje

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Abstract

Chronic kidney disease (CKD) is associated with high morbidity and mortality, decreased quality of life and economic repercussions. Neurological complications are diverse, despite advances in medical management, replacement therapies and kidney transplantation. The location of damage secondary to CKD may involve the central nervous system (CNS), the peripheral nervous system, and the autonomic nervous system. Cortical alterations include cognitive impairment, encephalopathy, dementia, asterixis, myoclonus, cerebral vascular events, and seizures. These are a frequent complication in CKD and their origin may be related to the underlying disease, due to a decrease in the glomerular filtration rate, hemodynamic, electrolyte, or hormonal disturbances, or because of renal replacement therapies. The management of seizures in CKD requires extensive knowledge of the pathophysiological aspects and early detection of the risk factors associated with their appearance. The main causes of seizures in kidney disease are uremic encephalopathy, dialysis imbalance syndrome, hydro electrolyte disorders, kidney transplant or associated with drugs. The appearance of seizures is a very common complication and requires a multidisciplinary approach between the different areas of medicine involved, especially neurology and nephrology.

Keywords: *Epileptic seizures. Kidney. Chronic kidney disease. Central nervous system.*

Resumen

La enfermedad renal crónica (ERC) se asocia a una elevada morbi-mortalidad, disminución en la calidad de vida y repercusiones económicas. Las complicaciones neurológicas son diversas a pesar de los avances en el manejo médico y en las terapias de sustitución y el trasplante renal. La localización del daño secundario a la ERC puede involucrar el sistema nervioso central (SNC), el sistema nervioso periférico y el sistema nervioso autónomo. Las alteraciones corticales incluyen deterioro cognitivo, encefalopatía, demencias, asterixis, mioclonías, eventos vasculares cerebrales y crisis epilépticas (CE). Las CE son complicaciones frecuentes en la ERC y su origen puede estar relacionado con la enfermedad subyacente, por la disminución en la tasa de filtrado glomerular, alteraciones hemodinámicas, electrolíticas, hormonales, o como consecuencia de las terapias de sustitución renal. El manejo de las CE en la ERC requiere un amplio conocimiento de los aspectos

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fisiopatológicos y la detección temprana de los factores de riesgo asociados a su aparición. Las principales causas de CE en la enfermedad renal son encefalopatía urémica, síndrome de desequilibrio por diálisis, trastornos hidroelectrolíticos, trasplante renal y asociada a fármacos. La aparición de CE es una complicación muy frecuente y requiere un enfoque multidisciplinario entre las diferentes áreas de la medicina involucradas, especialmente neurología y nefrología.

Palabras clave: *Crisis epilépticas. Riñón. Enfermedad renal crónica. Sistema nervioso central.*

Introduction

Chronic kidney disease (CKD) is defined as a slow and progressive loss of glomerular filtration rate (GFR). Although it can result from many conditions, the clinical signs are the same. Immediately after the loss of kidney function, compensatory mechanisms develop in the remaining nephrons, with hypertrophy of the glomeruli and functional tubules to maintain extracellular fluid composition and internal balance. As renal failure progresses, these adaptive mechanisms are lost, leading to systemic complications such as hypertension, anemia, left ventricular hypertrophy, CKD-associated bone disease, increased cardiovascular risk, dyslipidemia, inflammation, malnutrition, and death[1].

The incidence and prevalence of CKD are difficult to determine due to its silent nature, as it often causes signs and symptoms very late in its course. Additionally, there are few existing records, especially at national level. Currently, there has been an increase in the prevalence and incidence of CKD by more than 10% in the adult population and 20% in those older than 60 years, with variations depending on the studied population. This results in a high number of undiagnosed and untreated cases, leading to poor prognoses[2,3].

An analysis by the Global Burden of Disease (GBD Chronic Kidney Disease Collaboration) group, using published literature, civil registration systems, end-stage renal disease registries, and household surveys, determined that globally in 2017, there were 697.5 million (95% confidence interval [CI]:,649.2-752.1) cases of CKD. Nearly one-third of these patients lived in two countries, China and India, while Bangladesh, Brazil, Indonesia, Japan, Mexico, Nigeria, Pakistan, Russia, U.S.A., and Vietnam each had over 10 million CKD cases. The global prevalence of CKD was estimated at 9.1%, remaining constant since 1990[4].

To diagnose CKD, the presence of damage indicators, such as imaging abnormalities and proteinuria, is required, along with a reduced GFR calculated using creatinine. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines classify CKD into five stages based on disease progression and GFR levels, with stage 5 corresponding to a GFR below 15 mL/min. Recently, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines were updated for diagnosis, evaluation, and treatment[5,6] (Tables 1 and 2).

The clinical signs of uremic syndrome are diverse and affect virtually all organs. Many depend on the GFR level, as per the KDIGO classification for CKD, and the level of uremic solutes. Traditionally, the term uremia refers to what happens in CKD patients with elevated blood urea levels or those with renal failure. Its spectrum of manifestations is broad: hypertension due to volume overload, tetany caused by hypocalcemia, and anemia due to erythropoietin deficiency, among others. The increase in uremic solutes leads to the development and manifestation of uremic syndrome[7].

Uremic toxins in CKD are numerous and diverse. The most well-known include urea, creatinine, pseudouridine, methylguanidine, indoxyl sulfate, orthohippuric acid, parathyroid hormone, β2-microglobulin, polyamines, purines, phenols, indoles, phosphates, urofuranic acids, trace elements, dimethylarginine, oxalates, nitric oxide, and homocysteine[7].

Neurological complications are diverse and highly prevalent, despite advances in the medical management of advanced stages of the disease, such as dialysis therapies and kidney transplantation[8,9]. These complications have multiple mechanisms, including uremia, hydroelectrolyte imbalances, and vascular changes, among others[9].

The main complications in the central nervous system (CNS) can be categorized into cortical and subcortical abnormalities. The former include cognitive impairment, encephalopathy, dementia, asterixis, myoclonus, cerebrovascular events, and epileptic seizures (ES). The latter include cranial neuropathies and movement disorders such as Parkinson's disease, chorea, or dystonia[8,9].

Epileptic seizures in chronic kidney disease

Epileptic seizures are not uncommon in CKD patients, with an approximate incidence of 10%[10]. Their origin may be related to the cause of kidney disease, the

Table 1. Criteria for CKD (any of the following for at least 3 months)

Markers of renal damage (one or more)	Albuminuria (AER ≥ 30 mg/24 h; ACR ≥ 30 mg/g)
	Abnormal urinary sediment
	Electrolytes and other abnormalities due to tubular disorders
	Abnormalities detected by histology
	Structural abnormalities detected by imaging
	History of kidney transplant

AER: Albumin excretion rate; ACR: Albumin-to-creatinine Ratir; CKD: chronic kidney disease.
Modified from Eknoyan et al., 2013[6].

Table 2. Categories according to GFR

Category	GFR (mL/min/1.73 m²)	Name
G1	> 90	Normal or high
G2	60-89	Slightly decreased
G3a	45-59	Mild to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	< 15	Kidney failure

GFR: glomerular filtration rate.
Modified from Eknoyan et al., 2013[6].

alterations caused by reduced GFR, resulting hemodynamic, electrolyte, or hormonal changes, or due to renal replacement therapies[11].

Regarding seizure semiology, myoclonic seizures, focal seizures with impaired awareness, generalized tonic-clonic seizures, and convulsive or non-convulsive status epilepticus have been described[12]. When seizures first appear in CKD patients, an evaluation including serum electrolytes (mainly calcium, sodium, phosphorus, and magnesium), neuroimaging, and, in selected cases, lumbar puncture to exclude infections is required[13].

The management of seizures in CKD patients requires a thorough understanding of the pathophysiological aspects and early detection of associated risk factors[9]. The prescription of antiepileptic drugs (AEDs) in CKD patients requires careful consideration due to potential alterations in their pharmacokinetics. In patients on renal replacement therapy, it is important to know the protein-binding properties and molecular size of AEDs, as their clearance by hemodialysis may require dosage adjustments post-therapy. Among the highly protein-bound AEDs are phenytoin and valproic acid[10].

Etiology of epileptic seizures in chronic kidney disease

Uremic encephalopathy

Uremic encephalopathy (UE) is a syndrome that occurs in advanced CKD patients with a GFR < 15 mL/min/1.73 m² who have not received replacement therapy or in whom replacement therapy is inadequate or insufficient. Seizures are a late manifestation and are estimated to occur in 10% of patients[14].

Clinical presentation

The manifestations of UE fluctuate over hours or even days and can vary in severity depending on the GFR level and measurable uremic toxin levels, such as urea. The most severe symptoms occur primarily when the GFR is < 10 mL/min/1.73 m²[.8] Early symptoms may be subtle and nonspecific, with mild forms presenting only fatigue, apathy, and attention and concentration disturbances; moderate forms may include emotional lability, memory problems, and sleep-wake cycle inversion. As it progresses, it can lead to frontal lobe dysfunction, with paratonia or frontal release signs such as palmar grasp or palmomental reflex[15]. Finally, delirium, visual hallucinations, and agitation may occur, progressing to stupor, catatonia, coma, and seizures, which are usually focal onset with preserved awareness and/or impaired awareness, evolving to focal motor status epilepticus and generalized seizures such as myoclonus and/or generalized tonic-clonic seizures[8].

Pathophysiology

Proposed mechanisms explain the development of seizures in UE. In CKD, cerebral metabolic activity is reduced due to decreased neurotransmission, associated with lower neuronal oxygen consumption. Uremic toxins accumulate due to the inability to be eliminated via the kidneys, leading to an imbalance between excitatory and inhibitory neurotransmitters.

Guanidino compounds, guanidinosuccinic acid, and methylguanidine have been identified as neurotoxins; these are elevated in the cerebrospinal fluid (CSF), antagonize γ-aminobutyric acid receptors, and act

agonistically on N-methyl-D-aspartate glutamate receptors, causing increased cortical excitability and the onset of seizures[16,17].

The activity of the sodium/calcium exchanger and the calcium-ATPase pump plays an important role; they export calcium out of excitable cells, which is crucial for maintaining the normal gradient between the exterior and interior of neurons (10,000:1). In uremia, there is an increase in calcium transport, leading to elevated intracellular calcium, which plays a significant role in neuronal excitation; this causes the calcium content in the cerebral cortex to double[18] (Fig. 1).

Previously, parathyroid hormone activity was considered an important mechanism; it was observed that in CKD, cognitive abnormalities and electroencephalogram (EEG) changes improved after parathyroidectomy[18]. Currently, there is evidence of UE improvement following renal replacement therapy, with renal hyperparathyroidism being a contributing factor but not the primary cause[8].

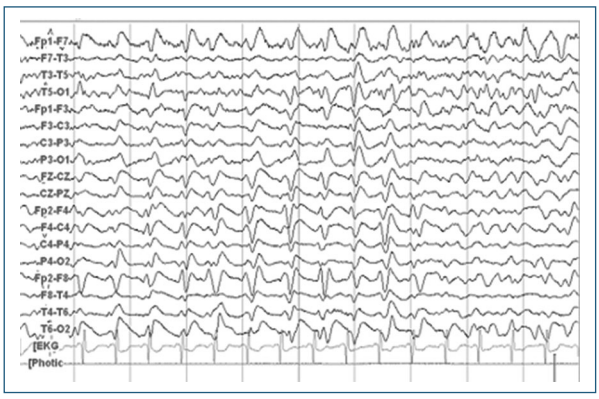

Figure 1. Electroencephalographic findings in a patient with uremic encephalopathy showing generalized slowing with triphasic waves (electroencephalogram of a patient seen in consultation at the Epilepsy Clinic, informed consent was obtained).

Diagnosis

The diagnosis of UE is based on clinical presentation and a favorable response to appropriate renal replacement therapy. In patients with uncertain clinical diagnosis, imaging and laboratory studies are useful[18]. The CSF may be abnormal, showing moderate pleocytosis (usually < 25 cells/mm³) and hyperproteinorrhachia (usually < 100 mg/dL).

EEG may show abnormalities, mainly during the acute phase of UE; although nonspecific, it may be normal in early stages[19]. Abnormalities may include generalized dysfunction with frontal predominance, abundant delta and theta slow waves, and, when UE progresses to coma, generalized triphasic waves[8].

Magnetic resonance imaging (MRI) typically shows cerebral parenchymal atrophy with ventricular enlargement and elongation[18]. The "lentiform fork sign" on T2WI/FLAIR sequences has been described as a hyperintense border delineating the lateral (external capsule) and medial (internal capsule, internal and external medullary laminae) boundaries of both putamina in a fork-like shape, which is a reliable sign for early UE diagnosis[20].

Treatment

Treatment modalities for neurological complications associated with UE include renal replacement therapy, kidney transplantation, correction of metabolic and nutritional disorders, and specific symptomatic treatment. Most CNS abnormalities are reversible within days or weeks after starting replacement therapy; however, some symptoms may persist or recur, often due to insufficient dialysis doses. Increasing the frequency and duration of dialysis may be a reasonable approach[8].

Treating anemia in dialysis patients is a key point in comprehensive and multidisciplinary management to achieve hemoglobin targets of 11-12 mg/dL. Erythropoiesis-stimulating agents are associated with the restoration of cognitive functions and reduced slow EEG activity; however, rapid correction and high doses of these agents have been reported to be associated with seizures due to increased blood viscosity, peripheral resistance, and blood pressure[17,21].

Suppression of parathyroid hormone with vitamin D analogs or calcimimetics is advisable given its potential as a neurotoxin, considering its effects on neuronal calcium transport[18]. Parathyroidectomy may be considered when various medical management alternatives have failed[8].

Dialysis disequilibrium syndrome

Dialysis disequilibrium syndrome (DDS) is defined as neurological deterioration associated with sudden metabolic changes occurring in relation to renal replacement therapies, either hemodialysis or peritoneal dialysis[8,9]. It most frequently occurs after the first session but can occur (though less commonly) at any point during therapy in patients receiving hemodialysis. The exact prevalence is unknown; currently, there is a trend

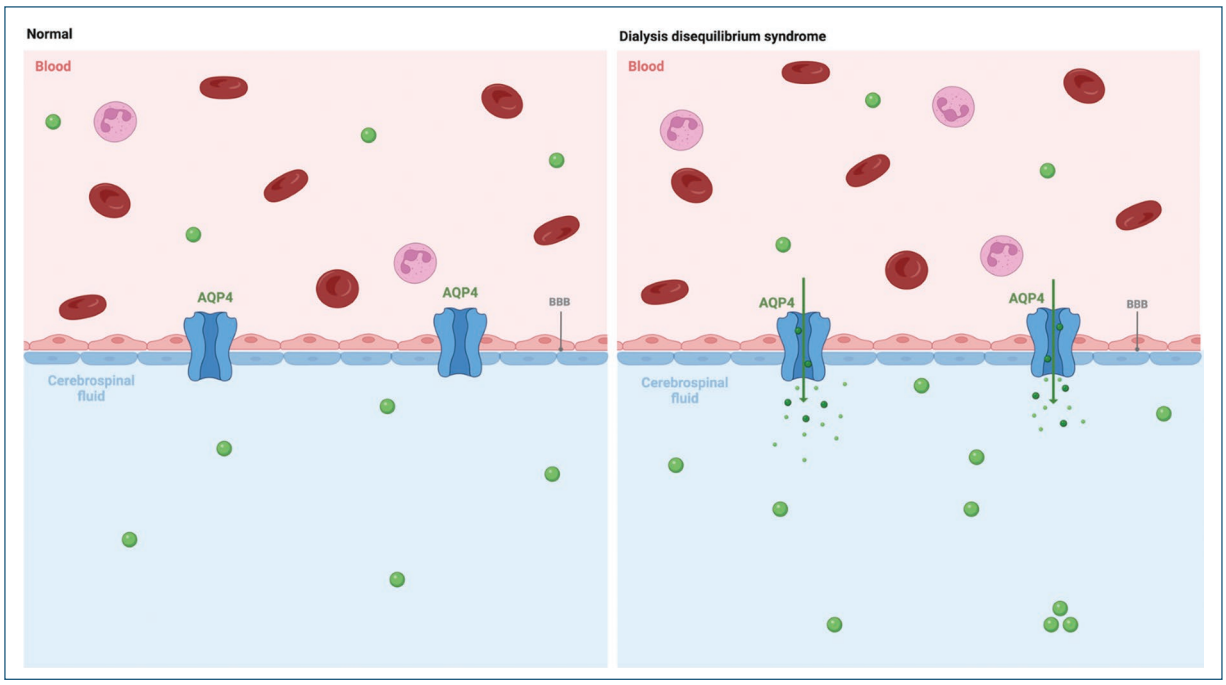

Figure 2. Pathophysiology of cerebral edema due to dialysis disequilibrium syndrome. After the hemodialysis session, urea in the CSF is at higher concentrations than in the blood, the BBB can undergo structural changes with hyperosmolarity that alters transport regulation, in turn increasing the concentration gradient that causes water movement towards the central nervous system, facilitated by AQP4, ending in increased intracranial pressure that explains the presence of cerebral edema and seizures (*image created by the authors*). AQP4: aquaporin 4; BBB: blood-brain barrier.

toward its reduction due to earlier initiation of replacement therapy and more conservative prescriptions[22].

Clinical presentation

Symptoms vary, including anxiety, muscle spasms, nausea, headache, and, in severe cases, confusion, delirium, generalized onset seizures, increased intracranial pressure (ICP) and intraocular pressure, coma, or even potentially fatal arrhythmias[9,23]. Neuroimaging often shows diffuse cerebral edema[24].

Pathophysiology

It is important to establish the relationship between urea and its impact on the CNS. The non-fenestrated endothelial cells of the cerebral microvasculature forming the blood-brain barrier (BBB) control the composition of cerebral extracellular fluid and CSF; the primary function of this barrier is to regulate the movement of small organic solutes and ions between the blood and cerebral extracellular space. The properties of BBB cells include: a) low permeability to ions; b) high reflection coefficient for solutes; and c) high electrical resistance. Urea permeability through the BBB is relatively low compared to other organic solutes, and its entry into the brain is slower than into other tissues[8].

The BBB can suffer structural disorganization due to hyperosmolarity, altering transport regulation. In CKD patients on replacement therapy, post-hemodialysis, urea concentrations in the CSF are higher than in the blood, due to rapid clearance of urea and other solutes, creating higher osmolarity in the CSF, which causes water movement into the CNS, leading to increased ICP, cerebral edema, and subsequent seizures[8,9,19,22] (Fig. 2).

Water transport in the BBB is facilitated by aquaporin-4 (AQP4), while urea transport is mediated by the urea transporter B[18]. There are 2 theories on the development of cerebral edema in uremia. The first, called the "reverse urea effect," is based on urea concentrations in the CNS remaining elevated due to slower diffusion from the CNS to blood vs the increased diffusion rate of urea from blood to the dialyzer compartment. The second, called "idiogenic osmolarity," proposes that the difference in osmolarity

cannot be fully explained by changes in electrolytes and urea, suggesting an additional mechanism of new organic molecules called idiogenic osmoles contributing to increased CNS osmolarity as a compensatory mechanism to increased blood osmolarity[22]. Despite differences, the 2 theories support the idea that higher urea and other osmolyte concentrations in the CNS vs blood at the end of dialysis cause water movement to areas of higher osmolarity. Similarly, patients on medications and dialysis experience alterations in drug distribution, metabolism, and clearance, making them more susceptible to lowering the seizure threshold[17].

Preventive management

Prevention is based on measures aimed at avoiding the formation of the concentration gradient described above. A useful strategy to prevent sudden osmotic changes in conventional hemodialysis patients is to initiate dialysis gradually, with shorter and more frequent intervals and low blood flows in the artificial kidney. These measures aim for a < 40% reduction in urea in dialysis prescriptions[8,22].

An additional measure is the implementation of osmotic agents in the blood flow, which helps prevent sudden osmotic changes, such as the administration of sodium or other osmotic agents. High concentrations of intravenous glucose or mannitol prior to hemodialysis result in fewer DDS-related symptoms. A study by Patel et al. reported that using both agents in combination reduced blood osmolarity changes, with symptoms occurring in only 10% of patients[25].

Treatment

Treatment aims to reduce ICP. Standard maneuvers include administering mannitol or hypertonic saline to increase osmolarity, followed by hyperventilation. This has been described in various case reports with significant symptom reduction[24] but with variable outcomes, as the crucial point lies in preventive actions[26].

Hydroelectrolyte and metabolic disorders

CKD can cause changes in serum electrolyte levels and metabolic abnormalities, which, if not promptly identified, treated, or inadequately managed, can lead to disabling repercussions and permanent damage to the CNS and peripheral nervous system[9].

Sodium

The dangers of hyponatremia have been widely described, defined by serum sodium levels < 135 mEq/L[9]. Seizures generally occur at < 120 mEq/L, and the relationship between hyponatremia and seizures is well-known; a rapid sodium drop > 15 mmol/L is a significant risk factor even when absolute sodium levels are > 120 mEq/L[27,28]. Decreased serum sodium levels create a concentration gradient between the CNS and blood, leading to a compensatory physiological response with osmotic water transport into neuronal cells, causing cerebral edema, which is responsible for neurological symptoms such as lethargy, agitation, disorientation, nausea, muscle spasms, and seizures[9,29].

Hypernatremia, defined as serum sodium levels > 145 mEq/L, can predispose to or cause seizures. In acute hypernatremia, the brain activates a homeostatic mechanism of osmotic water loss, causing cerebral parenchymal compaction, which can be associated with focal hemorrhages or lesions from rapid rehydration[9,14].

Proper management involves prevention through early identification of high-risk patients and monitoring of fluid and electrolyte protocols post-replacement therapy. Crystalloids are considered first-line for volume replacement, with administration schemes varying by institution, always with constant monitoring of serum sodium levels[30].

Calcium

Circulating calcium in the blood represents 1% of the total body calcium content. Normal serum total calcium levels are 9-10 mg/dL. Calcium consists of a diffusible component (freely ionized portion) and a non-diffusible component bound to proteins (mostly albumin).

The freely ionized calcium component is biologically active; hydrogen concentrations affect ionized calcium levels, as both hydrogen and calcium bind to albumin. In acidosis, correction to alkalosis causes hydrogen ions to dissociate from albumin, allowing calcium to bind to it, decreasing ionized calcium levels. Acute hypocalcemia can present clinically with tetany, carpopedal spasm, laryngeal stridor, decreased cardiac muscle contractility, hypotension, and seizures[31].

These manifestations can also occur with serum calcium levels > 11 mg/dL[9]. Seizures due to hypocalcemia are more common than those caused by hyponatremia, as decreased calcium levels can cause focal seizures without necessarily correlating with structural brain abnormalities[14].

Magnesium

Hypomagnesemia is defined as serum magnesium levels < 1.5 mEq/L. Clinically, it can present with generalized chorea and nystagmus[9]. Generalized seizures typically develop with serum levels < 0.8 mEq/L. Management involves slow intravenous infusion of magnesium and calcium gluconate, avoiding hypermagnesemia, which could lead to respiratory muscle paralysis[14].

Acid-base disorders

Acid-base balance is the homeostatic result of maintaining the body's normal pH; it is achieved through an adequate and maintained relationship between bicarbonate, whose production and excretion are mediated by the kidneys, and carbon dioxide, whose elimination is managed by the lungs. Imbalances, predominantly metabolic acidosis, initially manifest with altered consciousness and have a high likelihood of progressing to epileptic activity or even coma if the underlying cause is not resolved[9]. CKD, as a renal function impairment, directly disrupts the mechanisms maintaining this balance.

Kidney transplantation

Neurological abnormalities are common in post-transplant patients due to the direct neurotoxicity of immunosuppressive therapy and disruption of the BBB. The most described complications include encephalopathy, movement disorders, and seizures, with the latter causing significant neurological sequelae and, in severe cases, death. Studies have documented incidence rates of up to 20% of seizures in pediatric post-transplant patients[32,33]. Currently, the incidence rate has decreased due to changes in CKD patient management before and after transplantation, such as changes in the type and dose of immunosuppressive agents used and optimal hypertension management[34].

Pathophysiology

The etiologies of seizures after renal transplantation are multifactorial. Metabolic disorders (hyponatremia, hypocalcemia, or hypomagnesemia), immunosuppressant treatment, ischemic or hemorrhagic lesions, and CNS infections are prominent[35].

Immunosuppression is a fundamental pillar in the pathophysiology of seizures post-renal transplantation, creating conditions that facilitate their occurrence. Neuronal toxicity and damage to the blood-brain barrier caused by immunosuppressants produce axonal damage, extracellular edema, and demyelination. All of this, as a consequence of the inflammatory process, can generate reversible posterior leukoencephalopathy[18]. Tacrolimus and cyclosporine increase the risk of common and opportunistic infections (*Nocardia asteroids, Listeria monocytogenes, Mycobacterium tuberculosis, Cryptococcus neoformans, Aspergillus fumigatus* or *Paracoccidioides, Toxoplasma gondii,* and *Trypanosoma cruzi*), especially within the first 3 months after transplantation, when immunosuppressive action reaches its peak. This leads to the uncontrolled development of seizures, particularly in those with a diagnosis of epilepsy[19]. In addition, the possibility of uncontrolled or new-onset seizures increases due to numerous pharmacological interactions between antiepileptic drugs and immunosuppressive therapy, especially in relation to hepatic cytochrome P450 3A4[36].

Prevention and management

Prevention of seizures after renal transplantation is based on managing the underlying causes. Most seizures that occur as a complication do not recur once the underlying etiology has been treated, with a favorable prognosis for neurological functions and without the need to initiate management with antiepileptic drugs (AEDs)[33]. Therefore, they are considered acute symptomatic seizures, as they do not meet the criteria for the diagnosis of epilepsy in subsequent controls[37]. Continuous laboratory monitoring allows anticipating the risk and preparing an adequate treatment for the possible appearance of hydroelectrolytic alterations[33].

Conclusions

CKD is a highly prevalent problem both worldwide and in Mexico. The lack of timely diagnosis is one of the main obstacles, as it makes it difficult for the patient to start immediate treatment, which can lead to advanced stages of the disease with imminent complications. Neurological repercussions of CKD include alterations in the CNS, PNS, and autonomic nervous system. The occurrence of seizures is a frequent complication that requires priority attention due to its negative repercussions, both physical and cognitive, that affect the quality of life of this vulnerable population.

Critical signs of renal failure can be considered acute symptomatic seizures, as the necessary criteria for a

diagnosis of epilepsy are not met in subsequent evolutionary controls.

Although the challenge posed by this public health problem is considerable, its approach will become increasingly feasible through multidisciplinary collaboration between the different areas of medicine involved (especially neurology and nephrology) which will allow resolving these pathological conditions from various perspectives and with varied approximation strategies.

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Authors' contributions according to CRediT taxonomy

M.A. Sebastián-Díaz: conceptualization, methodology, original drafting. S. Martínez-Medina: conceptualization, methodology, original drafting. J. González-Salido: conceptualization, visualization, formal analysis, validation. J. Colado-Martínez: conceptualization, visualization, formal analysis, validation. C.D. Tamayo-de León: methodology, original drafting. S. Herrera-Rivera: methodology, original drafting. M. Fernández-González-Aragón: conceptualization, supervision, writing-review and editing. I.E. Martínez-Juárez: conceptualization, drafting-review and editing, conceptualization, methodology, original drafting.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of people and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the institution's Ethics Committee.

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

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence to write this manuscript.

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CASE REPORT

Intracerebral hemorrhage associated with use of sildenafil: case report

Hemorragia intracerebral asociada al uso de sildenafilo: reporte de caso

*Hugo Rico-Hernández[1,2], Vanessa Cano-Nigenda[2], Charles A. Huamaní-Saldaña[2], Antonio Arauz[2], and Andrés A. Mercado-Pompa[2]**

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Abstract

Intracerebral hemorrhage results from the degeneration of penetrating arterioles in the brain parenchyma. This report presents the case of a 47-year-old man who experienced a hemorrhagic stroke with a direct temporal relationship to sildenafil consumption. A computed tomography (CT) scan confirmed a cerebellar hemorrhage predominantly involving the vermis and the left hemisphere. Hemorrhage associated with sildenafil use is an extremely rare phenomenon. Its causative relationship can only be considered after ruling out more common etiologies, such as hypertension, cerebral amyloid angiopathy, or aneurysms. Moreover, sildenafil could only be classified as a causative agent if it was ingested within two hours prior to symptom onset.

Keywords: *Intracranial hemorrhage. Sildenafil citrate. Phosphodiesterase 5 inhibitor. Adverse reaction. Hypertensive microangiopathy.*

Resumen

La hemorragia intracerebral es el resultado de la degeneración en las arteriolas penetrantes del parénquima cerebral. Este trabajo presenta el caso de un hombre de 47 años cuyo ictus hemorrágico presentaba una relación temporal directa con el consumo de sildenafilo. Se realizó tomografía computarizada de cráneo que corroboró la hemorragia ubicada en el parénquima cerebeloso con predominio vermiano y en el hemisferio izquierdo. La hemorragia intracerebral asociada al consumo de sildenafilo es un fenómeno muy poco frecuente cuya relación solo puede inferirse una vez descartadas las causas más frecuentes, tales como hipertensión, angiopatía amiloide cerebral y aneurismas. Sin embargo, solo puede catalogarse como agente causal si su consumo se realizó dentro de las 2 horas previas a la aparición de los síntomas.

Palabras clave: *Hemorragia intracerebral. Citrato de sildenafilo. Inhibidor de la fosfodiesterasa 5. Reacción adversa. Microangiopatía hipertensiva.*

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Introduction

Intracerebral hemorrhage (ICH) accounts for approximately 15% of all types of cerebrovascular disease. Its most common etiological factors include hypertensive microangiopathy, cerebral amyloid angiopathy, arteriovenous malformations, venous thrombosis, and coagulopathies[1]. ICH is generally thought to result from the degeneration of penetrating arterioles in the brain parenchyma, with mechanical injury and disruption of the blood-brain barrier identified as key mechanisms underlying tissue damage[2].

Sildenafil is a drug that structurally mimics the purine ring of cyclic guanosine monophosphate (cGMP). Its a mechanism of action involves selective inhibition of phosphodiesterase type 5 (PDE5)–with more than 10,000-fold higher affinity for PDE5 compared to other isoforms[3]. The increase in cGMP levels triggers changes in the resting membrane potential by opening potassium channels and closing calcium channels, leading to hyperpolarization and relaxation of smooth muscle cells. Currently, sildenafil is approved for the treatment of erectile dysfunction and pulmonary arterial hypertension[4].

The objective of this report is to present the case of a 47-year-old man who experienced a hemorrhagic stroke with a direct temporal relationship to sildenafil use, after other etiological causes were excluded during diagnostic evaluation.

Case report

A 47-year-old male presented to the emergency department following sexual activity, reporting thunderclap headache accompanied by nausea, vomiting, diaphoresis, pallor, gait instability with lateropulsion, ataxia, somnolence, and dysarthria. He denied any significant family history and reported no relevant personal medical history aside from sildenafil use two hours prior to the event and regular alcohol consumption.

On admission, his vital signs included a blood pressure of 110/80 mmHg, a heart rate of 88 bpm, and a respiratory rate of 16 breaths per minute. Neurological examination revealed somnolence, scanning dysarthria, dysmetria, and dysdiadochokinesia in all four extremities, a positive Stewart-Holmes maneuver bilaterally, and nuchal rigidity. The remainder of the physical examination was unremarkable.

A computed tomography (CT) scan of the brain confirmed an intracranial hemorrhage (ICH) involving the cerebellar parenchyma, predominantly in the vermis and the left hemisphere, with an estimated volume of 14 ml. The hemorrhage extended into the subarachnoid space, causing obliteration of the fourth ventricle but did not necessitate neurosurgical intervention. During his hospital stay, further imaging studies, including magnetic resonance imaging (MRI) (Fig. 1), CT angiography (CT-Angio), and digital subtraction angiography (DSA), revealed no evidence of vascular abnormalities or parenchymal lesions suggestive of a specific cause for the ICH (Fig. 2).

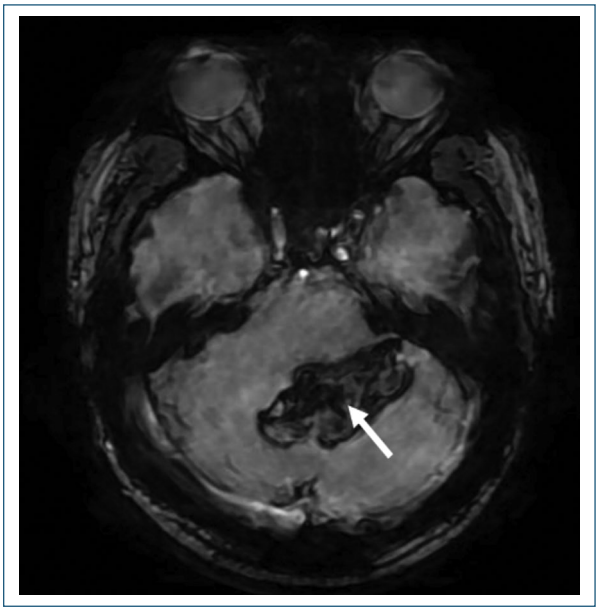

Figure 1. Magnetic resonance imaging susceptibility sequence showing hemorrhage in the left cerebellar parenchyma involving the vermis, as well as IV ventricle obliteration (arrow).

At discharge, the patient exhibited persistent ataxia in his left limbs. However, gradual symptomatic improvement has allowed him to return to work.

Discussion

We present the case of a 47-year-old male with cerebellar hemorrhage temporally associated with sildenafil use, after excluding other causes of intracranial hemorrhage (ICH). Although the association between sildenafil with ICH is poorly documented, there are reports suggesting a direct relationship where sildenafil acts as a triggering factor for the event[5-8]. It is hypothesized that this adverse effect may be secondary to the inhibition of phosphodiesterase (PDE) isoforms 1 and 2, the latter of which is implicated in increased cerebral blood flow. This process may lead to sympathetic overactivation and, consequently, blood infiltration into the brain parenchyma.

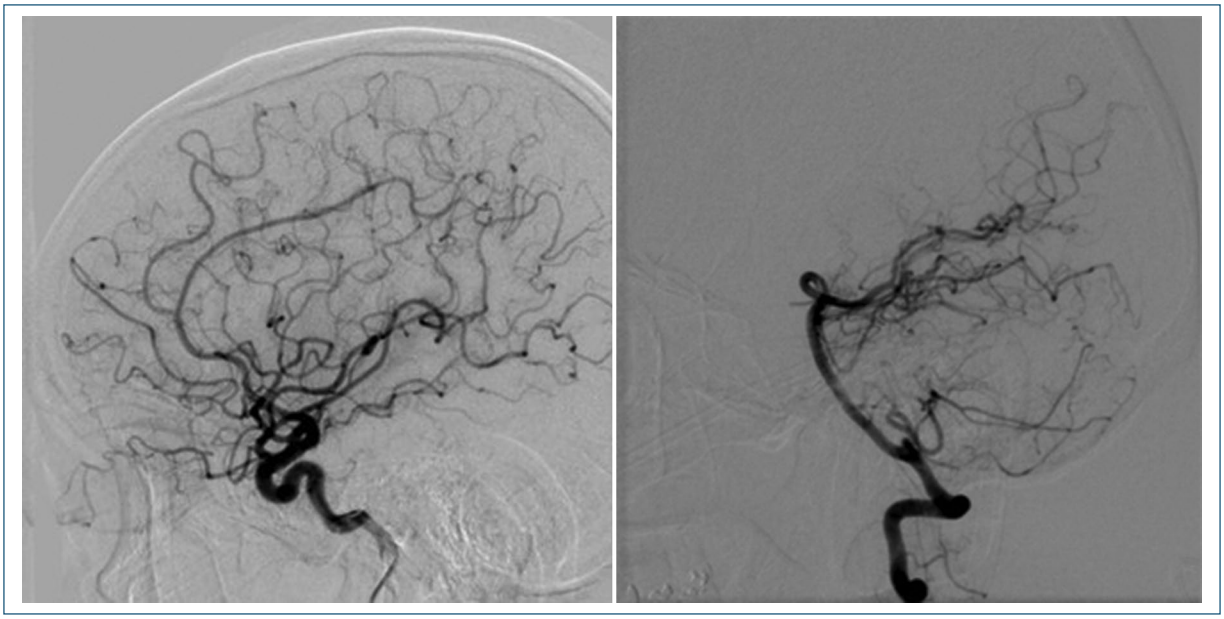

Figure 2. Digital subtraction angiography without evidence of cerebral vascular abnormalities.

Lucchese et al.[5] reported a 69-year-old male with recurrent lobar hemorrhage temporally linked to the use of PDE5 inhibitors during both events[5]. Similarly, Buxton et al.6 described a case of left temporal lobe ICH in a 44-year-old male following a sildenafil overdose. The patient died, and autopsy revealed no neurovascular abnormalities[6]. Regarding sildenafil's use in pulmonary hypertension treatment, Samada et al.[7] reported ICH in an 11-month-old female with congenital heart disease, triggered by a sudden increase in sildenafil dosage[5].

Alpsan et al.[8] documented a 62-year-old male who developed symptoms one hour after first-time sildenafil use. However, in this case, a causal relationship is questionable as the patient had a history of hypertension and reported nonadherence to antihypertensive medications. A CT scan revealed thalamic hemorrhage, a pattern commonly associated with hypertensive microangiopathy, suggesting an alternative etiology unrelated to sildenafil. It is noteworthy that no consistent anatomical localization patterns have been observed for sildenafil-associated ICH.

Conclusions

Intracranial hemorrhage (ICH) associated with sildenafil use is an extremely rare phenomenon. Its relationship can only be inferred after ruling out more common causes of hemorrhage, such as hypertension, cerebral amyloid angiopathy, or arteriovenous malformations, as well as excluding secondary causes based on the patient's age and the absence of common risk factors. Sildenafil could only be considered a causal agent for ICH if it was consumed within two hours prior to symptom onset, given that the drug reaches its peak plasma concentration approximately one hour after ingestion (range: 30-120 minutes)[4,9] and has a short half-life.

It is crucial to specifically inquire about the use of medications with potential risk for ICH in all patients presenting with this condition.

Authors' contributions

Conceptualization: V. Cano-Nigenda and A.A. Mercado-Pompa. Investigation: H. Rico-Hernández and A. Mercado-Pompa. Methodology: V. Cano-Nigenda. Project administration: C.A. Huamaní-Saldaña, A.A. Arauz-Góngora, and A. Mercado Pompa. Resources: C.A. Huamaní-Saldaña. Supervision: V. Cano-Nigenda, A.A. Arauz-Góngora, and A. Mercado Pompa. Visualization: V. Cano-Nigenda, A. Mercado-Pompa, and A.A. Arauz-Góngora. Drafting: H. Rico-Hernández. Drafting, reviewing, and editing: V. Cano-Nigenda and A.A. Mercado-Pompa.

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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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CASE REPORT

Generalized myoclonus following a tarantula spider bite: a case report

Mioclonía generalizada tras picadura de tarántula: reporte de un caso

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Abstract

Myoclonus, characterized by sudden, involuntary muscle movements, typically arises from several acute neurological insults. This case report introduces a unique instance of generalized myoclonus triggered by a spider bite from a species phylogenetically linked to tarantulas. A 41-year-old woman presented with sudden jerky movements following a spider bite 2 weeks earlier. Accompanying symptoms included skin lesions, pain, itching, and fever. Examination revealed generalized, action-triggered jerky movements, classified as myoclonus. Despite thorough evaluation, including brain magnetic resonance imaging, electroencephalography, and extensive laboratory tests, no abnormalities were detected except for abnormal electromyography findings consistent with myoclonus. Excluding infectious, metabolic, and structural causes, the spider bite emerged as the most plausible etiology, involving a spider from the Mygalomorphae suborder. Treatment with clonazepam, trihexyphenidyl, and doxycycline significantly improved myoclonus within 24 h. One month later, the patient remained asymptomatic. This case challenges conventional diagnostic paradigms and underscores the importance of considering unconventional etiologies in cases that defy traditional explanations. In Mexico, only black widow and violinist spiders are recognized for their medical significance. However, this case involved a spider from the Mygalomorphae suborder, which includes tarantulas. Tarantula venom typically induces pain, local tissue necrosis, and, rarely, muscle cramping, with a generally favorable prognosis. The venom consists of low molecular mass compounds, antimicrobial peptides, cysteine-rich neurotoxic peptides, enzymes, and proteins, potentially acting synergistically. This case suggests that components of the Mygalomorphae suborder venom may induce exaggerated responses in sensitive individuals. It offers insights into the complexities of arachnid envenomations and their neurological consequences.

Keywords: *Myoclonus. Spider bite. Tarantula. Neurological disorder. Venom-induced symptoms.*

Resumen

El mioclono es un trastorno de movimientos musculares involuntarios que generalmente se desencadena por lesiones neurológicas agudas. Presentamos el caso de una mujer de 41 años que experimentó mioclono generalizado después de ser picada por una araña relacionada con las tarántulas. Acompañando la picadura, presentó lesiones en la piel, dolor, picazón y fiebre. Aunque los análisis revelaron mioclono, no se encontraron otras anormalidades, sugiriendo la picadura de araña como la causa más probable. El tratamiento con clonazepam, trihexifenidilo y doxiciclina resultó en una mejoría rápida. Este caso desafía los paradigmas diagnósticos convencionales y destaca la importancia de considerar causas no tradicionales

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en casos difíciles. En México solo se consideran médicamente significativos dos géneros de arañas: viuda negra y araña violinista. Sin embargo, este caso involucró a una araña del suborden Mygalomorphae, que incluye a las tarántulas. Su veneno, compuesto por diversas sustancias, puede desencadenar respuestas exageradas en individuos sensibles, como en este caso. Esto ofrece perspectivas sobre las complejidades de las picaduras de araña y sus efectos neurológicos.

Palabras clave: *Mioclono. Picadura de araña. Tarántula. Trastorno neurológico. Síntomas inducidos por veneno.*

Introduction

Myoclonus is a hyperkinetic movement disorder characterized by sudden, brief, jerky, and involuntary movements affecting one or multiple muscle groups[1]. The most common presentation is symptomatic myoclonus, typically emerging as a result of acute neurological insults originating from diverse etiologies[2]. Bites from certain spiders, such as black widows, cause neurotoxicity through alpha-latrotoxin, leading to intense pain, headache, and neuromuscular symptoms. Funnel-web spiders' delta-atracotoxins mimic neurotransmitters, causing sensory changes, muscle paralysis, and autonomic issues such as diaphoresis, hypotension, and arrhythmias[3] While previous case reports have mentioned arachnid bites associated with muscle spasms[4-6], this report presents a distinctive case of generalized myoclonus induced by a spider bite phylogenetically linked to tarantulas.

Case presentation

A 41-year-old female presented to the emergency room with complaints of sudden, jerky movements. Approximately 2 weeks before admission, she reported experiencing what she described as an insect bite or sting while asleep. The bite occurred on her left distal leg, awakening her due to pain. Upon inspection, she discovered a spider in her room (Fig. 1A). Within 2 days of the incident, she observed the development of skin lesions around the bite site. Over the subsequent days, these lesions progressively expanded, accompanied by symptoms of burning, itching, and fever. In addition, she noted the emergence of similar lesions on her contralateral leg and an increase in their size, concomitant with the onset of generalized jerky movements. Consequently, she sought urgent medical attention.

The patient presented with normal vital signs. Her examination revealed sudden, generalized, jerky movements triggered by actions and tactile stimuli, phenomenologically categorized as myoclonus. The rest of her neurological examination was unremarkable. Physical examination further revealed erythematous plaques merging into vesicles with ill-defined borders, causing pain and persisting under digital pressure. Predominantly located on the left leg, these lesions extended to the right leg and lower abdomen (Fig. 1B).

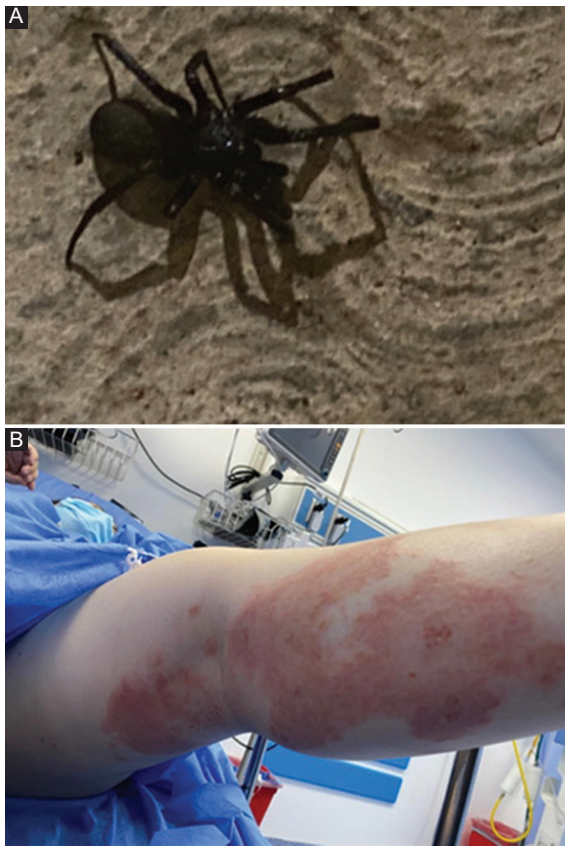

Figure 1. A: the spider identified as belonging to the Mygalomorphae suborder, which includes spiders colloquially known as tarantulas. **B:** erythematous plaques merge into vesicles with ill-defined borders, predominantly on her left leg.

A thorough evaluation showed no abnormalities, whereas simple and contrast-enhanced brain magnetic resonance imaging and electroencephalography were included. Laboratory tests, including a complete blood count, metabolic panel, Lyme disease and Rickettsia panel, and thyroid profile, all returned within normal ranges. Electromyography (EMG) indicated irregular muscular activity at rest, characterized by nonrhythmic

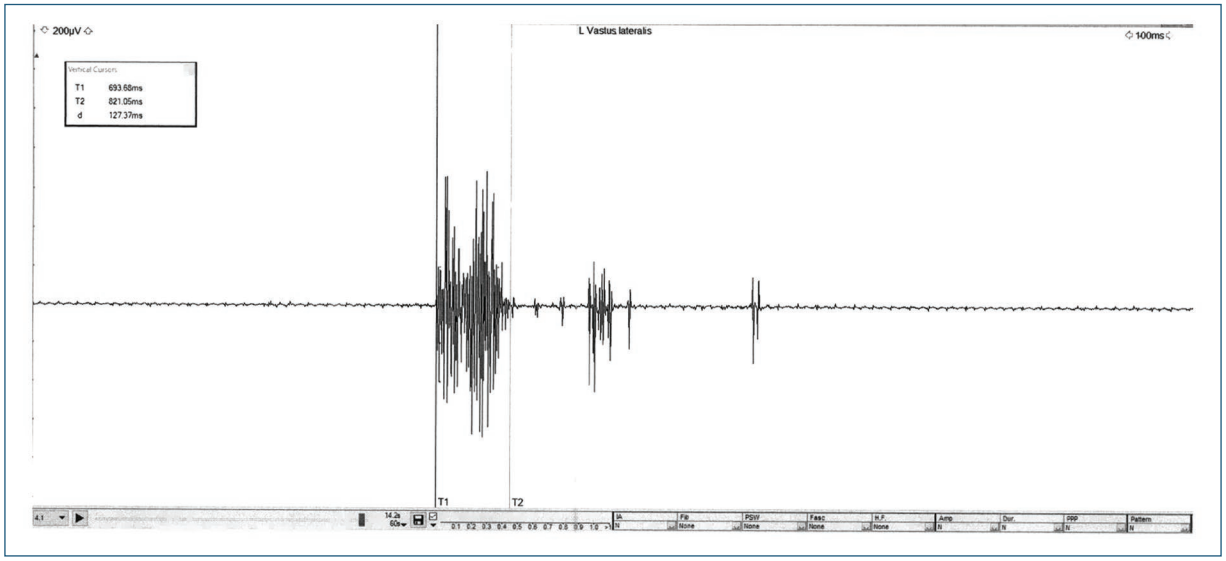

Figure 2. Electromyography of Left Vastus Lateralis. Normal insertion activity. At rest, irregular, non-rhythmic muscle activity is observed, with variable frequency that increases with tactile stimulus. This activity comprises multiple motor units with simultaneous activation and lasts up to 211 milliseconds. Partial and maximum contractions are not assessable due to interruption by involuntary movement.

and variably frequent contractions exacerbated by tactile stimuli. The EMG revealed multiple motor units with simultaneous activation, lasting between 67 and 211 milliseconds. The movement disorder was classified as generalized myoclonus based on the clinical and neurophysiological findings (Fig. 2). Infectious, metabolic, and structural etiologies were ruled out through initial assessment. Given the clear temporal association, the spider bite was the most plausible etiological factor. A biologist identified the spider as belonging to the Mygalomorphae suborder, which includes spiders colloquially known as tarantulas. Treatment for the patient included clonazepam 1 mg tid, trihexyphenidyl 1 mg tid, and doxycycline 100 mg bid. Within 24 h, her myoclonus showed significant improvement, allowing for a tapering of treatment. One month later, the patient remained asymptomatic while continuing the same medications and dosages.

Discussion

The presented case highlights a unique instance of generalized myoclonus induced by a spider bite, specifically from a spider phylogenetically related to tarantulas. Myoclonus often results from various neurological insults; this case adds to the limited literature documenting arachnid bites associated with myoclonus.

In Mexico, only two genera of spiders are known to have medical significance: the black widow (*Latrodectus* spp.) and the violinist spider (*Loxosceles* spp.)[7,8] The specimen found in this case was not associated with these genera but belongs to the Mygalomorphae suborder. This suborder includes many families colloquially known as tarantulas[9].

The venom from these spiders typically induces pain, local tissue necrosis, and, in rare instances, muscle cramping in humans. In general, the prognosis is favorable[10] Tarantula venom comprises substances with low molecular mass compounds, antimicrobial peptides (also referred to as cytolytic or cationic peptides, present in select spider families), cysteine-rich neurotoxic peptides, and enzymes and proteins. These include polyamines, free amino acids, nucleotides, and hyaluronidase, among others. Theoretically, these components act in synergy, contributing to the manifestation of symptoms associated with tarantula envenomations. These venom components may collaborate to quickly immobilize prey, while in humans, they can cause pain, localized tissue damage, and, in rare instances, severe muscle cramps[10,11].

While there is no official recognition of tarantulas from Mexican territory as medically significant, experiences with spiders from related families have demonstrated a range of neuromuscular disorders. It is imperative to consider that although this case demonstrates correlation

rather than causation, it is conceivable that components within the venom of Mygalomorphae suborder members may provoke exaggerated responses in sensitive individuals for unclear reasons. Such responses may lead to reactions akin to those observed in our patient.

This case stands as a direct correlation between a toxic agent and the subsequent development of myoclonus-type movement disorder, with the notable outcome of complete symptom resolution. It underscores the importance of vigilance and consideration of unconventional etiologies when encountering cases that challenge traditional diagnostic paradigms, offering an intriguing glimpse into the complexities of arachnid envenomations and their potential neurological consequences.

Author´s contributions

Conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, visualization, writing – original draft, writing – review and editing: C.A. Díaz-Garza, C.D. Acevedo-Castillo, C.N. Esparza-Hernández, J.A. Echeverría-Vargas, and D. Martinez-Ramirez.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors have 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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LETTER TO THE EDITOR

Use of intraoperative magnetic resonance imaging in transsphenoidal resection of pituitary adenomas: what results have been obtained?

Uso de resonancia magnética intraoperatoria en la resección transesfenoidal de adenomas hipofisiarios: ¿qué resultados se han obtenido?

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To the Editor,

Pituitary adenomas are a type of central nervous system tumor, accounting for 10 up to 15% of neoplasms in this system, with benign behavior. They produce specific symptoms depending on their composition and size[1]. They may be functioning or non-functioning, and if functioning, depending on their secretion, they can cause conditions that significantly affect quality of life, morbidity, and survival of those affected[2,3]. The definitive approach to these tumors is multidisciplinary. However, surgery, specifically transsphenoidal resection, is usually the technique of choice[3]. Intraoperative magnetic resonance imaging (MRI) has been described as a potential adjunct to enhance the efficacy of this surgery, as it improves visualization of the tumor and allows for personalized resection extent[4]. Nevertheless, evidence on its impact on short- and long-term outcomes is heterogeneous.

Zhang et al.[4] conducted a systematic review and meta-analysis to evaluate the impact of MRI on short- and long-term outcomes after transsphenoidal resection of pituitary adenomas, including 33 studies with a total of 2,099 patients. A total of 70.6% of these tumors were non-functioning. It was found that the gross total resection rate with MRI was 66.8 vs. 29.4% without this tool (relative risk [RR], 1.32; $p < 0.001$). Additionally, it was observed that both microscopic and endoscopic approaches showed an increase in gross total resection by 35 and 31%, respectively, with MRI. In terms of visual symptom improvement (96.5 and 84.9% in the short- and long-term, respectively) and endocrine symptoms (73% at 3 months), significant advantages were seen with the MRI-assisted approach, with a very low postoperative complication rate. Based on these findings, the authors conclude that MRI offers a significant advantage during transsphenoidal resection of pituitary adenomas[4].

These results were similar to those reported by Celtikci et al.[5] who conducted a retrospective analysis evaluating the need for MRI use during endoscopic resection of

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pituitary adenomas. They showed that for tumors classified as Knosp 0 up to 2, the concordance between the surgeon's assessment and the MRI finding was 98.6% (n = 150), while for those classified as Knosp 3 or 4, the concordance was 66.6% (n = 32). After an exhaustive analysis of cases where the prediction was incorrect, it was found that MRI should be essentially used in tumors that extend to the supra- or parasellar regions or invade the cavernous sinus[5].

Pala et al.[6] conducted a retrospective analysis of 59 resections and reported an increase in gross total resection from 33.9 up to 49.2%. Large tumor size (odds ratio [OR], 1.6; p = 0.004) and use of microscopic technique (OR, 4.4; p = 0.009) were significantly associated with greater resection volume with MRI. Specifically, they found that patients with large recurrent tumors benefited the most[6].

In a series of 114 consecutive cases of resected functioning adenomas, MRI use was associated with very low postoperative morbidity (2.5%), complete resection in 83% of cases, and hormonal remission in 59%. However, unlike previous evidence, the researchers in this series reported that supra- and parasellar extension predicted incomplete resection despite MRI use. Nevertheless, resection was greater in these cases following the use of MRI[7].

In this context, the evidence suggests that MRI has the potential to personalize and facilitate the surgical approach to pituitary adenomas, being especially useful in challenging cases and depending on the size, extension, and invasion of the tumor. Additional research is needed, especially in low- and middle-income countries, to determine cost-utility, cost-effectiveness, and benefit-risk balance to standardize its use and improve the performance and health outcomes of this surgery.

Authors' contributions

M.L. Boschetti-Saer: study conception and design, data analysis and interpretation, manuscript drafting, critical review, and approval of the final version. Levino R. Boschetti: data analysis and interpretation, manuscript drafting, critical review, and approval of the final version. J.P. Linarez-Veloz: data analysis and interpretation, manuscript drafting, critical review, and approval of the final version. M.G. Ortega-Sierra: data analysis and interpretation, manuscript drafting, critical review, and approval of the final version.

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